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EDITORIAL

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Beyond Standard Protocols: The Dawn of Personalised Critical Care Nutrition

Medical nutrition therapy (MNT) is essential in managing intensive care unit (ICU) patients. Poor nutritional status can negatively impact patient survival and morbidity due to metabolic stress, profound inflammation and increased proteolysis of body protein. ICU patients are particularly prone to malnourishment, with prevalence rates ranging between 38% and 78%. Research demonstrates that providing optimal nutrition intervention in malnourished critically ill patients has consistently reduced hospital stay length, decreased infection rates, and lowered healthcare costs. During critical illness, increased catabolism leads to significant muscle mass loss, resulting in weakness and challenges in weaning from ventilatory support. To address these challenges, MNT provides essential macronutrients, micronutrients and electrolytes while maintaining metabolic homeostasis.[1]

As MNT is a rapidly evolving field, personalisation of ICU nutrition has become crucial for improving patient outcomes. This personalised nutrition approach helps to avoid the harmful effects of over- or underfeeding while preserving muscle mass. However, implementing personalised nutrition therapy in ICU settings remains in its infancy, i.e. at the "beginning of knowledge". Our ability to objectively measure patients' nutritional requirements and responses to nutritional interventions is still limited, making it challenging to optimise nutrition delivery.[2] Medical nutritional therapy must be customised based on individual patient factors, including their unique characteristics, medical condition, and the metabolic state as they progress from the acute phase of illness through recovery, using detailed analysis of their physical traits (phenotyping) and underlying biological patterns (endotyping).

A thorough nutritional assessment is crucial for identifying malnutrition risks in patients. The Modified Nutrition Risk in Critically Ill (mNUTRIC) score and the Global Leadership Initiative on Malnutrition (GLIM) criteria are widely used tools for evaluating nutritional status. While these tools provide standardised approaches, they have limitations and require ongoing validation research for improvement. The GLIM framework employs a two-step approach: first utilising phenotypic and etiologic criteria for diagnosing malnutrition, then grading its severity. Malnutrition is classified as either moderate (stage 1) or severe (stage 2) based on three key factors: unintentional weight loss percentage, low body mass index (BMI), and degree of reduced muscle mass. Although this consensus aims to standardise malnutrition diagnosis globally and improve clinical outcomes across different healthcare settings, the criteria's sensitivity and specificity in various patient populations still need further validation.[3]

When assessing lean body mass (LBM) at the bedside, healthcare providers have access to various tools, each with advantages and limitations. While available, predictive formulas often show significant variations from actual LBM measurements. More sophisticated methods like Dual-energy X-ray absorptiometry, CT, and MRI scans provide highly accurate results but are impractical for routine bedside use due to cost and logistical constraints. Bioelectric impedance analysis (BIA) has become a more practical and affordable bedside option. However, fluid overload can affect its measurements, though this limitation can be addressed using multifrequency BIA to assess extracellular water surplus. Bedside ultrasonography presents another viable alternative, though its accuracy depends on operator expertise and experience.

Personalised medicine is described as an innovative approach that tailors treatment to the individual characteristics of each patient, integrating molecular and clinical data. It is often used interchangeably with precision medicine, which focuses on individual differences in genetics, environments and lifestyles to create unique treatment plans. Personalised nutrition therapy, rooted in phenotyping and endotyping, presents a more practical approach for critically ill patients

than traditional which is based on specific patient characteristics and metabolic markers. Tailored energy and protein strategies and careful micronutrient management can optimise patient outcomes. Personalized phenotypic assessment enables the determination of patient-specific characteristics and body compositional data, facilitating precise calculations of macro- and micronutrient requirements during both acute illness and rehabilitation periods. The process of endotyping reveals specific disease mechanisms through metabolic marker analysis, which guides the development of targeted nutritional strategies. Metabolic biomarkers, particularly the urea-to-creatinine ratio (UCR), serve as potential indicators for monitoring protein metabolism and predicting clinical outcomes. Individualised energy strategy involves utilising indirect calorimetry (IC) to assess energy expenditure, offering a more accurate measure of individual energy needs. Predictive formulas are less reliable, potentially deviating by up to 1000 kcal/ day from actual needs. While one study showed that IC-guided feeding reduced mortality by 23%, a more recent trial (TICACOS-II) could not confirm this benefit. A key challenge is that IC cannot measure endogenous energy production during the early critical phase, and no reliable bedside method exists for this measurement. VCO^2 measurements can be an alternative when IC is unavailable, though they tend to overestimate energy expenditure. Furthermore, the potential benefits of early nutritional therapy are challenged by evidence suggesting that such intervention may suppress autophagy, increases hyperglycaemia and anabolic resistance.

Critically ill patients experience severe muscle wasting, losing up to 15% of muscle mass within the first week of ICU admission. This rapid deterioration, occurring at approximately 2% per day, leads to ICU-acquired weakness (ICU-AW) in about half of patients and significantly impacts outcomes. Each 1% loss in quadriceps muscle thickness corresponds to a 5% increase in 60-day mortality. The pathophysiology of ICU-AW involves multiple interrelated mechanisms. At its core is a severe protein imbalance driven by three key factors: systemic inflammation and sepsis, which disrupt normal protein homeostasis; impaired insulin/IGF-1 signalling, which reduces protein synthesis through suppressed mTOR activity; and enhanced protein breakdown through upregulated proteolytic pathways.[4] These processes are further exacerbated by immobilisation and mitochondrial dysfunction, creating a cycle of accelerated muscle loss. Understanding these mechanisms is crucial for developing effective interventions to preserve muscle mass in critically ill patients and improve their clinical outcomes.

There is a complex and multifaceted relationship between protein intake and muscle preservation in ICU patients. While muscle mass loss is common during ICU stays, providing high amounts of protein may not be the solution. Studies have shown that although higher protein intake helps reduce muscle loss, it does not necessarily translate into functional benefits. Instead, early resistance training combined with protein intake might be more effective than protein supplementation alone. Recent research has revealed that ICU patients have 60% lower protein incorporation into muscle than healthy individuals, even when they can absorb protein normally. This reduced effectiveness may be attributed to several factors, including anabolic resistance, immobilisation, inflammation, and low muscle ATP levels. These findings highlight several challenges in determining optimal protein dosing: whether to use total body weight or lean mass for calculating daily needs, the lack of validated biomarkers for identifying patients who would benefit from higher protein intake, and the limitations of nitrogen balance measurements, particularly in patients with renal failure.

Further research is needed to develop better methods for assessing muscle anabolism, improving practical measurements of whole-body protein balance, and understanding whether higher protein intake can overcome the anabolic resistance observed in critical illness. Persistent inflammation has been identified as a key factor driving muscle catabolism, as it disrupts the balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB), favouring the latter. One promising avenue of research involves omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These compounds play a crucial role in synthesising specialised pro-resolving

mediators (SPMs), which may help resolve inflammation and promote muscle health. Combining these fatty acids with adequate protein intake could prove more effective than either intervention alone, potentially offering a more comprehensive approach to combat inflammation-related muscle loss and improve clinical outcomes in ICU patients.[5]

Integrating artificial intelligence (AI) in critical care nutrition represents a transformative approach to personalised patient care in the ICU setting. AI systems leverage machine learning algorithms to analyse real-time patient data, including metabolic parameters, laboratory values, and vital signs, enabling personalised nutritional interventions. Through various AI methodologies, including natural language processing, automated monitoring, machine learning and deep learning, these systems can predict energy requirements, assess malnutrition risk, and optimise the timing of nutritional support initiation. While the evidence base continues to develop, AI demonstrates significant potential in processing complex datasets and identifying correlations between nutritional interventions and patient outcomes. Implementation requires addressing multifaceted challenges, including data management, privacy concerns, and financial considerations. AI's capability to analyse diverse data sources facilitates a more responsive approach to patients' evolving needs while accelerating research through improved patient stratification and pattern recognition in feeding protocols. This technological advancement promises to enhance clinical decision-making and streamline documentation processes, ultimately improving patient outcomes through evidence-based MNT in critical care settings. While AI holds promise for enhancing nutrition research and practice, significant gaps in research, ethical considerations, and clinical validation remain.[6]

The evolving landscape of medical nutrition therapy in ICU settings highlights the complexities of nutrition management for critically ill patients. Personalised nutrition therapy tailors treatment based on individual patient characteristics, integrating phenotyping and endotyping. This method involves customising energy and protein strategies according to specific patient data and metabolic markers. Continued research and innovation in personalised approaches, assessment tools and the integration of AI are essential for improving patient care and outcomes in critical care nutrition.

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EXPERT OPINION

Postgraduate Clinical Training in Malaysia: The Beginning of a New Era

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INTRODUCTION

Postgraduate clinical training refers to the advanced medical education that follows a doctor's initial medical degree. Currently, the landscape of postgraduate clinical training in Malaysia is undergoing a transformational shift from Outcome Based Medical Education (OBME) towards Competency Based Medical Education (CBME). In CBME, the assessment of required competencies is being conducted formatively and continuously using workplace-based assessments (WBAs) throughout the training period. This is in contrast to OBME where the assessments are summative and occur at the end of the programme.[1] This change is not only necessary to address the evolving demands of healthcare but is essential to support the development of highly skilled medical professionals in a constantly evolving learning and working environment.

In Malaysia, postgraduate training occurs during periods of service as a house officer, medical officer, or specialist, as doctors work towards advanced career roles to Medical Officer with Area of Interest, Subject Matter Expert, Specialist, Specialist with Area of Interest, or Subspecialist.

Having a structured training program for house officers and medical officers would provide a strong foundation in knowledge, skills, and professional behaviour. This training would better equip them to face challenges during postgraduate training.

Laying the Foundation for House Officers

House officer training is a legal requirement for all new doctors in Malaysia. This is structured, supervised practical training that has been progressively improved, with the addition of syllabus and curriculum. In a latest development, MMC has published the `Malaysian Standards for Housemanship Training' on their website.[2] In these standards, doctors are now required to demonstrate competencies aligned with the Malaysian Qualifications Framework. And as currently being practiced, they are being evaluated through a range of structured assessments in the workplace (WBAs), portfolios, and supervisor reports. These standards ensure the trained house officers are not only clinically competent to work within the complexities of the Malaysian healthcare system but they can make informed decisions about their future career pathways.

The Overlooked Majority: Medical Officers in Need of Structured Training

Medical officers make up over 80% of the doctors in the Ministry of Health, yet they lack a structured training pathway to develop their careers.[3] This workforce category is often trapped between meeting immediate healthcare demands and finding the time and resources to pursue postgraduate qualifications. In 2022, an internal survey conducted among surgical medical officers by the author revealed 85% out of 201 respondents expressed interest in postgraduate training, yet most reported feeling neglected and not given the protected time for learning activities. This issue has persisted long enough, echoing a similar predicament faced by the "lost tribe" of Senior House Officers in the United Kingdom (UK) during the 1990s.[4]

To address the training gap for medical officers, General Surgery has taken the lead by introducing the Basic Surgical Training (BST) program which has become part of the training pathway in general surgery.[5] This two-year curriculum provides the necessary foundation with expected core competencies, preparing medical officers to transition into Master of Surgery programme. BST has

been available to the general surgery community since 2022 and is included in their selection criterion for the intake into the Master of Surgery program in 2025.

Malaysia's healthcare system must consider a national-level initiative to create similar structured programs across specialties and transforming the career trajectories for medical officers.

Adapting to Modern Learning: The Rise of Online Training

With the expansion of online learning, doctors in Malaysia now have the flexibility to pursue postgraduate training from anywhere in the world. Reputable online learning platforms such as Diploma MSc (Learna) and Future Learn have partnered with over eight universities in the UK, offering fourty six and twenty three master's programs, respectively.[6,7] These online training programmes can lead to professional credentials such as postgraduate certificates, diplomas, and master's degrees. This mode of online learning has become increasingly popular, especially in the post-COVID era, as it offers busy clinicians greater accessibility, flexibility and cost-effectiveness.[8] This virtual education is a valuable additional learning tool but the scope of training is limited due to lack of hands-on patient experience.

More Specialists Are Needed

Specialisation in medicine in Malaya (changed to Malaysia after 1963) commenced only after World War I. In the 1920s, pioneering Asian doctors pursued specialist qualifications on their own initiative by training at specialties colleges in UK. By the 1960s, arrangements were made for medical training in Malaysia to be recognized toward qualifications for Royal College examination in the UK.[9] Today, this Fellowship and Membership programs are still available but the educational provider not only come from the UK but other countries as well, and the training is being conducted mainly in MOH's hospitals. This pathway is currently known as the `Parallel Pathway', and it is an alternative pathway for postgraduate training other than Master Programme.

The Master's program in Malaysia has been developed and tailored to meet the specific needs of the country. It was first introduced in 1973 and to date, there are thirty Master's programs being conducted by eight public universities and one private university, and has produced more than 10 000 specialists. Majority of the trainees are government sponsored, and the training scholarship increased from 1,220 slots for the 2020/21 session to 1,650 slots for the 2024/25 session.[10]

Malaysia's need for specialists has reached a critical point as both the Master's Program and Parallel Pathway are unable to produce enough specialists to meet the country's needs. There are currently 8,853 specialists representing 15.7% of doctors in MOH, and this figure falls short of meeting the MOH's target of a 30% specialist to 70% non-specialist ratio.[3] This shortage is further complicated by various governance issues within the training pathways with dropout rates and low graduation on time ranging from 30% to 40%. Other challenges include lack of qualified candidates, functionality upon graduation, lack of competent trainers, and constraints on training resources, and case-loads.

Malaysian Standards for Medical Specialist Training

In 2019, the `Malaysian Standards for Specialist Medical Training', developed by the Malaysian Medical Council (MMC), came into effect. The standards are divided into seven key areas, with the training programme learning outcomes mapped to the Malaysia Qualification Framework (MQF) level 7 learning domains.[11] They govern the quality of training, supervision, and assessment for all medical specialist training programs, ensuring that graduates meet the requirements for registration in the MMC Specialist Register. Currently, Specialty Specific Requirements (SSR) is being developed by each specialty. This document endeavour to specify the minimum specialty specific requirement pertaining to training curriculum, trainers, educational resources, head of programme, the basic and core competencies expected upon graduation.[12] As of November 2024, the MMC has approved nineteen SSRs, with the remaining still under development. These standards and SSRs serve as crucial

regulatory measures to ensure consistency and quality in postgraduate training programs.

In another significant development, the National Postgraduate Medical Curriculum (NPMC) project, led by the Majlis Dekan Fakulti Perubatan Universiti Awam Malaysia, has completed twenty-two NPMC Specialty Applicant Guides, including one for Cardiothoracic Surgery.[13] This historic step is achieved through collaboration among the National Specialty Committees, the Ministry of Higher Education and the Ministry of Health. The document provides a unified structure and training framework for each specialty, aligned with Malaysian Standard for Medical Specialist Training and the Specialty Specific Requirements (SSR). These curricula are largely CBME-based, where WBAs play a significant role. As part of the NPMC Project, the NPMC Training the Trainer (NPMC TtT) programme was developed, covering 18 topics across 15 core areas of knowledge and skills essential for trainers.[14] To date, over 1,600 trainers and programme directors from both the Ministry of Health and universities have been trained, to effectively bridging the gap between a well-designed curriculum and development of skilled specialists.

The Unregulated Realm of Subspecialist Training

The training for subspecialty and area of interest (AOI) has long been provided by Ministry of Health (MOH) that benefits from the large patient load and diverse case mix. A survey conducted in February 2023 among Malaysian specialists, collated responses from 1,326 specialists, revealed that there are at least 126 subspecialty and 206 areas of interest. The recent Medical Act (Amendment) 2024 has included a Fifth Schedule, which list only 66 recognised subspecialties.[15] This significant discrepancy underscores the lack of governance and regulation in postgraduate training for subspecialties and areas of interest. The need to govern and regulate subspecialist training is clear. With regulations in place, Malaysia can ensure that the competencies of its subspecialists meet both the national needs and training standards, guaranteeing a high quality of care. Subspecialty training need to comply to the Malaysian `Standards for Specialist Training', and subsequently develop their `Subspecialty Specific Requirements` before being subject for accreditation or peer review process.

Conclusion: Embracing Change for a Stronger Future

The shift towards Competency-Based Medical Education (CBME) in postgraduate training is more than an educational reform, it's a commitment to building a healthcare workforce ready for the future as we embrace the evolving challenges in our learning and working environment. From house officers to specialists, each stage of training is now guided by MMC Standards with clearly defined programme learning outcomes. However, the training gap for medical officer need to be addressed and subspecialty training need to encompass a stronger regulatory governance. The Medical Act (Amendment) 2024 has recognised the Ministry of Health (MOH) as a specialised training provider, and it serves as a major training ground for house officers, medical officers, specialists, and subspecialists. It is timely for the MOH to reinvent itself by establishing a dedicated Postgraduate Training Unit with an expanded team to strengthen governance and oversight, better balancing the needs of both service and postgraduate training.

As Malaysia transitions into this new era, the role of trainers, regulators and training institutions are crucial to ensure these changes lead to an improvement in the quality of healthcare. With the foundation laid and the commitment in place, Malaysia is on the path to becoming a regional leader in medical education and healthcare. The next step is ours to strive for it.

CONFLICT OF INTEREST

None

Funds

None

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REVIEW ARTICLE

Scoping Review of Community-Based Interventions to Improve Diabetes Control in Malaysian Adults

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a major non-communicable disease globally including Malaysia. Despite a huge amounts of funds spent for the management of T2DM including community-based interventions (CBIs), the national statistics on the prevalence, treatment outcomes and summary measures of these population health have not improved. Thus we conducted a scoping review to map the details of CBI used for diabetes control among adult T2DM in Malaysia. A scoping review that followed the standard PRISMA guideline in conducting and reporting a scoping review was conducted. A search for relevant journal articles were conducted on four electronic databases (PubMed, SCOPUS, Cochrane Library, and Google Scholar). The titles and abstract of the search results were screened to select eligible papers for full text retrieval. Eligible papers were those reporting CBI studies of adults diagnosed with Type 2 diabetes mellitus in Malaysia. Only studies using intervention designs were included. Thirteen studies were reviewed and had individually-oriented or group-based interventions, or a combination of both. There was limited adoption of behavioural theories in guiding these diabetes interventions. Outcomes of the interventions were inconsistent. Most studies yielded significant positive results on HbA1c, diabetes knowledge, blood pressure, blood sugar, and foot care practices; few demonstrated positive outcomes on self-efficacy, body mass index, physical activity; self-monitoring of blood glucose, medication adherence, smoking and alcohol consumption. Studies varied in their approaches and yield mixed effects on diabetes control. Nevertheless, most interventions demonstrated reductions of HbA1c, which is the main clinical outcome measured following the CBIs.

Keywords
diabetes education, diabetes mellitus, diabetes control, health promotion, self-management

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major public health concern across the globe including in Malaysia. National Health and Morbidity Survey 2019 (NHMS 2019) reported that approximately 3.9 million Malaysians are living with diabetes and the prevalence rate of diabetes has risen from 13.4% in 2015 to 18.3% in 2019.[1] Study has shown that obesity, advancing age, family history of diabetes, and living in a rural area are the important factors that drive the escalating prevalence of T2DM in Malaysia.[2]

Community-based interventions (CBIs) is a programs that target the entire population living within a specific location outside clinical or healthcare settings.[3] CBIs constitute a strategy employed to promote self-management among individuals living with diabetes, aligning with the overarching approach of strengthening community actions outlined in the Ottawa Charter for Health Promotion, endorsed in 1986. Despite a significant number of reviews assessing the effectiveness of community-based strategies in enhancing diabetes control among adults, the evidence concerning clinical parameters, knowledge transfer, and behaviour change remains inconclusive [3-5]

In view of insufficient evidence supporting specific approaches of CBIs in diabetes control and the impact of cultural influences on health behaviour modelling among Malaysian population, an analysis of the data via a scoping review on this subject shall provide an insight on the way forward for diabetes control among affected Malaysian populations. A scoping review seeks to examine the evidence found in relevant literature to present an overview and map key concepts underlying a particular research topic. Hence the use of a scoping review to investigate this topic is appropriate as the scope of studies may include heterogeneous studies in terms of design, methodology, and outcomes.

The objective of our scoping review is to map the CBIs which had been done to improve diabetes control among Malaysian adults. The following are the review questions:

I. What are the types of study designs used in published studies investigating CBIs to improve diabetes control among Malaysian adults?
II. What are the characteristics and types of these interventions that have been developed and implemented within Malaysian communities to improve their diabetes control?
III. What are the outcomes of these CBIs?

MATERIALS AND METHODS

Study design

The study was conducted in accordance with the JBI methodology for scoping reviews.[6] The study protocol has been registered with Open Science Framework (OSF registration number: osf-registrations-jmw6s-v1) and is accessible at this link: https://archive.org/details/osf-registrations-jmw6s-v1.

Eligibility criteria

We had only included community-based interventional (CBI) studies investigating adults in Malaysia who have been diagnosed with 2DM and excluded studies involving Type 1 Diabetes Mellitus (T1DM), prediabetes, and gestational diabetes. The CBIs which were reviewed and included were educational programmes, lectures, videos, hands-on activities, community projects, digital platforms and devices. Then, the relevance of the intervention in improving T2DM outcomes step was scrutinised and any intervention studies that were not related to improvement of health outcomes were excluded. In order to ensure that all reported efforts were accounted in the study, no timeframe was imposed as the eligibility criteria.

Data Extraction

Data were extracted from the eligible papers by three independent reviewers using a data extraction tool developed by the team. The extracted data were the specific details about the study participants, concept, context, study methods, and key findings relevant to the review questions. A drafted template of the extraction form was developed using Microsoft Word to collect data for analysis. The drafted data extraction tool was modified and revised necessarily during the data extraction process from each included evidence source. Any disagreements that arisen between the reviewers were resolved through discussion, or with the additional reviewers.

Assessment of Quality

The Effective Public Health Practice Project Quality Assessment Tool (EPHPP) (https://www.ephpp.ca/quality-assessment-tool-for-quantitative-studies/) was adopted to assess the methodological quality of the studies included in the review.[7] The quality assessment were performed by three independent reviewers. Each article was rated on the EPHPP six domains as strong (3 points), moderate (2 points) or weak (1 point). Domain scores were averaged to produce total scores with the maximum total score per study being 3.00. Based on the total scores, the studies were assigned an overall quality rating of strong (2.51–3.00), moderate (1.51–2.50) or weak (1.00–1.50) as recommended by the EPHPP guidelines. Studies with poor methodological quality were not excluded.

Data Analysis and Presentation

The extracted data were summarised and reported in a tabular form (numerical summary, using tables and charts), and as descriptive format. Quantitative analysis

(eg, frequency analysis) indicates the design and background of the targeted population (age); mode of educational delivery; duration; theoretical models used; and domain of the interventions. This provides a summary of the common intervention characteristics, coded and classified into overall categories, and main outcomes related to diabetes control. We reported the full review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). [8]

Literature Search

A total of 382 articles were imported for screening from the selected electronic database search in which 28 duplicate studies were removed and 354 articles were remained. Further screening on abstracts and titles resulted in the exclusion of 287 articles, leaving 67 articles for full-text screening. After a full-article screening performed, 13 articles were included into the final analysis (Figure I).

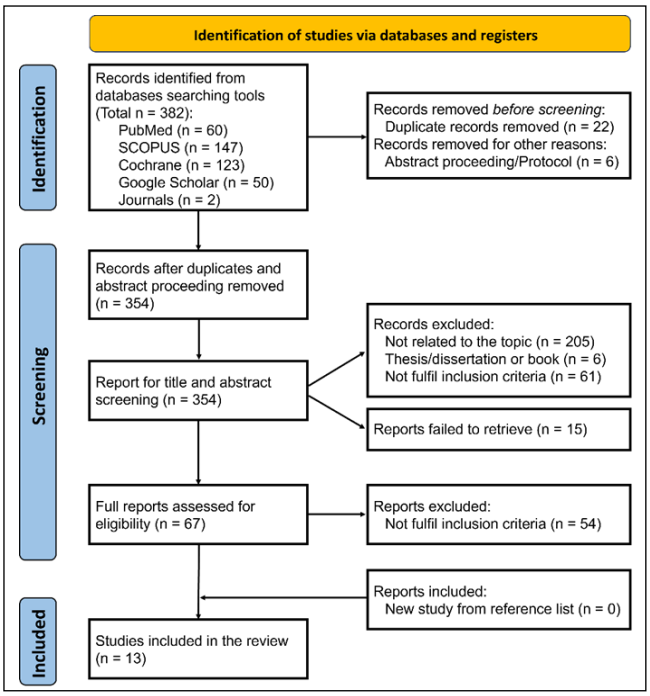

Figure 1: Selection of sources of evidence

Characteristic of the Identified Studies

The studies included in the final analysis were studies conducted between 2015 to July 2023. Although no timeframe was imposed on the study eligibility, the fact that all analyzed studies were between 2015-2023 indicated that CBIs have only recently taken hold in Malaysia. The types of study design, intervention, and behavioural theories employed are summarised in Table I. Majority of the studies employed randomised controlled trials (RCT) while two studies were of quasi-experimental design.

Out of the 13 studies analysed, four studies focused on improving the participants' medication adherence,[9-12] while another four aimed to improve on the participants' dietary habit or nutrition.[13-16] Conversely, the study by Sharoni *et al* had focused only on foot care among diabetes patients.[17] However, out of all studies analysed, only one study included oral health in their diabetes intervention programme.[18]

The use of tele-health approaches was reported by more recent studies, started from year 2018. The use of telecommunication was employed in two studies. Chan *et al* conducted personalised care reminder via phone call every three months while Zainordin *et a*l resorted to making phone call follow-ups due to the movement restriction during the pandemic.[16,19] A web-based health education programmes were reported by two studies[14,18] and Lee *et al* utilised digital technology to monitor patients' glycemic control via a gluco-telemeter that uploads patient's glucose readings to an online portal, and automated feedback is provided based-on the reading.[20]

In the analysis of theories behind these interventions, we found out that only four out of 13 studies documented the use of specific behaviour theories to guide their programs.[11,14,15,21] Our review revealed that the theories used for the interventions were the Chronic Care Model (CCM), Participatory Research Action (PAR), Transtheoretical Model (TTM), Stages of Change Model (SOC), A Hierarchical Model for Self-Efficacy, Extended Theory of Planned Behaviour (TPB), and Information-Motivation-Behavioural Skills Model (IMB).

Table I: Study design, intervention, and underpinning behavioural theory

Author, Year	Study design	Intervention	Underpinning Behavioural Theory
Butt M et al, 2015	RCT	Patient Education by Pharmacist Programme (PEPP)	None
Ramli AS et al, 2016	Cluster-RCT	EMPOWER-PAR (PAR=Participatory research action),	Chronic Care Model (CCM), Participatory Research Action (PAR)
Chee WSS et al, 2017	RCT	Malaysian customized Transcultural Diabetes Nutrition Algorithm (tDNA)	None
Sharoni SKA et al, 2017	Prequsi-experimental and Postquasi -experimental	Self-efficacy education programme on improving foot self-care behaviour	None
Ramadas A et al, 2018	RCT	Web-based dietary intervention programme	Transtheoretical Model (TTM), Stages of Change Model (SOC)
Gilcharan Singh HK et al, 2020	RCT	Malaysian customized Transcultural Diabetes Nutrition Algorithm (tDNA)	A Hierarchical Model for Self-Efficacy
Lee JY et al, 2020	RCT	Telemonitoring with gluco -telemeter	None
Rosli MR et al, 2021	RCT	Home medication review	None
Ting CY et al, 2021	RCT	Group-based intervention (MEDIHEALTH) to improve medication adherence	Extended Theory of Planned Behaviour (TPB), Information-Motivation-Behavioural Skills Model (IMB)
Zainordin NA et al, 2021	RCT	Meal replacement plan of low carbohydrate diet	None
Atoglable ET et al, 2023	RCT	Electronic educational materials on diabetes knowledge and medication adherence	None
Chan JCN et al, 2022	RCT	JADE Web-Based Management Guide on Risk Factors	None
Rusly NFS et al, 2022	Quasi-experimental	Online Diabetes Wellness Programme	None

Study outcomes

Table II summarises the key findings of the clinical outcomes as well as learning and behavioural outcomes. For clinical outcomes findings, ten studies reported HbA1c as an outcome measure. Out of these ten studies, nine studies reported significant improvements in HbA1c[9-11,13,15,16,19,21-20] while one study showed no change.[14] There were four studies reported on the fasting-blood glucose (FBG) level in which three studies[10,16,17] demonstrated a significant improvement in FBG whereas one study showed no improvement.[14] The other relevant clinical parameters that showed improvement include BMI,[13,16,18] body weight,[15,16,18-19] waist circumference,[13,16] LDL,[16] systolic blood pressure,[13] and inflammatory marker interleukin (IL)-6.[16]

For learning and behavioural outcomes, the measures that were reported include self-efficacy, diabetes-related knowledge, and behaviour. Self-efficacy improvements were noted in studies by Ting[11] and Gilcharan,[15] however, no changes were observed in Lee's study.[26] Improved diabetes-related knowledge was demonstrated by two studies.[14,18] Most studies reported on the behavioural change of their patients; namely improved medication adherence[9-10,12] foot care[17] information-seeking behaviour,[12] dietary intake, and longer duration of exercise.[13]

Table II: Outcomes of the community-based intervention

Author/ Year	Key Findings Post-intervention	
	Clinical outcomes	Learning & behavioural outcomes
Butt M et al, 2015	Improved HbA1c	Improved medication adherence
Ramli AS et al, 2016	Improved HbA1c	-
Chee WSS et al, 2017	Improved HbA1c, BMI, body weight, waist circumference and systolic blood pressure	Reduced calorie intake and longer exercise duration
Sharoni SKA et al, 2017	Improved FBG	Improved foot care
Ramadas A et al, 2018	No improvement in HbA1c and FBG	Improved Dietary Knowledge, Attitude and Behaviour
Gilcharan Singh HK et al, 2020	Improved HbA1c and reduced body weight	Improved self-efficacy
Lee JY et al, 2020	Improved HbA1c at 24 weeks but not sustained at 52 weeks	No improvement in self-efficacy
Rosli MR et al, 2021	Improved HbA1c and FBG	Improved medication adherence
Ting CY et al, 2021	Improved HbA1c	Improved self-efficacy
Zainordin NA et al, 2021	Improved HbA1c, FBG, increased LDL, BMI, body weight, waist & hip circumference and IL-6	Reduced calorie intake, higher protein intake
Atoglabe et al 2023	-	Improved medication adherence and information-seeking behaviour
Chan JCN et al, 2022	Improved HbA1c and LDL	-
Rusly NFS et al, 2022	Improved body weight and BMI	Improved knowledge and dietary intake

Study Quality

The overall quality of the studies in this review is weak, as measured by the EPHPP Tool (Table III). Only three studies scored strong[19] and moderate [10,11] respectively in the global rating, while the majority obtained a weak score. Of all the items used to assess the study quality, flaws were seen especially in selection bias, and the lack of blinding.

Table III: Study Quality

No	Author	Selection Bias	Design	Con-founders	Blinding	Data Collection Method	Withdrawal and drop-outs	Global rating
1	Butt, M.	Strong	Strong	Strong	Moderate	Strong	Strong	Strong
2	Chee, W. S. S.	Weak	Strong	Weak	Weak	Strong	Strong	Weak
3	Gil-charan Singh, H. K.	Weak	Strong	Weak	Weak	Strong	Strong	Weak
4	Lee, J. Y.	Weak	Strong	Strong	Weak	Strong	Strong	Weak
5	Ramadas, A.	Weak	Strong	Strong	Moderate	Strong	Weak	Weak
6	Ramli, A. S.	Weak	Strong	Strong	Weak	Strong	Strong	Weak
7	Rosli, M. R.	Weak	Strong	Strong	Moderate	Strong	Strong	Moderate
8	Sharoni, S.K.A.	Weak	Strong	Strong	Weak	Moderate	Strong	Weak
9	Ting, C.Y.	Weak	Strong	Strong	Strong	Strong	Strong	Moderate
10	Zainord in, N. A.	Weak	Strong	Strong	Weak	Strong	Strong	Weak
11	Atoglabe	Weak	Strong	Strong	Weak	Strong	Strong	Weak
12	Chan	Strong	Strong	Strong	Moderate	Strong	Moderate	Strong
13	Rusly	Weak	Moderate	Weak	Weak	Weak	Strong	Weak
	Sum weak n (%)	11 (84.6)	0 (0.0)	3 (23.1)	8 (61.5)	1 (7.7)	1 (7.7)	9 (69.2)
	Sum moderate n (%)	0 (0.0)	1 (7.7)	0 (0.0)	4 (30.8)	1 (7.7)	1 (7.7)	2 (15.4)
	Sum strong n (%)	1 (9.1)	12 (92.3)	10 (76.9)	1 (7.7)	11 (84.6)	11 (84.6)	(15.4)

DISCUSSION

Effective self-management of diabetes is essential for reducing complications, improving health status, and enhancing the quality of life for individuals living with the disease. In order to support this goal, many countries, including Malaysia, have adopted the approach of community-based interventions.[22-24] Considering limited evidence on the scope, extent, and outcomes of such interventions, we conducted a scoping review to identify the features of these interventions employed in Malaysia so that the findings may be used as a reference to establish future interventions and research directions.

Need for more collaborative work

The need for collaborative approaches in diabetes care had been emphasised in a recent systematic review and meta-analysis by Siaw and Lee which stated that "*multidisciplinary collaborative care will have a positive impact on the clinical, humanistic, and economic outcomes of patients with uncontrolled diabetes*".[25] However, many of the reviewed studies did not deliberate on the multidisciplinary aspects of diabetes care. Mostly focused on a single factor and only one out of all studies involved oral health. Involvement of dental intervention as part of diabetes patient care has been suggested to increase the likelihood to improved health, wellbeing, and quality of life in people with diabetes as has been established by previous studies.[26-27] Studies undertaking interventions that investigate multiple facets associated with diabetes would offer a comprehensive approach to managing the condition.

Limited adoption of behavioural framework

The limited adoption of specific behavioural framework in guiding diabetes management interventions deserves further reflection. A theoretical framework is needed to incorporate the factors and processes that influence behaviour change into the intervention. Theory helps in organising and applying the existing knowledge about what causes (mediators) and affects (moderators) behaviour change, as well as the basic assumptions about human behaviour and its determinants. The incorporation of these theories in the design and execution of self-management and behaviour change interventions has shown promise in enhancing their effectiveness. [28]

Evolving uptake of telemedicine

The evolving landscape of healthcare has seen a significant shift towards telemedicine, and this trend is evident in our findings where five studies utilised telemedicine as a part of the CBIs. Telemedicine is a "*subset of e-health that involves the use of communication networks to offer healthcare services and medical education remotely*".[29] The use of telemedicine is particularly beneficial in improving access to healthcare in that it may help provide continuous patient care and manage chronic health conditions like diabetes and ultimately helps reduce healthcare cost.[30]

Clinical and non-clinical study outcomes

The clinical outcomes assessed in the studies reviewed in this scoping analysis were diverse in which not all studies reported on HbA1c despite its prominence as a key marker in diabetes control. The omission of HbA1c parameters could be attributed to resource constraints or a limited study duration. As expected, in most of the studies, a change in the behaviour was seen to be parallel with the HbA1c reduction. This observation emphasises the importance of behaviour interventions, notwithstanding the need of proper alignment with a behavioural framework, as an effective strategy in tackling

self-management of the HbA1c level in T2DM patients.[31] Two behavioural aspects that many T2DM patients struggle with are the eating disorder and inactivity, which are related to worse glycaemic control and a higher risk for various complications.[32]

Implementation of carbohydrate (CHO) counting, calorie restrictions, pre- and post-meal blood glucose monitoring, evaluating blood glucose trends in between meals, and exercise have proved to be able to reduce the HbA1c level.[33] A domino effect on the reduction of other clinical manifestations such as FBG,[34-35] blood pressure,[34] and LDL[36] were also observed alongside these lifestyle changes. Since these behavioural changes are essential to ensure the important clinical parameters are at an optimum level, incorporation of disease self-management[37] such as self-efficacy and self-care measurements and the involvement of caregivers[38] are to be considered as effective strategies in encouraging behaviour change in people with diabetes.

Quality of community-based intervention studies

While the overall study quality assessment revealed weaknesses in selection bias and blinding, it is essential to recognize the strengths observed in other aspects of the studies such as study design, data collection methods, and management of withdrawals and drop-outs. Strong study design contributes to the credibility of the findings, providing a solid foundation for the research.

Future research in this area should aim to address the identified limitations, particularly in the areas of selection bias and blinding, to enhance the overall quality and validity of studies focused on diabetes management within the Malaysian context. Additionally, improved reporting and transparency in methodology can aid in the critical evaluation of study quality and contribute to more robust and reliable evidence in the field of diabetes management. Countries that share similar socio-demographic and cultural backgrounds, as well as health systems' resources and constraints may also gain perspectives from our findings to improve their diabetes control initiatives.

CONCLUSION

This comprehensive review provides useful insights on diabetes management interventions in Malaysia which are multi-faceted in nature. The studies exhibited diverse approaches and produced inconsistent effects on diabetes control. Nonetheless, most interventions demonstrated reductions of HbA1c, which is the main clinical outcome measured following interventions. Learning and behavioural outcomes highlight improvements in self-efficacy, knowledge, and patient behaviour, thus acknowledging the role of behavioural interventions in equipping individuals for self-management. These findings, though promising, reveal a need for enhancements in study quality, particularly addressing issues related to selection bias and blinding.

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CONFLICTS OF INTEREST

None of the authors have any conflicts of interest related to this project.

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REVIEW ARTICLE

The Effects of Mindfulness-Based Cognitive Therapy in Multicultural Settings: A Scoping Review

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ABSTRACT

Mindfulness-Based Cognitive Therapy (MBCT) is an experiential group intervention adapted from Buddhist meditational practice aimed at treating recurrent depression. Our scoping review explored the MBCT effectiveness in multicultural settings and whether any adaptations were made to enhance it. By using Arksey and O'Malley's framework, our review examined randomized controlled trials (RCTs) published between 2010 and 2023, focusing solely on studies from non-English speaking countries. Out of 1461 published RCT, only 15 of them met our study criteria and they were mainly from China, Denmark, Germany, Hong Kong, Iran, Netherlands, and Switzerland. Out of 15 selected RCT publications, 10 studies shown that MBCT significantly improved symptom-based measures (e.g., Beck Depression Inventory-II), one study shown little difference between MBCT compared to Cognitive Behavioural Therapy (CBT), and four studies shown that comparative treatments were more effective than MBCT, in which two of them were culturally specific interventions, Traditional Yoga and Qigong. Two studies found MBCT effective when combined with Mindfulness-Based Stress Reduction (MBSR) and Loving-kindness meditation. Common themes including (1) reduction in psychological distress across all studies, (2) trials used small sample sizes, and (3) the feasibility of using MBCT in multicultural settings, with cultural interventions showing greater effectiveness. MBCT interventions reported promising results when used in a multicultural setting, with a potential for culturally integrated intervention. Our results conclude an opportunity for future research to embed psycho-spirituality with MBCT.

Keywords
MBCT, RCT, non-English speakers, Culture

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INTRODUCTION

Mindfulness was first introduced into therapy by Jon Kabat-Zinn who drew the Mindfulness-Based Stress Reduction (MBSR) programme from Buddhist meditational practice of de-centring, self-awareness, impermanence, and compassionate acceptance.[1] Mindfulness was then combined with aspects of cognitive therapy, including behavioural activation through scheduled homework and activities, metacognitive awareness of negative thoughts and feelings, and attention regulation.[2]

Mindfulness-Based Cognitive Therapy (MBCT) is an evidence-based intervention that was initially used for patients with recurrent episodes of depression.[3] MBCT is an eight-session group intervention focused on developing mindful presence, which involves acknowledging thoughts and feelings without judgment and practicing self-compassion and acceptance. Participants learn to manage challenging situations and emotions, embracing impermanence and letting go.[4]

Research Statement of Problem

As many other minorities and migrant communities worldwide, Singaporean Malays, the largest minority group in Singapore, at 13.5% of the population, are susceptible to mental health challenges.[5] Fourteen per cent of Singaporeans are Muslims, with 99.6% of Malays professing the Muslim faith.[6] Singaporean Malays aged 18 to 34, especially those with higher academic achievements, are reportedly more dedicated to prayer and spiritual practices. They tend to prefer traditional complementary and alternative medicine over primary

care for mental illness due to the socio-emotional support and spiritual upliftment it provides.[7] Their cultural misconceptions and misinformation about mental illness makes them less likely to seek or value psychological help.[8] Thus, local researchers call for the cultural contexts of mental illness to be integrated into healthcare systems. Adaptations of Western mental health treatment models have been recommended for targeted minority communities to utilise.[9,10,11]

As Major Depressive Disorder (MDD) was identified as the most common mental disorder in Singapore[12], MBCT has been chosen as the treatment of choice to be culturally integrated for Singaporean Malay because of its solid empirical evidence in reducing MDD.[13] The concern is whether the Singaporean Malay Muslims would accept and comply with a psychological treatment that is culturally integrated from Buddhist practice.

REVIEW OBJECTIVES

Although previous literature has shown that MBCT is effective in treating recurrent depression, little is known if MBCT works well in multicultural settings. Thus we have reviewed research literatures to identify randomised controlled trials (RCT) where MBCT was administered for psychological distress. Since there is a lack of integrated treatment for the Singaporean Malays, our review aimed to:

a) Examine the effects of MBCT in multicultural settings.
b) Examine if adaptations were made to enhance the effectiveness of MBCT in multicultural settings.

We hypothesised that if the literature supported MBCT interventions in multicultural communities or where English is not a primary native language, MBCT might also be effective for the Singaporean Malay Muslims.

METHODOLOGY

A scoping review was employed to obtain literature identifying crucial concepts and possible research gaps while evaluating current research practices, trends, and evidence from previous studies. By utilising a five-stage scoping review framework, the scoping review (1) identified the research question, (2) identified relevant studies, (3) selected the studies, (4) tabled the data, and (5) collated, summarised, and reported the results.[14]

Step 1. Identification of the main study's research question

This main study investigated the effectiveness and feasibility of MBCT for the Singaporean Malays. In addition, the main study compared MBCT with another intervention to determine if social, religious, cultural, and spiritual norms influence treatment outcomes.

Step 2: Sourcing Relevant Studies

A preliminary search terms of "mindfulness-based cognitive therapy" or "MBCT" was conducted on Scopus, EBSCO, Jstor, ProQuest and Taylor & Francis. An advanced search on Scopus and EBSCO included search terms ALL ("Mindfulness-based cognitive therapy" AND mbct) AND NOT ALL (geriatr* AND NOT elder* AND NOT senior) AND NOT ALL (youth AND NOT child* AND NOT teen*) AND ALL (spirit* AND cultur* AND soci* AND religio*). Next, 1,461 titles and abstracts were combed for RCT, specifically in MBCT, published between January 2010 and December 2020. Search alerts were activated for the database from January 2021 to April 2023. Then, only the MBCT RCTs from countries with national languages other than English were extracted for full-text review. Finally, a total of forty-one full-text articles were assessed for eligibility.

The Population, Intervention, Comparison and Outcome (PICO) framework[15] was used to identify eligible research papers.[16]

Populations. Studies involving adults between 18 and 65 years of age, where English was not the primary native language spoken, who were experiencing mental health issues were selected for our review. Studies researching children, adolescent, and geriatric populations; psychosis, neurocognitive, and neurodevelopment conditions were excluded.

Intervention. Randomized Controlled Trials (RCTs) where MBCT was among the interventions explored to alleviate symptoms of mental health issues.

Comparisons. We sought to compare MBCT with other active interventions (e.g., CBT, Traditional Yoga, Tai Chi) or waitlist.

Outcome. Symptom-based measures were identified for improvements in depression (Example: Beck's Depression Inventory (BDI), Depression Anxiety Stress Scale (DASS-21), Montgomery–Asberg Depression Rating Scale (MADRS) and/or anxiety, example Beck's Anxiety Inventory (BAI), Generalized Anxiety Disorder questionnaire (GAD-7).

Step 3: Selecting the studies

Restrictions were imposed to review only full-text RCTs on MBCT with depression, anxiety, or stress-related conditions as primary mental health issues. A total of 41 full-text articles underwent eligibility assessment. We had excluded 26 studies which focused primarily on neurodevelopmental disorders (e.g., ADHD, Autism), neurocognitive deterioration (e.g., dementia), and psychological distress stemming from physical conditions with comorbid symptoms (e.g., tinnitus, cancer, diabetes perinatal). The PRISMA diagram[17] in Figure 1 illustrates the selection process for the 15 full-text articles reviewed.

Step 4: Charting the data

The review identified relevant literature to highlight research gaps and inform future research, policy, and practice. In testing the hypothesis that MBCT can reduce symptoms of distress and improve positive mental health, the first reviewer used an adapted Matrix Method (see Table 1) to document the methodology and intervention.[18] The data were extracted and summarised to highlight key aspects of the articles as follows:

i. Publication year, author(s), title, study design.
ii. Number of participants, country, diagnosis/condition, age of participants, interventions employed.
iii. Measures utilized, time of assessments, minimum sessions required for completion evaluation, attrition.
iv. Identity of facilitators.
v. Methodology for analysis and findings.
vi. Reported limitations.

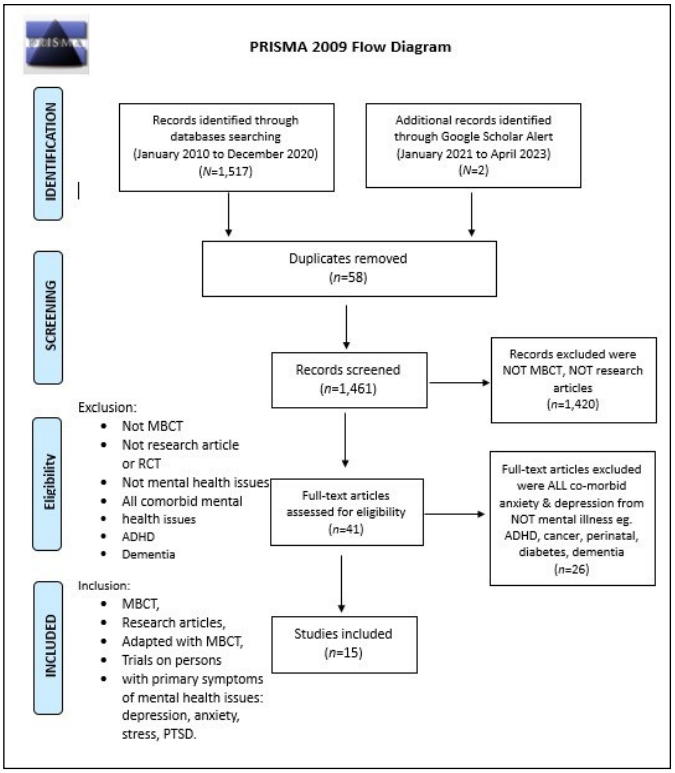

Figure 1: Selection process of 15 articles on MBCT in socio-cultural-religious settings.

Step 5: Summarise, synthesise, and report.

A content analysis was employed to address the research questions, which aimed to investigate the effectiveness of MBCT, assess the influence of culture on treatment outcomes, and summarize the scope of the studies reviewed. The extracted data were further subcategorized. The second author vetted the chart and categories for conformity, resolving discrepancies through discussion.

RESULTS

A total of 15 randomised controlled trials (RCT) were reviewed in Table 1. Studies from Denmark (n=1), Germany (n=1), China (n=3), Iran (n=6), Netherlands (n=2), Sweden (n=1), and Switzerland (n=1) were thoroughly examined to reflect adaptations or feasibility of MBCT in various cultural settings.

Table 1: Adapted Scoping Review Matrix for Mindfulness-based Cognitive Therapy in non-English native language environments.

No.	Publication year / Author / Title / Design	Participants / Age / Intervention	Measures / Time of assessments / Minimum sessions for completion / Attrition	Conducted by	Analysis / Outcomes	Limitations
1	2010. Piet J., Hougaard E., Hecksher M.S., Rosenberg N.K. A randomised pilot study of MBCT and group CBT for young adults with social phobia. Pilot study. RCT crossover design	26 Danish youth Female *n*=18 (69%) Anxiety & Social Phobia 18-25 years *M*=21.9 • Grp 1 (*n*=14) MBCT + GCBT (8+12 sessions) • Grp 2 (*n*=12) GCBT + MBCT (12+8 sessions)	BAI, BDI-II, FFMQ-SF, FNE, IPP, LSAS, RRS-EXT, RPA-NL, SCL-90-R, SCS-SF, SDS, SIAS, SPC, SPS • Pre-Post MBCT & GCBT • Follow-up 6-mths & 12-mths minimum session = 75% of treatment Attrition: • MBCT: 5/26 (19%) • GCBT: 3/26 (11%)	• GCBT therapist with >10yrs experience in CBT for Anxiety disorders (2 therapists: 6 clients) • MBCT therapist trained by Mark Williams (1 therapists: 14 clients)	• ANCOVA, *t*-tests, Intention to treat (ITT), Per protocol (PP) • +ve improvements in both groups • no significant differences between 2 groups. • Outcome variables favour GCBT compared to MBCT	• small sample size • no waitlist/ placebo • crossover design limits conclusion from follow-up data
2	2010. Bondolfi G., Jermann F., der Linden M.V., et. al. Depression relapse prophylaxis with MBCT: Replication and extension in the Swiss health care system Replication trial across language and culture. RCT stratified block randomisation.	60 Swiss patients Female, *n*=43 (71%) In remission (unmedicated) from recurrent depression (<3 episodes) 27–66 years, *M*=47.5 • Grp 1 (*n*=31) MBCT + TAU + 4 booster MBCT sessions every 3 months during follow-up • Grp 2 (*n*=29) TAU alone	• MADRS, • BDI-II, • Interview • Pre-Post • Follow-up every 12 weeks (i.e. month 5, 8, 11, 14). Minimum session = unreported Attrition: • MBCT: 4/31 (13%) • TAU: 1/29 (3%)	• 3 senior CBT psychologist • 1 senior CBT psychiatrist • All attended training by Z. Segal. • 1 therapist:7 participants • Adherence rate 93.33%	• Fisher's exact test for proportions and Mann–Whitney U-test for continuous and ordinal variables. ITT & PP • MBCT + TAU maintained wellness longer, with time to relapse of a median of 29 weeks, compared to TAU of 10 weeks	• secondary analyses conducted only on MBCT + TAU group possibly limit statistical power
3	2011. Kaviani H., Javaheri F., Hatami N. Mindfulness-based cognitive therapy (MBCT) reduces depression and anxiety induced by real stressful setting in non-clinical population. Preliminary feasibility study new cultural population RCT, blinded randomisation.	45 Iranian university students Female, *n*=45 (100%) Self-reported high level of anxiety and depression Age= unreported *M*= 20.5 • Grp 1 (*n*=20) MBCT + TAU • Grp 2 (*n*=25) Waitlist	• BDI, • BAI, • DAS, • ATQ • Pre, mid (session 4), post (session 8) • Follow-up 1-mth, 6-mths. Minimum session & attrition = unreported	• Therapist • therapist: participants ratio unreported.	• 2-way ANOVA with repeated measures. Per protocol. • Significant reduction of anxiety and depression in MBCT group.	• only females • no 2nd intervention grp • repeated data collection and experimenter's demand • no mindfulness measure
4	2012. Kaviani H., Javaheri F., Hatami N. The impact of MBCT on mental health and quality of life in a sub-clinically depressed population RCT, simple randomisation.	30 Iranian University students Female, *n*=30 (100%) Sub-clinically depressed population Age= unreported *M*= 21.7 • Grp 1 (*n*=15) Farsi MBCT • Grp 2 (*n*=15) Control group	• BDI, • BAI, • DAS, • ATQ, • WHOQOL-BREF • Pre, mid (session 4) & post (session 8) • Follow-up 1-mth& 6-mths. Minimal session and attrition: unreported	• psychologist trained in MBCT. • 1 therapist: 15 participants.	• 2-way ANOVA with repeated measures • +ve improvements in WHOQOL • Significant reduction of anxiety and depression in MBCT group.	• mostly females • no 2nd intervention grp • no stress scale

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No.	Publication year / Author / Title / Design	Participants / Age / Intervention	Measures / Time of assessments / Minimum sessions for completion / Attrition	Conducted by	Analysis / Outcomes	Limitations
5.	2013. Abdollah, O., Mohammadkhani P., Mohammadi A., Zargar F. Comparing MBCT and traditional CBT with treatments as usual on reduction of major depressive disorder symptoms RCT with qualitative exploratory design (interview before and after intervention), • 3-arm design	90 Iranian patients referred to the university clinic Female, *n*=60 (67%) History of major depressive disorder Aged 18–45 years, *M*=28 • Grp 1 (*n*=30) Farsi MBCT • Grp 2 (*n*=30) CBT • Grp 3 (*n*=35) TAU	• BSI • Pre-Post Minimal session and attrition: unreported	• therapist unreported. • therapist: participants ratio unreported.	• ANCOVA • +ve improvements in both MBCT & CBT groups • no significant difference between MBCT & CBT • both reduced symptoms of stress and increased healthy state of mind • correlated improvement to homework	• unreported
6.	2013. Collip D., Geschwind N., Peeters F., Myin-Germeys I., van Os J., Wichers M. Putting a Hold on the Downward Spiral of Paranoia in the Social World: A RCT of MBCT in Individuals with a History of Depression RCT sequence generator randomisation (www.random.org)	129 Dutch patients Female, *n*=98 (76%) At least one episode of MDD Age range unreported. *M*=44 • Grp 1 (*n*=63, MBCT • Grp 2 (*n*=66) Control	• ESM self-assessment set with a digital wristwatch • Pre-Post Minimal session: 4 sessions Attrition: 4% invalid entries	• experienced trainers in a centre specialising in mindfulness training. • 1 therapist: 10-15 participants	• Multilevel linear regression analyses, ITT & PP • +ve improved feelings of acceptance. In MBCT groups • MBCT decreases feelings of paranoia about social acceptance	• 1st study on social insecurity & paranoia. But the absence of an active control group • no measure of MBCT fidelity to both adherence and competence • single item measures used, restricting construct validity
7.	2016. Wong S.Y, Yip B.H, Mak W.W, Mercer, S., et. al. MBCT v. group psychoeducation for people with generalised anxiety disorder: randomised controlled trial • RCT simple blinded randomisation. • 3-arm design	182 Chinese patients in Hong Kong Female, n=144 (79%) Generalised anxiety disorder Aged 21 – 65 years *M*=50 • Grp 1 (*n*=61) Cantonese MBCT • Grp 2 (*n*=61) Group psychoeducation • Grp 3 (*n*=60) TAU	• BAI • PSWQ • CES-D • SF-12 • FFMQ • Pre-Post • Follow-up: 3 months Minimal session: 7 Attrition: • MBCT: 29% • Group psychoeducation: 11%	2 clinical psychologists, one social worker intensive MBCT and MBSR training retreats & at least 2 years experience in leading an MBCT group. • 1 therapist: 15 participants	• Linear mixed models PP and ITT • +ve improvements in both MBCT and Group psychoeducation. • Both MBCT and group psychoed treatment decreased worry and anxiety symptoms with no significant difference compared to usual care. • group psycho-ed reported greater acceptability.	• lower adherence in MBCT • self-reported questionnaires are only available for MBCT & CBT • follow up only for 3 months • possible selection bias from self-referred participants • Unable to tell if differences resulted from modality/ result of attention/ time differences • Possible Type 1 error from 2 primary outcome measures and 2 comparisons.

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No.	Publication year / Author / Title / Design	Participants / Age / Intervention	Measures / Time of assessments / Minimum sessions for completion / Attrition	Conducted by	Analysis / Outcomes	Limitations
8.	2018. Grensman A., Acharya B.D., Wändell P., Nilsson G.H., Falkenberg T., Sundin, Werner S. Effect of traditional yoga, MBCT, and CBT, on health-related quality of life: A RCT on patients on sick leave because of burnout. • RCT blinded to block • first RCT on burnout • 3-arm design • Swedish-translated interventions	94 Swedish primary health care patients, 20 to 100% on sick leave for burnout. Female, *n*=70 (90%) Exhaustion Syndrome Aged 18–65 years *M*=44 • Grp 1 (*n*=31) MBCT • Grp 2 (*n*=32) TY • Grp 3 (*n*=31) CBT	• SWED-QUAL (HRQoL) • Pre-Post Minimum sessions: unreported Attrition (13.8%) • MBCT: 5/31 • TY: 6/32 • CBT: 2/31	Trained TY teacher & licensed psychotherapist 1 therapist: 9-11 participant	• Wilcoxon's rank sum test & sign rank; Bonett-Price calculation calculates median; multiple comparisons, using Holm-Bonferroni correction on STATA. ITT • +ve improvements in all groups • TY scored more on the scale of improvements out of 13 QoL subscales: • MBCT 7/13 • TY 10/13 • CBT 7/13	• small group size • fewer men • restricted sample size did not allow sub-analyses • no scale for burnout
9	2018. Omidi A., Hamidian S. Effectiveness of a combined MBCT and MBSR intervention on depression symptoms and quality of life in a group of Iranian veterans with PTSD • RCT	62 Iranian patients all male Female, *n*=0 (0%) Comorbid PTSD and depression. Aged 35 – 49 years, *M*=42 • Grp 1 (*n*=31) MBCT + TAU • Grp 2 (*n*=31) Control Grp + TAU	• SCID-IV • BDI-II • SF-12 • Pre-Post Minimum 6 sessions Attrition = 0	Clinical psychologist therapist: participant ratio unreported	ANCOVA ITT & PP. • +ve improvements in QoL • Depression scores of the MBCT group significantly decreased	• not tested in 3 arms • limited participants (male only)
10	2018. Jasbi M., Sadeghi Bahmani D., Karami G., et. al Influence of adjuvant MBCT on symptoms of PTSD in veterans –results from a randomised control study. • RCT	48 Iranian veterans Female, *n*=0 (0%) PTSD Aged 50–55 years *M*=52.7 • Grp 1 (*n*=24) MBCT • Grp 2 (*n*=24) Control Grp	• PCL-5 • DASS-21 • Pre-Post Minimum 6 sessions Attrition = 0	Experienced psychologists and mindfulness instructors Nurses, social workers & psychologists organized the socio-therapeutic events. 1 therapist: 7-12 participant	• ANCOVA ITT • MBCT reduced DASS symptoms	• The sample size was small • only male patients with PTSD were assessed • no neurobiological data were collected, • sleep and nightmares were not assessed
11	2019. Cladder-Micus M.B, Becker E.S., Spijker J, Speckens A.E.M, Vrijsen J.N. Effects of MBCT on a Behavioural Measure of Rumination in Patients with Chronic, Treatment-Resistant Depression • 1st RCT measuring rumination	• 62 Dutch patients Chronic, Treatment-Resistant outpatients Female, *n*=42 (68%) Depression Aged above 18, *M*=46 years old • Grp 1 (*n*=26) MBCT + TAU • Grp 2 (*n*=36) TAU	• BFT • RRS-EXT • IDS-SR • FFMQ 39 • VAS • Pre-Post minimum session and attrition: unreported	mindfulness teachers therapist: participant ratio unreported	• mixed model ANOVAs ITT • MBCT + TAU reduced thought intrusion. negative thoughts reduction in negative thought intrusions	• BFT is a new measure which needs validation • study is pre-post design, without follow-up • insights only for effects of MBCT for patients with chronic, treatment-resistant depression

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No.	Publication year / Author / Title / Design	Participants / Age / Intervention	Measures / Time of assessments / Minimum sessions for completion / Attrition	Conducted by	Analysis / Outcomes	Limitations
12	2020. Chan S.H.W., Chan W.W.K., Chao J.Y.W, Chan P.K.L, et al. An RCT on the comparative effectiveness of MBCT & Health Qigong-based cognitive therapy among Chinese people with Depression and Anxiety RCT • 3-arm design	187 Chinese participants Female, *n*=unreported (70.5%) Depression and anxiety. Aged 18 – 70 years, *M*=50.5 • Grp 1 (*n*=62) MBCT • Grp 2 (*n*=62) Health Qigong-CT • Grp 3 (*n*=63) Waitlist Grp	• DASS-21 • SF-12 • CPSS • PSQI • GSE • Pre-Post Minimal sessions unreported Attrition: *n*=4, 2.14% • MBCT: 1 • HQCT: 1 • Waitlist: 2	Qualified therapists with 2 years of experience in conducting MBIs. therapist: participant ratio unreported	• ANOVA, linear mixed models (LMM) and investigated through individual growth curve (IGC) models, analysed ITT • Qigong scored better in most measures. • +ve improvements in all groups	• lack of CBT only control group • no breakdown of mood disorder into subtypes • small sample of motivated participants in a single clinic • Only used Baduanjin type of Health Qigong
13	2020. Probst T, Schramm E, Heidenreich T, Klein J-P, Michalak J. Patients' interpersonal problems as moderators of depression outcomes in an RCT comparing MBCT and a group version of the cognitive-behavioural analysis system of psychotherapy in chronic depression -RCT simple randomisation. • 3-arm design	106 German patients Female, *n*=42 (MBCT+CBASP (62%) Chronic depression Aged Above 18 years old. *M*=49.6 • Grp 1 (*n*=36) MBCT + TAU • Grp 2 (*n*=35) TAU + CBASP • Grp 3 (*n*=35) TAU	• HAMD • BDI-II • IIP-32 • Pre-Post • Follow-up 6 mths Minimal session: unreported Attrition: MBCT: 2 CBASP: 1 Lost to follow-up: 5 each	MBCT-certified Clinical Psychologist & Psychiatrist with 5 years of Mindfulness practice therapist: participant ratio unreported	• Two linear multilevel models IIT • Both MBCT & CBASP reduced depression symptoms • MBCT had greater benefits with vindictive/self-centred patients • CBASP had greater benefits with non-assertive patients	• Small sample size • only analysed interpersonal problems as moderators
14	2021. Wang Y, Fu C, Liu Y, Li D, Wang C, Sun R, Song Y. A study on the effects of mindfulness-based cognitive therapy and loving-kindness mediation on depression, rumination, mindfulness level and quality of life in depressed patients RCT simple randomisation.	125 Chinese Female, *n*=72 (58%) Depression Aged 19-58 yrs old. *M*=36.5 • Grp 1 (*n*=63) MBCT + LKM • Grp 2 (*n*=62) Control Grp	• HAMD • RRS21 • FFMQ39 • WHOQOL-BREF • SAQ16 • SSPM11 • Pre-Post Minimal session / Attrition: unreported	Clinical Nurse Specialists therapist: participant ratio unreported	• multi-point ANOVA, ITT • MBCT + LKM can effectively improve depression, rumination, mindfulness level, quality of life, the sense of stigma and degree of self-acceptance in depressed patients • At 2, 4, 6 and 8 weeks after the intervention, HAMD scores were decreased in both groups • HAMD scores in the observation group were lower than before the intervention. • HAMD scores in the MBCT group were lower than in the control group (P<0.05). • At 8 weeks after the intervention, HAMD scores in the control group were lower than those before the intervention (P<0.05)	• The study is general • Effects on depressed patients with different characteristics are not analysed • Effects not demonstrated to affect primary conditions (e.g., age, gender and course of the disease) • Effects of MBCT or LKM not demonstrated individually.

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No.	Publication year / Author / Title / Design	Participants / Age / Intervention	Measures / Time of assessments / Minimum sessions for completion / Attrition	Conducted by	Analysis / Outcomes	Limitations
15	2023. Shokri, A., Kazemi, R., Narimani, M. & Taklavi, S. Compare the effectiveness of mindfulness-based cognitive therapy and cognitive emotion regulation training on psychological well-being of mothers with aggressive students. RCT, simple randomisation Cross-sectional design • 3-arm design	60 Iranian mothers Female, *n*=60 (100%) Mothers with aggressive children Aged 20-50 yrs old. *M*=35.32 • Grp 1 (*n*=20) MBCT • Grp 2 (*n*=20) Cognitive emotion regulation training • Grp 3 (*n*=20) Control Grp	• psychological well-being questionnaire • Pre-Post Minimal session / Attrition: unreported	unreported therapist: participant ratio unreported	• multivariate covariance analysis +ve improvements in MBCT compared to Cognitive emotion regulation training and control group • participants in MBCT had a higher average level of awareness for independence, mastery of the environment, personal growth, positive relationship with others, and acceptance than the cognitive emotion regulation training group	• unable to perform follow-up. • only females

[1]Notes: BAI: Beck Anxiety Inventory, BDI-II: Beck Depression Inventory II, FNE: Fear of Negative Evaluation, IPP: Inventory of Interpersonal Problems, LSAS: Liebowitz Social Anxiety Scale, SIAS: Social Interaction Scale, SCL-90-R: Symptom Checklist-90-Revised, SDS: Shehan Disability Scale, SPC: Social Phobia Composite, SPS: Social Phobia Scale, MADRS: Montgomery–Asberg Depression Rating Scale score, WHOQOL-BREF: World Health Organization Quality of Life Brief instrument.

[2]ATQ: Automatic Thoughts Questionnaire–Negative, BAI: Beck Anxiety Inventory, BDI-II: Beck Depression Inventory II, DAS: Dysfunctional Attitudes Scale, BSI: Brief Symptom Inventory,

[3]PCL-5: Post-traumatic stress disorder scale for DSM, DASS: Depression, anxiety, and stress scale, HRSD-17: Hamilton Rating Scale for Depression, WHOQOL-BREF: World Health Organization Quality of Life, short version, FFMQ: Five Facets Mindfulness Questionnaire, KIMS: Kentucky Inventory of Mindfulness Skills, RRS-NL-EXT: Ruminative Response Scale, extended version, RRS-NL: Ruminative Response Scale, BFT: Breathing Focus Task, IDS-SR: Inventory of Depressive Symptomatology Self-Report, VAS: Visual Analogue Scales.

[4]HAMD/HDRS: Hamilton Depression Rating Scale, RSS: Ruminative Response Scale, SMQ: Southampton Mindfulness Questionnaire

Design

All studies were RCTs, with a maximum of three-arm groups (*n*=5). A Danish study reported utilizing a crossover design.[19]

Participants

The study participants were recruited from schools (*n*=96, 7.2%), universities (*n*=184, 13.8%), and hospitals (*n*=1062, 79%), with the ages ranging between 18 and 65 years old. A total of 1,306 were recruited, in which 786 (59.2%) were female. There were two Iranian studies included only male veterans of the war in their studies.[20,21]

The sample size ranged from 26 to 182 participants. The smallest sample size recruited was 26 university students[19], while the largest recorded was 182 patients with Generalized anxiety disorder (GAD).[22] The trials' conditions varied from social phobia (*n*=26, 1.99%)[19], anxiety (*n*=182, 13.9%)[22], depression (*n*=602, 46.1%) [23,24,25,26,27,28,29] both depression and anxiety (*n*=232, 17.76%)[30,31], exhaustion (*n*=94, 7.2%)[32], caregiver's stress (*n*=60, 4.59%)[33], and Post-Traumatic Stress Disorder (PTSD) (*n*=110, 8.42%).[21,20]

Interventions

All 15 studies compared eight sessions of 2.5 hours MBCT to at least one other active intervention (e.g., CBT (*n*=4), Traditional Yoga (*n*=1), Qigong (*n*=1) psychoeducation (*n*=1), control group (*n*=6) or treatment-as-usual (TAU) (*n*=3). Only one study had its intervention groups attended both MBCT and CBT (i.e., crossover design).[19] Two studies conducted the MBCT day retreat.[21,27] Two studies integrated MBCT with another intervention, MBCT with MBSR[20] and MBCT, including loving-kindness meditation.[29]

Three studies (*n*=3) conducted MBCT while participants were treated with TAU and compared it to a TAU-only group.[23,20,27]

Five studies (*n*=5, 33.3%) conducted 3-arm interventions; MBCT was compared to CBT and TAU-only[25]; MBCT, group psychoeducation, and TAU-only.[22] MBCT, traditional yoga, and CBT[32]; MBCT, Health Qigong cognitive therapy, and a waitlist group.[31] MBCT with TAU was also compared to the cognitive-behavioural analysis system of psychotherapy (CBASP) with TAU and TAU-only.[28]

Six studies (*n*=6, 40%) compared MBCT to a control group. Some control groups are waitlist groups that did not receive any interventions.[30,24,26,33] The minimum number of participants for MBCT was 7,[23] and the maximum was 15 participants to one therapist.[24,22]

Module translation and adaptation

All 6 Iranian studies[30,24,20,21,34,33] utilised a Farsi version of MBCT[35] and meditations.[36] Other MBCT studies were translated to Cantonese,[22] the Dutch language,[27] and the German language.[28] One study required participants to be fluent in Swedish.[32] Another study integrated the Chinese culture into their intervention.[31] Other studies did not report language translations or cultural adaptations in their interventions.

Measures

The most used scale of measure was the BDI-II: Beck Depression Inventory-II (*n*=6, 40%). [19,23,30, 24,20,28] The WHOQOL-BREF: World Health Organization Quality of Life Brief instrument was used by 3 studies with a variation for Swedish-QoL.[24,32,29] The BAI: Beck Anxiety Inventory were used in 4 studies.[19,30,24,22] Four (*n*=4) studies utilised the FFMQ: Five Facets Mindfulness Questionnaire.[19,22,27,29]

Lesser used scales were the RRS-NL-EXT: Ruminative Response Scale (*n*=3), SF-12: Short Form Health Survey (*n*=3), DASS: Depression, anxiety, and stress scale (*n*=2), HAMD: Hamilton Depression Rating Scale (*n*=2), SCID-IV: Structured Clinical Interview For DSM-IV, (*n*=2), DAS: Dysfunctional Attitudes Scale (*n*=2), ATQ: Automatic Thoughts Questionnaire–Negative (*n*=2).

One study utilised a unique tool, the Experience Sampling Method (ESM) self-assessment digital wristwatch, to investigate the interaction between experience and behaviour.[26]

All studies conducted pre-post intervention, with 6 studies conducting follow-ups (46.7%). One study conducted 3 months of follow-up,[22] three studies conducted 6 months follow-up[30,24,28] and two studies conducted 12 months or more follow-up.[19,23]

There were five studies that reported minimum requirements for participants to be considered treatment adhering in which one study required 75% attendance[19]; another required 7 sessions[22]; two required 6 sessions[20,21] while another required only 4 sessions of attendance.[26]

Attrition was only reported by seven studies. One study reported 5 dropouts from MBCT (19% out of 40% total number of attrition in the study).[19] Another reported 13% dropout from MBCT out of 16% of total attrition.[23] A Hong Kong study reported 40% total attrition, with 29% being from MBCT.[22] A Swedish study reported 13.8% of total drop-outs, 5.3% from MBCT.[32] A Chinese study reported 2.14% of total dropouts, with only 1 dropout from MBCT.[31] Two Iranian studies reported 0 attrition.[20,21]

Therapists

MBCT-certified therapists conducted 6 of the studies. [19,23,24,21,27,28] Three studies reported that MBCT was facilitated by therapists who either attended mindfulness retreats or had experience conducting mindfulness-based groups.[26,22,31] Five studies had therapists[30,25] licensed psychotherapists,[32] clinical psychologists,[20] clinical nurse specialists[29] conducting the interventions. Two studies did not report who conducted their intervention.

Analysis

Six of 15 studies utilised both intention-to-treat (ITT) and per protocol (PP) analysis.[19,23,26,25,22,20] Six studies utilised an ITT approach to analyse data.[21,27,28,29,31,32] Two utilised only the PP approach.[30,24] One study did not report their approach.[33]

Outcome of Interventions

MBCT More Effective

Five out of 6 Iranian studies compared MBCT against controlled groups showed MBCT faring better in outcome measures.[30,24,20,21,33] The findings were consistent with 5 RCTs from Switzerland[23], the Netherlands[26,27], Germany[28] and China.[29]

No Significant Difference Between MBCT and Another Treatment

One Iranian Farsi MBCT study found that MBCT showed little difference compared to CBT.[20]

Other Treatments More Effective Than MBCT

While MBCT generally reduced symptoms and improved mood, 4 studies found that the comparative interventions scored better in assessment measures than MBCT.

The Hong Kong study[22] found that CBT was reportedly more appreciated and beneficial in reducing worry and depressive symptoms. Similarly, young adults in the Danish study[19] found their outcome variables scoring better in group CBT to reduce their anxiety and social phobia than in MBCT. A Swedish study[32] found that traditional yoga improve more subscales for treating burnout and exhaustion than MBCT and CBT. Likewise, the Chinese study[31] found that Health Qigong-based cognitive therapy scored better in all measures for depression and anxiety than MBCT and waitlist.

Integrated MBCT with another intervention

Two studies, from Iran[20] and China[29], revealed that it was feasible to integrate MBCT with another treatment (Mindfulness-Based Stress Reduction (MBSR) and Loving Kindness Meditation (LKM) and still achieved improvement in patients' symptoms for PTSD and depression.

Positive results in all studies

All fifteen studies reported that MBCT reduced symptoms of depression, anxiety and stress, improved mindfulness awareness (as measured by FFMQ) in six studies, and quality of life in five studies.

DISCUSSION

The study aimed to examine the effects of MBCT in multicultural settings and if adaptations were made to enhance the effectiveness of MBCT in multicultural settings.

MBCT Feasible for Muslim Communities

Iranian researchers found a unique correlation between Iranian Muslim conservative religiosity and increased religious commitment, positive mental health, self-knowledge, self-regulation and mindfulness.[37,38,39] Iran's Islamic fundamentalism with the truth of texts and teachings enabled them to see wisdom in other religious traditions.[39] Of the fifteen studies, six were from Muslim communities in Iran, showing substantial feasibility and improved psychological distress scores, especially in Depression (n=3), anxiety (n=1), Post-Traumatic Stress Disorder (n=1) and caregiver stress (n=1). All six studies were conducted in Farsi by experienced Iranian therapists.

Previous research reported that female meditators had more significant emotional well-being improvements than male meditators. Researchers reasoned that female youths experienced greater vulnerability to adverse events, thereby more responsive to support-seeking than male youths.[40,41] In the small study sample[30] with female students self-reporting stress due to upcoming exams, MBCT significantly reduced anxiety and depressive symptoms. The same authors conducted another study with a larger sample size of a similar target population the following year[24] revealing that MBCT improved the quality of life for female university students while

decreasing symptoms of depression.

Research also shown mothers were more likely to benefit from mindfulness-based interventions.[42] Mothers in the MBCT group reportedly developed awareness, acceptance, independence for personal growth, mastery of the environment and better relationships with others, compared to mothers in the cognitive emotion regulation training or waitlist group.

There were also research which shown that elderly veterans perceived more significant benefits to MBCT compared to younger veterans. They completed the therapy when they perceived an increased mindful awareness and were interested in learning more about it.[43]

Integrating MBCT with cultural intervention is Feasible

Besides the aforementioned Iranian study[20], the Chinese study[29] that included loving-kindness meditation (LKM) to MBCT effectively improving depression, rumination, mindfulness level, quality of life, the sense of stigma and degree of self-acceptance in depressed patients. These studies reported the feasibility and effectiveness of integrated cultural intervention, reflecting the importance of integrating culture into therapies.

Areas Identified for Future Research

Ten of the 15 studies were limited to small sample sizes, with less than a hundred participants, proposing larger-scale research to be carried out. Nine studies compared MBCT to TAU or a control group and recommended a second treatment intervention arm to compare the effectiveness of MBCT. Across the studies, there was no unified method to measure depression, anxiety, or stress. Six studies used BDI-II as a scale, while other studies utilised other scales for depression. One study had three different measuring assessments for the three groups and recommended a consistent assessment measure. Four studies utilised only a single gender population from its convenience sample and recommended varying the gender sample.

Limitations and strengths of the review

The screening, data extraction, and findings summary were interpreted by only one author, assisted by the supervising author, without a blind reviewer. The current review also did not capture non-English language articles that may add to studying cultural integration with MBCT. All studies were conducted face-to-face in group settings across the nations. However, given the COVID-19 pandemic, therapies were facilitated online, which none of these studies explored. This review is one of the few that studied cultural adaptations or integration.

CONCLUSION

This scoping review identified that MBCT is more effective against treatment as usual or control groups to reduce symptoms of anxiety, depression, and stress in multicultural environments where the adult natives did not speak English as a first language. Findings were mixed as to whether MBCT is more effective than other psychological interventions. Integrating MBCT with another intervention also reported effectiveness compared to TAU or a control group. This review holds promise for ensuing research to hypothesise that integrating MBCT with a familiar cultural intervention may reduce psychological distress symptoms and increase general wellness.

Authors' Contributions

NAW conducted the database searches, screened the results and drafted the review. JHAK supervised the screening processes and reviewed the article.

CONFLICT OF INTEREST

This study is unfunded, and there is no conflict or competing interest.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

Approved by the International Islamic University Malaysia (IIUM) Institutional Research Ethics Committee (IREC) ID No.: IREC 2021-279 and Agency of Integrated Care (AIC)' s Institutional Review Board (IRB) Reference No.: 2022-001.

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REVIEW ARTICLE

Photobiomodulation Therapy for Wound Healing: A Narrative Review

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ABSTRACT

Photobiomodulation is a therapy method that employs light to stimulate cellular function. It has emerged as a promising approach to healing wounds due to its potential to accelerate tissue repair. Wounds can vary in severity from minor cuts to more serious injuries that involve deeper tissue damage. Wound healing is the natural process of the body to repair the injured tissue that causes disruptions to the integrity of the body's tissue. It has been known that photobiomodulation has established its positive effects on wound healing in various factors by modulating the inflammatory response. This review aims to understand the efficacy of photobiomodulation and the clinical application of light transmission as a therapy in enhancing the healing of wounds. Articles on photobiomodulation and its application in wound healing were searched from the available peer-reviewed journals. Published papers were collected from PubMed, Scopus, and Science Direct using photobiomodulation, wound healing, and soft tissue as the keywords. The initial paper search yielded 124 results, and 37 full-text eligible articles were assessed in this review. In conclusion, photobiomodulation has been seen to offer a promising therapeutic approach to enhancing wound healing despite ongoing development. Continued research is essential to comprehend the full potential of photobiomodulation therapy in accelerating wound recovery. It will provide insights into future research areas on photobiomodulation, thus improving the clinical treatment modality and the patient's quality of life.

Keywords
Photobiomodulation, Wound Healing, Light Therapy, Wavelength

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INTRODUCTION

Photobiomodulation (PBM) is a therapy that uses light to stimulate cellular activity and promote tissue healing. Since the discovery of lasers in the 1960s, this advanced therapeutic application has demonstrated enormous potential in assuring efficient and thorough wound healing for decades.[1] The mechanism of this therapy draws on the release of energy packets known as photons, resulting in light emission. The light emission produced by the photon's energy is influenced by the wavelength.

In PBM, the biological action begins upon the absorption of photons, which occurs within the chromophore molecule. The interaction between a chromophore and wavelengths is distinctive due to the chromophore's capacity to absorb light throughout a range of wavelengths.[2] The application is a non-invasive medical treatment that uses low-intensity lasers or LEDs consisting of various light spectra that have been introduced to enhance the biological effects of the healing. Researchers have found that the optimal wavelengths used in clinical practice are between 600 and 1100 nm.[3]

Wound severity can range from minor to severe injuries involving deeper tissue damage. The body's natural process of healing wounds, which disrupts tissue integrity, is called wound healing. This process eventually leads to wound closure by forming scars from connective tissue to replace the damaged area.

When the skin is damaged, the healing process begins with platelet activation, triggered by exposed components like collagen and tissue factors. Platelets then release chemokines and growth factors (GFs), which help form clots and achieve haemostasis. After clotting, neutrophils arrive at the wound site to clear debris and provide microbial defence, preparing the site for further healing stages. Macrophages facilitate phagocytosis by removing foreign agents from the wound area and restoring the tissue's internal integrity after damage. However, wounds can also have devastating consequences and could lead to chronic pain and loss of body parts, which persist long after the initial injury has healed. This can significantly diminish an individual's quality of life, interfering with daily activities and leading to emotional and physiological distress. Various approaches have been established to control and minimise wound progression. However, the probability of wound re-occurrence is still high. Therefore, an innovative application using light emission such as PBM is required to effectively promote reliable and comprehensive wound healing.

Individuals with long-term injuries, such as diabetic foot ulcers, have slower healing times, which raises the possibility of infection. Due to the condition, they are more vulnerable to injuries. Crucially, patients who consistently use conventional wound dressings have a higher risk of infection and experience a slower rate of recovery. This review aims to understand the efficacy of PBM in enhancing wound healing, its mechanism of action, and the clinical application of light transmission as a healing therapy. Further investigation into light therapy can promote its application as a wound healing treatment, thereby improving patients' quality of life by enhancing their cell production and progressively instilling optimism in the healing process of their lesion.

MATERIAL AND METHODS

This comprised of relevant article literature that was extracted, and databases searched for in this review were PubMed, Science Direct, and Scopus. Search terms were "photobiomodulation", "wound healing", and "soft tissue" as in **Table I**. All the retrieved articles were added to the Mendeley citation manager, and duplicates were eliminated.

Table I: Information on sources and search strategies for the review

Database	Search strategies	Results
PubMed	Photobiomodulation AND wound healing AND soft tissue	34
Science Direct	Photobiomodulation AND wound healing AND soft tissue	69
Scopus	Photobiomodulation AND wound healing AND soft tissue	21
	Total	124

The search was conducted between October 2023 and September 2024. Original research articles from 2018 until 2024 and other additional relevant articles were included in this review. The inclusion criteria applied were English literature, and using PBM/LLLT as an intervention.

DISCUSSION

WOUND HEALING

A wound is defined as any disruption or damage to the normal structure and function of the skin, resulting in a break in the epidermal integrity, characterised by loss of epithelial continuity with or without loss of underlying connective tissue. Usually, wounds can occur due to surgery, trauma, or disease processes.[4]

Phases of wound healing

Wound healing is essential to maintain epidermal integrity after injury-causing cuts and abrasion. The process involved specific sequential events starting from haemostasis, inflammatory, proliferative, and remodelling phases[5] as shown in **Figure 1**. The process of wound formation involves the initial injury, exposing sub-endothelium, followed by haemostasis by releasing tissue factors activating platelet aggregation, which results in degranulation and release of chemotactic factors (chemokines) and growth factors (GFs) forming clots to stop the bleeding. Concurrently, inflammatory mediators are released, initiating the subsequent inflammatory phase.[6] Neutrophils and macrophages are inflammatory cells that migrate to the wound's site, releasing growth

factors and cytokines that promote tissue healing. Pro-inflammatory mediators are also released during this phase, facilitating the release of immune cells and nutrients to the wound site by increasing vascular permeability and vasodilation.[6]

The immune system incorporates inflammation as a dynamic mechanism to eliminate the wound sites from debris, pathogens, and damaged cells. Subsequently, the proliferative phase facilitates tissue repair by forming granulation tissue for tissue regeneration and repair.[7] Fibroblasts, recruited to the wound site, synthesise and deposit extracellular matrix (ECM) components such as collagen, elastin, and proteoglycans, forming a provisional matrix that provides structural support for cell migration and tissue generation.[7] Endothelial cells proliferate to form new blood vessels (angiogenesis), enhancing oxygen and nutrient delivery to the healing tissue. Additionally, epithelial cells at the wound edges proliferate and migrate to cover the wound surface, restoring the epithelial barrier. The final phase of wound healing is the remodelling phase. This phase involves the maturation and reorganization of the newly formed tissue to accelerate its strength and functionality.[5] Excessive collagen synthesis, characteristic of the proliferative phase, is downregulated, and the ECM undergoes remodelling through the action of matrix metalloproteinase (MMPs) and tissue inhibitors of metalloproteinases (TIMPs).[7] This process leads to the alignment of collagen fibres along the lines of mechanical stress, increasing tissue tensile strength. Over time, the scar tissue matures, becomes less vascularised, and gains mechanical stability although it may never fully regain the structural and functional characteristics of the original tissue. In some cases, scar formation occurs.[8]

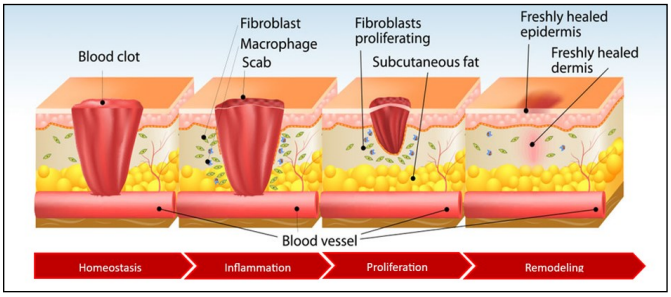

Figure 1: Stages of wound Healing. Adapted from John Maynard, 2015.[9]

PHOTOBIOMODULATION

Photobiomodulation is a therapeutic technique that involves the application of a low-level laser or LED to stimulate cellular function, promote tissue repair, reduce inflammation, and relieve pain.[10] The use of lasers has been discovered in the 1960s. This advanced therapeutic application has demonstrated significant potential for providing efficient and thorough wound healing for years. Although there was initial scepticism within the medical community in the late 20th century, PBM has gained recognition as a safe therapy for patients and has started to be incorporated into clinical practice for various medical conditions.[11] With the laser's development in recent years, this therapy continued to evolve pair with the advancement of technology nowadays, the development of PBM devices become more sophisticated and capable of delivering precise dosage and targeting specific tissues. PBM is now utilised across various medical disciplines, including sports medicine, rehabilitation, dermatology, and dentistry.

Therapeutic Effects of PBM

PBM exerts therapeutic effects by inducing photophysical and photochemical changes within cells without causing thermal damage. Biological effects from these changes lead to modifications in gene expression, metabolic arrangement, and the production of cellular metabolism.[2] Thus, the parameters which are wavelength (measured in nanometres, nm), fluence (measured in joules per square centimetres, J/cm^2), irradiance (measured in watts per square centimetres, W/cm^2), and timing (measured in seconds, s) require optimum value for treatment.[12]

PBM utilises light sources from the visible spectrum, including blue (405 to 470 nm), red (600 to 700 nm), and near-infrared (NIR). The light within the designated "optimal window" at red and NIR wavelengths (600 to 1070 nm) are commonly utilised for PBM.[13] Due to their limited penetration depth, superficial tissue is treated with the lower wavelengths within the red spectrum (600 to 700 nm). On the contrary, tissues located at greater depths are treated with longer wavelengths (780 to 950 nm), penetrating much deeper. The power of light typically lies in the range of 1 to 1000 mW and depends

on the application. The dose (fluence), which is a function of the combination of irradiance and time, is also important and varies depending on the application.[11,14]

Law of Biphasic Dose Response in PBM

The law of biphasic dose response presented by Arndt-Schultz is followed to prevent excessive light application toward the target cells.[15] This rule in PBM therapy states that low levels of irradiation must be applied upon each experiment and gradually the dosage so that the photons can be absorbed by subcellular chromophores present inside intracellular organelles and facilitate the cytochrome c oxidase (CCO) in the mitochondrial respiratory chain to trigger PBM effects without distressing the cells unexpectedly. It increases both adenosine triphosphate (ATP) production and oxygen consumption while simultaneously causing changes in nitric oxide (NO) and growth factor production.[15] At this very low-level starting point, energy is absorbed by the cell and, at the same time, receives moderate amounts of energy to prevent photochemical damage.[11]

MECHANISM OF PHOTOBIOMODULATION IN WOUND HEALING

Wound healing involves specific phases, and the process also comprises various types of cells to control and regulate cytokines and growth factor expression. The most common therapy for wound healing is the conventional, which treats the ulcers with antibiotics and gauze dressing to prevent infection. While there are alternative methods, some of them have not been able to accelerate the process of wound healing.[6]

PBM as a Potential Therapeutic Treatment for Wound Healing

PBM has emerged as a promising therapeutic modality for wound healing and enhances cellular stimulation by triggering mitochondrial function while promoting ATP production.[11] Furthermore, PBM can produce anti-inflammatory effects by suppressing pro-inflammatory cytokines and having analgesic properties to reduce pain. Collagen synthesis would also be enhanced to support the remodelling phase of tissue repair.[16]

Injured blood vessels constrict in wounds to reduce blood loss, and platelets aggregate to form temporary clots. PBM influences the haemostasis indirectly by improving microcirculation and blood flow to the wound site, facilitating the delivery of platelets and clotting factors.[17] A study has found that PBM modulates various biological effects and regulates disturbance in reparative processes for wound healing by adjusting ROS, cytokines, and platelet aggregation activity.[18] By mitigating excessive inflammation, PBM creates a conducive environment for subsequent stages of wound healing and prevents prolonged inflammation, which can impair tissue repair. PBM also stimulates cellular proliferation by enhancing ATP production, which fuels energy-dependent processes involved in cell migration. This is supported by a study of human gingival fibroblast cells showing high proliferation by utilizing the 980 nm wavelength with 4 J/cm^2 energy density.[19]

Application of PBM Using Different Wavelengths

Comparative studies examine the relative efficacy of PBM at different wavelengths in the range of light from the visible to infrared delivered at constant light intensity and fluence rate.[20] The influences of PBM can also vary based on the various light sources used and the dosimetry employed. The changes in cell proliferation and ATP migration production are among the few significant outcomes assessed in determining the effect of light therapy following irradiation.[21] Dungel and colleagues (2023) have applied three different wavelengths to measure the effects of PBM for wound care in diabetic wounds and found that the most optimal wavelength to accelerate wound closure is between green (540 nm) and red (635 nm) which significantly increased the formation of new blood vessel of the excision wound (Table II).[22]

Etemadi *et al.,* (2021) demonstrated four different wavelengths that delivered the same energy density towards human gingival fibroblast cells following a scratch assay and found that the most desirable setting for cell proliferation is 980 nm (at 1, 1.5, and 4 J/cm^2) and 635 nm (4 J/cm^2).[19] Effects of light therapy have also been found to influence the activation of MÜller cells that are responsible for maintaining retinal haemostasis

Table II: Effects of Photobiomodulation (PBM) on wound healing

Study type	Sample description	Phototherapy dosage			Treatment duration	Treatment outcome
		Wavelength (nm)	Irradiance (mW/cm²)	Fluence (J/cm²)		
In vivo* and *In vitro [23]	39 adult rats exposed to photo-oxidative damage and Scratch model using human Müller cell line (MIO-M1)	670	60	9	The rats are treated with light at 0, 3, and 14 days after 'photo-oxidative damage, and the Müller cells are irradiated following the scratch assay.	*In vivo*, the early treatment of light at 0-3 days showed that it reduces retinal stress, decreases pro-inflammatory cytokines expression decreases the photoreceptor loss thus slowing the retinal degradation progress. *In vitro,* shows that light therapy can activate cells by influencing gene expression and regulating transcription to mitigate damage
In vitro [19]	Human gingival fibroblast cells (HGF-P1)	635 660 808 980	0.33 0.22 0.4 0.25	1, 1.5, 2.5, and 4 each	Cell proliferation was assessed by MTT assay and conducted at 24, 72, and 120-h following the PBM irradiation	The PBM therapy increased the cell proliferation rate of HGF cells and 980 nm wavelength with 1, 1.5, and 4 J/cm² showing the highest proliferation rate of cells followed by 635 nm with 4 J/cm² fluence.
In vitro [35]	Diabetics induce normal and wounded (scratch assay) of Human skin fibroblast (ATCCCRL1502-WS1)	660	12.2	0 and 5 each	Laser irradiation exposure time was 410 sec (6 min 50 sec). Post-irradiation cells were then re-incubated for 24, 48, and 72h.	Cells exposed to the laser irradiation demonstrated quicker and more effective wound closure compared to the non-irradiated controls.
Clinical study [28]	Patients with chronic diabetes (n=60) LED Group: 30 patients Control Group: 30 patients	625[a], 660[b], 850[c] nm	-	5	The wound was treated with light for 5-min exposure time accordingly and the treatment was given three times a week for 8 weeks for both groups.	The phototherapy with LED showed significant improvement in healing for chronic diabetic wounds.
In vitro [36]	Normal and wounded L929 (Mouse Fibroblast), Normal and wounded HGF-1 (Human Gingival Fibroblast)	660	2.5 5.5 8.5	-	Cell proliferations were measured using MTT assay and wound healing assay after exposure for 5, 10, and 20 min. The cell migration was monitored at 12 and 24h after the scratch.	The optimal dose of cell proliferation at 660nm was 8.5 mW/cm² for 5 min (2.55 J/cm²) for HGF-1 and 5.5 mW/cm² for 20 min (6.6J/cm²) for L929. For cell migration rate, irradiation exposure times of 5 min and 10 min are optimum.
Clinical study [30]	Paediatric patients with bilateral primary molar teeth extraction (n=40)	980	0.5 mW	300 J	Pain assessment was performed using the Wong-Baker FACES Pain Rating Scale for seven days and the soft tissue healing was evaluated on the 3rd and 7th days following the extraction session.	The study found that the LLLT provided significant wound healing following the extraction of primary molar teeth and has the potential to effectively reduce post-operative discomfort.
In vivo [22]	Groups of mice (8 in each group) non-irradiated control group •Group 1: Blue Wavelength at 470 nm •Group 2: Green Wavelength at 540 nm •Group 3: Red Wavelength at 635 nm	470 540 635	40	14.4	The light treatment was applied to each group accordingly during day 0 and wound size was assessed every fourth day from day 0 to day 28.	Pulsed red (635 nm) and green (540 nm) LED light was found to be the most effective wavelength in accelerating wound closure and increasing angiogenesis of excision wounds in diabetic mice.
Clinical study [37]	30 patients with type 2 DM having Meggit-Wagner grade 1 foot ulcers.	660	50	3	The foot ulcers were given light exposure daily for 15 days.	Patients treated with LLLT showed significantly increased wound closure.
***In vitro* & Clinical study** [3]	Human fibroblast cells (HS 68)	450 520 633	3	0.9, 2.7, 8.1 respectively	Laser exposure times were 0, 5, and 15 min	There were no significant differences between the red light versus green and blue light for cell viability. A significant decrease in the relative expression of MMP-1, -2, and -9 was observed in the 633 nm group versus the 520 nm and 450 nm group.
	60 patients with chronic wounds	633	3	2-8	Treatment was given twice a week, with a minimal interval of 3 days for 8 weeks. Skin biopsies were performed to investigate the mechanism before LLLT and 4 weeks after the wound healed. Serum samples were collected after irradiation to measure the bFGF and VEGF.	Fibroblast collagen type I production increased which activated collagen production and remodelling. Significantly elevated bFGF and VEGF levels indicated their critical roles in wound healing.
Clinical study [6]	18 patients with chronic diabetic foot ulcers	660	30	6	LLLT sessions were done every 48 hours (16 sessions) for 4 weeks	LLLT enhances the progression of tissue repair in diabetic ulcers.

*bFGF, basic fibroblast growth factor; VEGF, vascular endothelial growth factor; LLLT, low-level light therapy; ATP, adenosine triphosphate; MMP, matrix metalloproteinase; a,b,c ,Contributing ratio of irradiance of corresponding wavelength.

following photo-oxidative damage by irradiating both *in vivo* and *in vitro* stress models using 670 nm wavelength at 60 mW/cm^2 delivering 9 J/cm^2 irradiation to the retina.[23] Furthermore, by incorporating two different methods in search of the most optimal wavelengths for wound healing, Yang *et al.,* (2020) began with an *in vitro* assay, testing three different wavelengths; 633 nm, 520 nm, and 450 nm on human fibroblast cells. They found that wavelength at 633 nm has the most significant results on cell proliferation. Following the result, in a clinical trial, they applied the same wavelength to patients with complicated wounds. The implied light exposure showed an increase in fibroblast collagen I which helps in tissue remodelling. These results served as proof that LLLT assists in the cell growth of damaged tissue and could become a foundation for further application of light as a tool in enhancing healing for chronic patients.[3]

CLINICAL APPLICATION OF PHOTOBIOMODULATION IN WOUND HEALING

Wavelengths in the 500-700 nm range are suitable for treating superficial tissue traumas, while wavelengths between 800-1000 nm are effective for more profound tissue injuries such as diabetic wounds or trauma after surgery.[24] There are various findings on PBM parameters for enhancing wound healing, however, effectiveness is determined by several parameters such as the wavelength (nm), power dosage (mW/cm^2), irradiation dose (J/cm^2), and treatment duration.[12]

Diabetic Wounds

PBM application has been utilised and found to be beneficial, especially for diabetic wounds. Visible light devices in the 400-800 nm range have demonstrated efficacy in treating venous foot ulcer patients where 90% of them showed a high wound closure rate.[25] This showed that the mechanism of light therapy reinforces the modulation of cellular processes, including increased cellular metabolism, ATP production, and collagen synthesis, leading to the enhancement of overall tissue repair.[22] In another clinical study, PBM illumination 660 nm with 30 mW/cm^2 light intensity and fluence of 6 J/cm^2 using LED irradiation exposure on the wound surface in a single application for 14 days resulted in the promotion of the natural healing process of the diabetic wound.

Healing of recalcitrant diabetic ulcers can be induced by PBM at 660 nm wavelengths in a pulsed manner at constant irradiance, peak power (30 mW), treatment duration in 4 weeks, and radiant exposure (6 J/cm^2) promotes more extensive healing. This treatment can also reduce inflammatory processes and increase tissue proliferation and granulation, thus significantly reducing lesions in the wound area.[26] Additionally it can also be seen in both diabetic and healthy human skin fibroblast cells irradiated at the same wavelength (660 nm) which respond with greater extents of cell migration, viability, and proliferation, leading to faster wound closure compared to the non-irradiated cells.

Some studies suggest that combining different wavelengths such as red and near-infrared light in a single application, may produce synergistic effects on tissue proliferation by targeting multiple aspects of cellular function and metabolism.[27] These different wavelengths work together amplifying the penetration and enabling simultaneous treatment of a broader range of tissue, thus promoting healing in both superficial and deeper wounds. A combination of 625, 660, and 890 nm wavelengths are found to improve blood flow and neovascularisation of patients with chronic diabetic wounds, which also induces better healing of recalcitrant diabetic ulcers giving the chance for the patients to have a better chance of full recovery.[28] Enhanced collagen accumulation and total wound re-epithelialisation are defining characteristics of the healing process as opposed to other wavelengths and non-illuminated controls.[29]

Oral Disease

In dental phototherapy, PBM has a wide range of applications in the treatment and management of various oral diseases. It has been seen to stimulate cellular processes that accelerate healing, reduce inflammation, alleviate pain, and promote tissue regeneration, especially during the post-operative dental treatment period.[30] PBM is also an adjunctive therapy for the initial healing process and can decrease pain reception following gingivectomy

oral surgery.[31] Previous research also found that applying 830 nm and 30 mW light therapy effectively reduces swelling and alleviates postoperative discomfort from mandibular third molar surgery.[32] Furthermore, in a study incorporating LED irradiation as part of periodontal therapy, light therapy contributed to restoring the periodontium and reducing inflammation.

In different conditions, patients usually encounter discomfort after treatment or dental surgery. The pain is usually unpleasant and is the most common complication faced during dental treatment. Managing pain tolerance will help a lot in reducing dental fear and anxiety when undergoing these treatments. It also encourages much faster healing.[33] PBM has an advantage in reducing pain perception following tooth extraction and provides significant wound healing in the extraction socket, especially among paediatric patients. Low-level light therapy was also proven to improve tissue healing after dental surgery [30]. A study found that exposure of 810 nm with an irradiation dose at 3.87 J/cm^2 showed favourable effects on pain and enhanced soft and hard tissue healing in the early phase of the healing period after endodontic surgery.[34]

CHALLENGES AND LIMITATION

A key challenge is the absence of standardised treatment protocols, with variations in device parameters, for example, the specific usage of wavelength, irradiance, fluence dosage, treatment duration, and treatment techniques.[38]

Despite insignificant evidence of side effects from PBM suboptimal parameter choices can lead to unsatisfactory findings or adverse therapeutic outcomes, and the lack of standardised protocols makes it difficult to compare study outcomes.[14] Healing trajectories also depend on wound aetiology since PBM effectiveness varies by wound type, location, and etiology.[11] Strategies to reduce cost and improve accessibility for developing countries in integrating PBM into the wound care protocol are needed to make this modality more attainable to patients and healthcare providers.

CONCLUSION

In summary, these data suggest that the most effective wavelengths for wound healing are in the red spectrum, between 635 and 670 nm, and the near-infrared wavelengths are between 810 and 960 nm. Therefore, the optimal wavelength range is 600-960 nm, though it also includes wavelengths that are inhibitory to wound healing. The optimum fluence or dose for the light therapy which induces photochemical damage, ranges from 1-16 J/cm^2. Additionally, the treatment duration must be considered, as it varies depending on the wound type and severity.

These findings indicate that PBM shows promise as a therapeutic approach for wound healing, and this review has evaluated its effectiveness. While the wavelength, radiant exposure, and light intensity were generally identified, several challenges and limitations need to be addressed. Continued research, innovation, and collaboration among clinicians and researchers are essential to overcoming these obstacles and realising the full potential of PBM therapy to accelerate wound healing and improve the patient's quality of life.

ACKNOWLEDGEMENT

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ORIGINAL ARTICLE

Hepatoprotective Effects and Testicular Toxicity of Centella asiatica L. Aqueous Extract in Diabetic Rats

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ABSTRACT

INTRODUCTION: Centella asiatica has been widely studied as an herbal substitute for treating diabetes mellitus (DM). This study aimed to investigate the effects of C. asiatica on the liver and testes in a rat model of type 2 diabetes mellitus (T2DM). **MATERIALS AND METHODS:** Forty adult male Sprague-Dawley rats were induced with diabetes using a single intraperitoneal injection of streptozotocin-nicotinamide (STZ-NA). Three days after induction of diabetes, the rats were treated with either 250 or 500 mg/kg body weight/day of C. asiatica aqueous extract (CAAE) for 48 days. Serum, liver, and testes were collected for analysis. Parameters measured included fasting blood glucose (FBG), body and organ weights, gonadosomatic and hepatosomatic index, testicular steroidogenesis activity (HSD17B3, testosterone levels, sperm count), and liver biochemical markers. Additionally, antioxidant and lipid peroxidation levels, together with sperm count were assessed in the liver and testes respectively. **RESULTS:** CAAE treatment improved FBG levels and mitigated weight loss in the STZ-NA group. Oxidative stress markers were ameliorated in both organs after CAAE treatment. Liver serum biochemical markers showed improvement, while testicular steroidogenic function declined. Sperm count decreased compared to the STZ-NA group. **CONCLUSION:** CAAE ameliorates hyperglycaemia and oxidative stress in the liver and testes but may cause testicular dysfunction in DM. In conclusion, the study demonstrated that C. asiatica is able to reverse STZ-NA-induced oxidative stress and hyperglycaemia but exacerbates testicular dysfunction.
evaluate our study outcome.

Keywords
Centella asiatica; antioxidant; antidiabetic; antifertility; liver.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease that affects the world's population. In Malaysia, the prevalence of DM is estimated to be 31.3% and could affect 7 million people aged 18 years and older by 2025.[1] Type 2 diabetes mellitus (T2DM) is mainly associated with a disturbance of glucose homeostasis in the body due to insulin resistance. Insulin resistance exacerbates the development of oxidative stress, leading to impaired cell and organ function, resulting in morbidity and mortality.[2,3] Increased oxidative stress and free radical formation tend to contribute to the development of diabetic complications affecting organs such as the testes, liver, kidneys, and eyes.[4-8]

In the liver, insulin resistance impairs its overall function, resulting in increased glucose production and breakdown, causing elevated blood glucose levels and dysregulation of liver enzymes.[9] Insulin resistance and oxidative stress serve as the key trigger in causing testicular dysfunction, decreased gonadotropin secretion and abnormal sperm parameters, ultimately contributing to infertility.[10-12]

Current T2DM treatments mainly consist of prescribing oral hypoglycaemic agents (OHA) with or without insulin along with lifestyle modification. However, the long-term use of OHAs poses risks such as hypoglycaemia, gastrointestinal discomfort, weight gain, allergic reactions, and vitamin B12 deficiency.[13] These side effects may lead to non-adherence to treatment, necessitating exploration of alternative therapies.

Centella asiatica, or '*pegaga*,' offers diverse pharmacological benefits including antioxidant, anti-inflammatory, antidiabetic, hepatoprotective, wound healing, sedative, and anxiolytic effects.[14-17] These properties stem from phytochemical compounds like triterpene glycosides (madecassic acid, asiatic acid), madecassoside, and asiaticoside,[18] which are beneficial to human health. *C. asiatica* increases insulin secretion,[19] aiding in pancreato-protection and alleviating diabetic nephropathy and neuropathy[20] through compounds like asiaticoside, brahmoside, and brahminoside.[21] However, potential side effects at standard doses remain unclear, including conflicting impacts on male reproductive function.[22,23]

The current study aimed to determine the effects of *C. asiatica* aqueous extract (CAAE) on liver and testicular function in a T2DM rat model. This study could fill the knowledge gap on the role and limitations of *C. asiatica* as an alternative treatment for T2DM.

MATERIALS AND METHODS

Centella asiatica Aqueous Extract (CAAE) Preparation

Fresh vacuum-packed *C. asiatica* powder was obtained from Secret Barn Sdn. Bhd., Sungai Petani, Kedah, and verified by a taxonomist at the Institute of Bioscience, Universiti Putra Malaysia (Voucher No: MFI 0212/21). The extraction method was adapted from Kumari et al. 2016 with slight modification involved mixing the powder with distilled water (1:6 ratio), immersing in a 95°C water bath for 20 minutes, macerating in an orbital shaker (Thermo Fisher Scientific, SHKE4000) for 48 hours at room temperature, and filtering using Whatman No. 1 filter paper. The filtered solution was freeze-dried and stored at -20°C.[22]

Experimental Animals

Forty healthy male adult Sprague-Dawley rats (150-250 g) were housed at 25±3°C with good ventilation and a 12-hour light-dark cycle. They had access to standard pellets and water *ad libitum* throughout the experiment. The MSU Ethics Committee guidelines (MSU-RMC-02/FR01/11/L3/004) were followed.

Induction of Diabetes

To induce diabetes, rats were injected intraperitoneally with 65 mg/kg streptozotocin-nicotinamide (STZ-NA) in cold 0.1M sodium citrate buffer (pH 4.5) after 16 hours of fasting with water provided *ad libitum*.[23] Nicotinamide (100 mg/kg) was administered before the STZ injection to minimize β-cell destruction. After 72 hours, blood glucose levels were measured from the tail vein using an ACCU-CHECK Active Glucose Monitor (Roche, Germany). Rats with blood glucose levels >16.7 mmol/L on day 7 were considered diabetic and used for further experiments.[23]

Experimental Design

Forty rats were divided into 5 groups of 8 (Figure 1). After confirming diabetes, each group received a fixed daily ration, pre- and post-weighed after 24 hours to determine food consumption. Daily consumptions were recorded and fresh provisions replenished. Treatment doses were based on Deshpande et al. (2015).[24]

Oral Glucose Tolerance Test (OGTT) and Intraperitoneal Insulin Tolerance Test (IPITT)

OGTT and IPITT were performed 48 days post-treatment. Rats were fasted overnight before each test. For OGTT, rats received glucose (2 g/kg), and blood glucose levels were measured from the tail vein at 0, 30, 60, 90, 150, and 210 minutes. For IPITT, conducted 48 hours later for recovery, same set of rats received insulin (0.75 units/kg), and blood glucose levels were measured at 0, 15, 30, 60, 90, and 120 minutes.

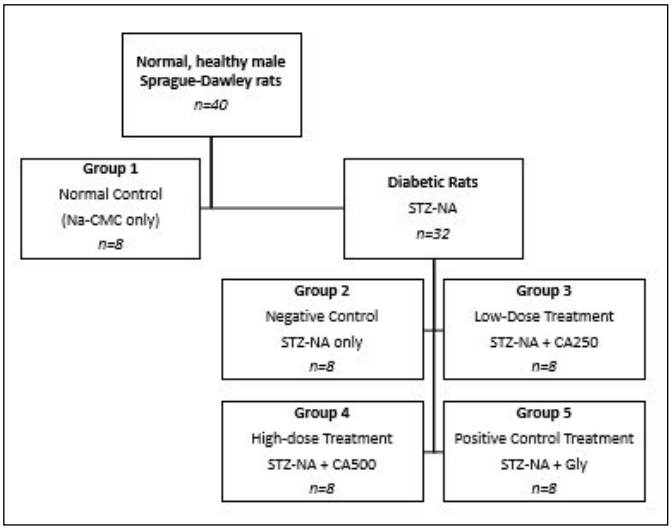

Figure 1. Animal grouping for study design

Sample collection

Blood samples were collected from overnight-fasted rats via cardiac puncture 48 days post-treatment. The samples were centrifuged at 2200 rpm for 10 minutes (Hettich EBA20, Germany) for plasma and serum analyses. Liver and testes were excised, weighed, washed in ice-cold saline, and stored at −80 °C. Tissue homogenates were prepared by homogenizing 0.1 g of tissue in 1 ml of phosphate-buffered saline (pH 7.4) and centrifuged at 5,000 g for 5 minutes at 4 °C to obtain the clear supernatant for specific assays.

Assessment of Serum Parameters

Testosterone levels were assessed using an ELISA kit (CSB-E05100r). 50µL each of supernatant, HRP-conjugate, and antibody solution were added to each well in duplicates, mixed, and incubated for 1 hour at 37°C. Wells were aspirated, washed with 200µL of wash buffer, and left to stand for 10 seconds. Then, 50µL each of Substrate A and Substrate B were added, incubated for 15 minutes at 37°C, and mixed with 50µL of stop solution. Optical density was measured at 450nm.

Liver enzymes (Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Alkaline Phosphatase (ALP)) were determined using diagnostic kits. Serum samples were analysed at the UPM Veterinary Centre (Case No.: R-2164). Serum was separated by centrifugation, and liver function parameters namely total bilirubin, and total protein were measured using established biochemical assays. Quality control measures were implemented, and data were analysed statistically.

Tissue Somatic Index

Before sacrifice, initial and final rat weights were recorded to calculate the gonadosomatic index (GSI) and hepatosomatic index (HSI). GSI and HSI assesses organs' size and weight. After sacrifice, testes and liver were weighed using an electronic scale (Shimadzu, BL2200H, Japan), fixed in 10% formalin, snap-frozen in liquid nitrogen, and stored at -20°C for future analysis. The tissue somatic index was calculated using the following formula:

$$Tissue\ Somatic\ Index\ (\%) = \frac{Organ\ Weight\ (g)}{Body\ Weight\ (g)} \times 100$$

Assessment of Antioxidant Activities

Lipid peroxidation in organs' tissue was measured using the ElabScience® Malondialdehyde (MDA) Colorimetric Assay Kit (E-BC-K025-S), with the TBARS method used to quantify MDA levels. Tissue homogenate in 10% phosphate buffer (pH 7.4) was prepared using an ultrasonic homogeniser (Ross, EQX-WT500-P2, USA), and post-mitochondrial supernatant (PMS) was obtained by centrifugation. Antioxidant activities were determined using the Catalase (CAT) Activity Assay Kit (E-BC-K031-S), Total Superoxide Dismutase (T-SOD) Activity Assay Kit (WST-1 Method) (E-BC-K025-M), and Glutathione Peroxidase (GSH-Px) Activity Assay Kit (E-BC-K096-S), following the manufacturers' instructions.

Assessment of Testicular Steroidogenic Enzymes Assay

Testicular tissue was homogenized (10%) in phosphate buffer (pH 7.4) using an ultrasonic homogenizer, followed by centrifugation at 10,000 rpm for 20 minutes at 4°C to obtain PMS. Enzyme activity of 17β-hydroxysteroid dehydrogenase (HSD17B3) was measured using the Human HSD17B3 ELISA Kit (EH14680) from FineTest. Results were expressed as enzyme activity per protein unit or as a percentage of control for the tissue samples.

Determination of Sperm Count

Epididymal sperm was diluted 1:20 to achieve optimal density for counting. Sperm count was determined using a haemocytometer under a Labomed LX-500 LED digital microscope (USA).

Statistical Analysis

Overall results were analysed using SPSS for Windows version 29.0 and GraphPad Prism 9 software. Values were expressed as Mean ± SD and analysed by one-way ANOVA. Tukey's post hoc test was used to detect differences between experimental groups. Statistical significance was set at $p<0.05$ and $p<0.001$, indicating different levels of significance. Results with $p<0.001$ were considered highly significant, while those with $p<0.05$ were considered statistically significant.

RESULTS

Effects of CAAE on Metabolic Parameters

Table 1 shows the body weight, food, and water intake data for the experimental animals. On Day 1 of treatment, the STZ-NA group exhibited significant changes ($p < 0.001$) in all three parameters compared to the normal group. Low-dose CAAE treatment increased weight by 20%, while high-dose CAAE and Glybenclamide (Gly) treatments showed a more substantial increase by 33.2% and 57% respectively. However, both food and water intake decreased by an average percentage of 13.86% in the CAAE group and 26.14% in the Gly-treated group when compared to the STZ-NA group.

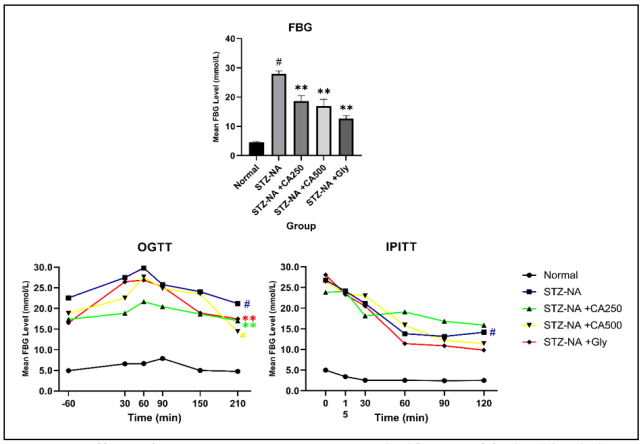

Figure 2. Effects of CAAE on serum parameters. Significance of fasting blood glucose (FBG); oral glucose tolerance test (OGTT), and intraperitoneal insulin tolerance test (IPITT) are presented as #p<0.001 vs Normal, **p<0.001 vs STZ-NA group; #p<0.001 vs Normal, *p<0.05 **p<0.001 vs STZ-NA group; #p<0.001 vs Normal, respectively.

Effects of CAAE on the Liver

Figure 3 illustrates the impact of CAAE on liver enzymes (AST, ALP, ALT), hepatic lipid peroxidation, antioxidant enzymes, and HSI. In the STZ-NA group, liver enzymes increased significantly by 73.9% compared to the normal group ($p<0.001$). CAAE treatment reduced liver enzyme levels, with the STZ-NA+Gly group approaching near-normal levels. Malondialdehyde MDA increased in the STZ-NA group by 147.2% and decreased significantly with CAAE or Gly treatment. GPx activity improved by 54.5% post-treatment, along with increased CAT, and T-SOD activities. HSI values in the untreated diabetic group were significantly higher (73.7%) compared to the Normal group, with all treatment groups showing a significant descent ($p<0.001$). The STZ-NA+Gly group approached the normal group's HSI. Higher CAAE doses correlated with a gradual decrease in HSI.

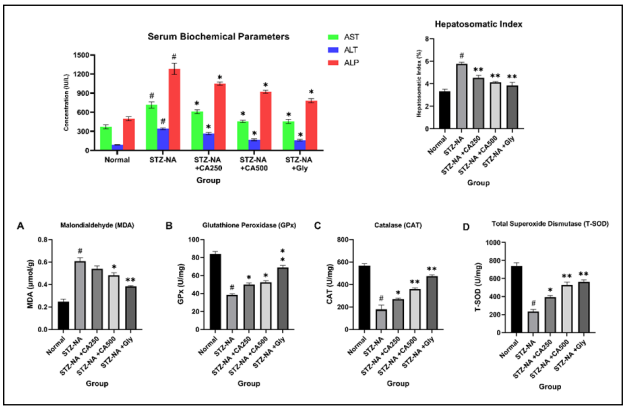

Figure 3. Effect of CAAE towards the liver. Significance of AST, ALT and ALP; Lipid peroxidation and antioxidative enzymes activity levels; HSI are presented as #p<0.001 vs Normal, *p<0.05 vs STZ-NA group; *p<0.05 **p<0.001 vs STZ-NA group; #p<0.001 vs Normal, **p<0.001 vs STZ-NA group, respectively.

Effects of CAAE Towards on Testes

Figure 4 shows the outcomes of lipid peroxidation, antioxidant enzymes, testicular steroidogenesis activity, and GSI levels. In the STZ-NA group, MDA levels increased fourfold in value compared to the normal group, indicating oxidative stress, whereas CAAE treatments approached normal levels. Our study showed a significant increase in antioxidant enzyme activity observed in the CAAE-treated and STZ-NA+Gly groups compared to the negative control group. Testicular HSD17B3 levels significantly decreased by 38.3% in the STZ-NA group, improving slightly ($p<0.001$) with CAAE treatment. Testosterone levels decreased by 50.6%

(p<0.001) in STZ-NA, further reduced with CAAE, while Gly-treated group increased by 11.86% relative to STZ-NA group. Sperm count decreased (p<0.01) in STZ-NA, with CAAE reducing it further, while Gly increased it. GSI decreased (p<0.01) in the STZ-NA group, with both CAAE treatments showing a similar decreasing trend.

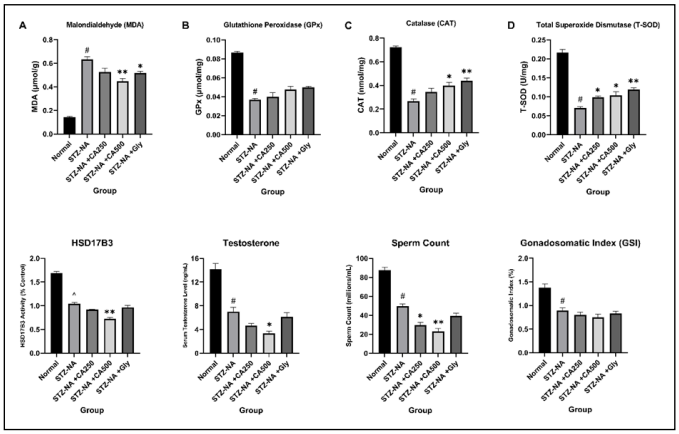

Figure 4. Effects of CAAE Towards the Testes. Significance of lipid peroxidation and antioxidative enzymes activity levels; HSD17B3; testosterone levels; Sperm count; GSI are presented as #p<0.001 vs Normal, *p<0.05 **p<0.001 vs STZ-NA group; ^p<0.05 vs Normal, **p<0.001 vs STZ-NA group; #p<0.001 vs Normal, *p<0.05 vs STZ-NA group; #p<0.001 vs Normal, *p<0.05 **p<0.001 vs STZ-NA group; #p<0.001 vs Normal, respectively.

DISCUSSION

Findings from this study demonstrated the protective effect of CAAE on liver function and potential toxic effects on the testes in STZ-NA-induced male diabetic rats. Dosages of 250 mg/kg/day and 500 mg/kg/day were chosen based on effective doses reported in previous study.[24] The treatment duration of 48 days was selected to evaluate the sub-acute progression of diabetes and observe diabetic complications such as polyphagia and polydipsia.[24]

Administering CAAE for 48 days improved fasting blood glucose levels, consistent with previous observations.[25] The hypoglycaemic effect of *C. asiatica* is attributed to active compounds such as asiatic acid,[26] asiaticoside,[27] and madecassoside,[28] known for their glucose-lowering activities. This was supported by the OGTT and IPITT results. The OGTT in the final week showed a rapid decline in hyperglycaemic peaks in the CAAE-treated group, indicating enhanced peripheral disposal of glucose load.[29] Similarly, IPITT results demonstrated reduced blood glucose levels compared to the diabetic control group, suggesting improved insulin sensitivity possibly through enhancements in insulin receptors, glucose transporters, or enzymes involved in glucose phosphorylation.[30]

Furthermore, *C. asiatica* stimulates insulin secretion from pancreatic β-cells,[31] enhancing insulin availability and alleviating symptoms of diabetes mellitus like polydipsia and polyphagia. Additionally, improved blood glucose levels contribute to reduced fat and muscle catabolism for energy,[30] thereby preventing excessive weight loss.

In this study, diabetic rats showed decreased liver weight with increased serum liver enzymes. Elevated AST and ALT levels may result from increased demand for gluconeogenic substrate and compromised hepatocyte membrane integrity, that led to substrate leakage.[32,33] Administering CAAE for 48 days reduced serum AST and ALT levels. Given hyperglycaemia-induced liver injury,[34] the hepatoprotective effect of CAAE likely stems from improved glucose control, as observed in this study. Choi et al. (2016) also reported a similar hepatoprotective effect of *C. asiatica*, showing improvement in liver histoarchitecture and fibrosis in dimethyl nitrosamine-induced liver injury in rats.[35]

In T2DM, overproduction of reactive oxygen species (ROS) contributes to liver disease progression by depleting antioxidant enzyme activities such as glutathione peroxidase (GPx), catalase, and superoxide dismutase (SOD). CAAE has proved to mitigate the disruption of oxidative redox balance that caused liver damage in T2DM by enhancing liver antioxidant enzymes.[35-37] Administering CAAE reverses the depletion of antioxidant defence enzymes (CAT, GPx, and SOD) in the liver and reduces lipid peroxidation. *C. asiatica* possess potent antioxidant compounds that can prevent the free radical-induced peroxidation of liver damage by its scavenging ability.[36]

Despite the hepatoprotective effect of CAAE, its effect on the testes remains controversial. Some studies have revealed the fertility-inhibiting effect of *C. asiatica,*[38-40] while other studies have reached opposite conclusions.[41]

In this study, administration of CAAE able to restored OS and lipid peroxidation in the testes. CAAE inhibits lipid peroxidation by scavenging free radicals,[42] while preserving the integrity of the testicular cell membrane,[41,43] and protecting against oxidative damage. It also restores depleted antioxidant enzymes such as SOD and GPx, which are critical for neutralizing free radicals and reducing oxidative stress.[44]

Interestingly, CAAE caused greater testicular dysfunction despite restoration of oxidative status, as evidenced by the reduction in sperm count, testosterone, and HSD17B3 enzymes in this study. These results suggest that, despite its strong antioxidant potential, CAAE may have a direct toxic effect on the male reproductive system. This reinforces the damage caused by the lack of insulin in DM, which blocks the secretion of gonadotropins, leading to a deficiency of testosterone.[45] In addition, the key enzyme required for the conversion of androstenedione to testosterone, HSD17B3 was decreased, which may indicate a direct toxic effect of CAAE on Leydig cells.

The Leydig cell is the primary androgen source that can be directly affected by the toxic effects of CAAE which disrupts spermatogenesis, reduces sperm count and overall sperm quality. *C. asiatica* caused decrement in these parameters, possibly due to lipocalin enzyme and sorbitol dehydrogenase activity.[46-48] Analysis expression of the lipocalin members, Lcn8 and Lcn9, also showed disappearance of lipocalin protein in the *C. asiatica*-treated group, indicating possible effects on sperm maturation and epididymal function.[46] Lipocalin proteins are significant in reproductive functions and sperm development in the male reproductive system.[46,47] Likewise, four weeks of treatment with *C. asiatica*, possibly due to damage to the Leydig and Sertoli cells involved in spermatogenesis.[49]

The toxic effect of CAAE on testicular tissue aligns with Yunianto et al. (2017), who reported that the ethanol extract of *C. asiatica* induced apoptosis of spermatogenic cells in normal rats. This was evidenced by increased apoptotic germ cells per testicular tubule and significant decreases in FSH, LH, and testosterone levels.[48] The observed toxicity may result from synergistic effects of the active substances in *C. asiatica*. Interestingly, asiatic acid has been shown to enhance spermatogenesis by inhibiting apoptosis in rats fed a high-fat diet.[43] However, other compounds in *C. asiatica* may counteract asiatic acid's beneficial effects on spermatogenic function.

It has been reported that diabetes-induced atrophy of male reproductive organs results from oxidative stress and apoptosis.[50] In our study, the gonadosomatic index (GSI) was initially low in the diabetic group and further decreased with CAAE administration. Additionally, the reduced testosterone levels could contribute to negative effects on somatic and germ-forming cells in the testes, ultimately leading to decreased testicular weight.

LIMITATION OF STUDY

Phytochemical analysis is essential to identify active components and assess potential hepatoprotective and testicular effects. Including spermogram and histology observations will enhance study findings. Future investigations should incorporate electron microscopy to examine *C. asiatica*'s impact on liver histo-architecture, offering insights into liver diseases like inflammation or cirrhosis. Advances in electron microscopy techniques, such as immunoelectron microscopy could elucidate complex molecular mechanisms and guide targeted therapeutic interventions.

CONCLUSION

In conclusion, CAAE alleviate hyperglycaemia in diabetic rats by improving insulin resistance and has a hepatoprotective effect by reducing oxidative stress and maintaining near-normal levels of liver enzymes. However, CAAE administration has toxic effects on the testes, worsening the outcome in male diabetic rats. Further studies should be conducted to identify the compounds responsible for these adverse effects so that safe administration of CAAE is possible without causing harmful side effects in the male population.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

The Clinical Characteristics and Outcomes of *JAK2/CALR/MPL* Mutation Related Myeloproliferative Neoplasms - A Single Centre Study from Malaysia

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ABSTRACT

INTRODUCTION: The pathogenesis of classical myeloproliferative neoplasm (MPN) driven by JAK2, CALR and MPL gene mutations affects the clinical course and survival. This study aimed to determine the prevalence of driver mutations in MPN patients and their association with clinical presentations and outcomes. **MATERIALS AND METHODS:** We conducted a retrospective study involving patients with classical MPN diagnosed from 2002 to 2019. The patient's clinical and laboratory information, as well as outcomes, were collected and reviewed. **RESULTS:** 267 patients with classical MPN were recruited into the study. Majority of these patients were Chinese (46.5%), followed by Malay (40.1%) and Indian (12.7%). Most of the patients had essential l thrombocythaemia (ET) (57.3%), followed by polycythaemia vera (PV) (30.0%) and primary myelofibrosis (PMF) (12.7%). JAK2V617F mutation was detected in PV (87.5%), ET (68.0%), and PMF (67.6%) patients whereas CALR mutation was present in 15.0% of ET and 8.8% of PMF patients and MPL mutation was present in 0.7% and 5.9% of ET and PMF patients respectively. CALR-mutated ET patients were less likely to develop vascular events compared to JAK2V617F mutated patients (Odds ratio 0.301, 95% confidence interval 0.097–0.939, p=0.039). As for clinical outcomes, triple negative PMF patients had shorter median overall survival than those with JAK2V617F mutation (24.0 months vs. 161.0 months, p=0.017). **CONCLUSION:** Majority of classical MPN patients were Chinese with ET being the most common MPN subtype. The mutation profiles, clinical features, and survival outcomes were comparable to previous reports. Mutation studies are therefore important for prognostication and should be performed routinely.

Keywords
myeloproliferative neoplasm, JAK2, MPL, CALR, clinical outcomes

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INTRODUCTION

The classical myeloproliferative neoplasm (MPN) which include polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF) are clonal diseases of the hematopoietic stem cell, classified under *BCR::ABL1*-negative MPN subtypes according to World Health Organization (WHO) classification.[1] The incidence rates for ET, PV and PMF were 1.55, 1.57 and 0.44 per 100,000 person-years, respectively in the United States.[2] These are comparable to the ranges reported in other continents, including Europe, Australia and Asia.[3-5]

The key driver mutations involved in the pathogenesis for classical MPN include Janus kinase 2 *(JAK2)*, calreticulin *(CALR)* and myeloproliferative leukemia virus oncogene *(MPL)* mutation. Somatic mutations in *JAK2* gene, both in the form of *JAK2V617F* or *JAK2 exon 12* mutation, drive the pathogenesis of PV and are observed in more than 90% of PV patients. In contrary, *CALR* mutation is present mainly in ET and PMF, albeit at a lower frequency with prevalence rate of 15% to 24% and 25% to 35% respectively.[6] *MPL* mutation is present at an even lower rate at 4% of ET patients and 8% of PMF patients.[7]

Approximately 10% of *BCR::ABL1* negative MPN have none of these three mutation and is termed as triple negative MPN.[8]

Variation in mutation profiles has been shown to be associated with different clinical characteristics and clinical course. As an example, *CALR* mutated ET is associated with lower hemoglobin levels, higher platelet counts, lower leukocyte counts, and younger age compared to *JAK2V617F* mutated ET.[9] There are a few *CALR* mutation variants that have been identified and they are found to be associated with different phenotypes; Type 1 and type 1-like mutations variants have greater risk of MF transformation, while type 2 and type 2-like mutations variants are associated with more indolent clinical course.[10,11] On the other hand, *JAK2V617F* mutated ET was shown to be associated with increased risk of thrombosis.[12]

Among patients with PMF, those harboring *CALR* mutations are younger and has lower risk of cytopenias.[13] In contrast to *CALR* mutated PMF, those harboring *JAK2V617F* mutation are associated with increased risk of thrombosis.[14] Amid all genetic mutations, triple negative PMF has the worst prognosis where there is higher risk of leukemic transformation and poorer overall survival.[13]

Although the prevalence of these molecular mutations is widely reported in the developed nations especially in the Caucasian populations, there is paucity of epidemiological data in the Southeast Asia (SEA) regions and even scarcer is the clinical outcome of these patients. Even though there are few reports on epidemiological data of classical MPN from different parts of Malaysia, complete information on the prevalence of *CALR* and *MPL* mutation and patient survival are limited.[15-17]

In view of this, this study aims to determine the prevalence of *JAK2/CALR/MPL* mutations in MPN patients and to determine their association with clinical presentations and outcomes.

MATERIALS AND METHODS

This was a retrospective study where patients diagnosed with classical MPN (ET, PV and PMF) and treated at a tertiary academic centre in Kuala Lumpur, Malaysia were recruited from year 2002 to 2019. The study was approved by the local institution ethic committee with the registration number of MREC-202123-9792.

Patients were included if they were ≥18 years old, had available results of mutational studies (*JAK2V617F, MPL, CALR* and *JAK2 exon12*) at the time of diagnosis; and fulfilled the criteria of MPN according to 2022 WHO classification criteria.[18] Patients with incomplete clinical information were excluded.

The clinical information that was collected included patients' demographic data, clinical presentations, clinical outcome, and their survival status. Clinical outcome was defined as occurrence of hematological transformation to acute leukemia, and vascular related complications. Vascular related complications were defined as clinical and/or radiological confirmed thrombotic or bleeding event, occurred after the initial diagnosis of MPN. Time to progression was defined as the duration from the date of diagnosis to the date of disease progression. Overall survival (OS) was determined from the date of diagnosis to the date of death or date of last known follow up.

All statistical analysis was conducted using SPSS Statistics for Windows Version 26. Descriptive statistics were utilized for categorical variables. Results were presented as frequencies and percentage for categorical data. Numerical data which are normally distributed are presented as mean and standard deviation while median and interquartile ranges were presented for numerical data which are not normally distributed. Fisher's exact test and Chi Square test were used to compare categorical variables. Mann Whitney or Kruskal Wallis were used to test the non-parametric continuous variable and One Way Anova was used to test for parametric continuous variables. Nominal regression was used to estimate Odd's ratio for categorical

variables. Survival analysis was estimated using Kaplan Meier method and compared by the log rank test. P value of 0.05 was considered statistically significant.

RESULTS

Clinical characteristics of classical MPN patients

A total of 267 patients with a mean age of 59.5 years were included in this study. These patients were followed-up for a median duration of 40 months. Most patients were diagnosed with ET (57.3%), followed by PV (30.0%) and PMF (12.7%). The gender distribution for ET (54.2% females) differed from PV and PMF where the majority were males (67.5% and 58.8% males, respectively) (p=0.006). Majority of patients with classical MPNs were Chinese (46.5%), followed by Malay (40.1%) and Indian (12.7%). The mutation profile of the patients is shown in Table I.

Table I: Clinical characteristics of classical MPN patients

n (%)	Total	PV	ET	PMF	P value
Number of patients	267 (100.0)	80 (100.0)	153 (100.0)	34 (100.0)	
Age at diagnosis, mean (SD)	59.5 (15.5)	57.7 (13.8)	59.7 (16.6)	62.5 (14.1)	0.310
Gender					
Male	144 (53.9)	54 (67.5)	70 (45.8)	20 (58.8)	*0.006*
Female	123 (46.1)	26 (32.5)	83 (54.2)	14 (41.2)	
Ethnicity					
Malay	107 (40.1)	37 (46.3)	57 (37.3)	13 (38.2)	0.236
Chinese	124 (46.5)	29 (36.3)	76 (49.7)	19 (55.9)	
Indian	34 (12.7)	14 (17.5)	18 (11.8)	2 (5.9)	
Others	2 (0.7)	0 (0.0)	2 (1.3)	0 (0.0)	
Mutation profile					
JAK2V617F	197 (73.8)	70 (87.5)	104 (68.0)	23 (67.6)	*<0.001*
CALR	26 (9.7)	0 (0.0)	23 (15.0)	3 (8.8)	
MPL	3 (1.1)	0 (0.0)	1 (0.7)	2 (5.9)	
JAK2 Exon12	1 (0.4)	1 (1.3)	0 (0.0)	0 (0.0)	
No mutation	40 (15.0)	9 (11.3)	25 (16.3)	6 (17.6)	
Clinical presentation					
Asymptomatic	202 (75.7)	54 (67.5)	128 (83.7)	20 (58.8)	*0.001*
Thrombotic events	35 (13.1)	17 (21.3)	17 (11.1)	1 (2.9)	*0.017*
Bleeding events	12 (4.5)	3 (3.8)	5 (3.3)	4 (11.8)	0.109
Constitutional symptoms	18 (6.7)	6 (7.5)	3 (2.0)	9 (26.5)	*<0.001*
Complications					
Vascular events	11 (4.1)	4 (5.0)	5 (3.3)	2 (5.9)	0.618
Secondary myelofibrosis	19 (7.1)	6 (7.5)	13 (8.5)	-	0.233
Leukemic transformation	11 (4.2)	3 (3.8)	6 (3.9)	2 (5.9)	0.819

Abbreviations: N, numbers; SD, standard deviation; PV, Polycythaemia Vera; ET, Essential Thrombocythaemia; PMF, Primary Myelofibrosis
P<0.05 is statistically significant.

PMF patients who were included in the study were risk stratified using Dynamic International Prognostic Scoring System (DIPSS), where 17.6% and 50.0% were classified as low and intermediate-1 risk groups, while 29.4% and 2.9% were categorized as intermediate-2 and high-risk groups.

Table II: Blood parameters, clinical presentations and complications of classical MPNs

Characteristics	*JAK2V617F* mutation	*CALR* mutation	*MPL* mutation	*JAK2 Exon12* mutation	No mutation	p value
Polycythaemia Vera (n=80)						
Hemoglobin (g/L)*	183 ± 26	-	-	174	194 ± 19	0.434
WCC count (x10⁹/L)*	17.5 ± 9.8	-	-	10.9	10.0 ± 3.4	0.069
Platelet count (x10⁹/L)*	544 ± 222	-	-	117	259 ± 123	*<0.001*
Clinical presentation						
Asymptomatic	49 (70.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)	0.246
Thrombotic events	15 (21.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	1.000
Bleeding events	1 (1.4)	0 (0.0)	0 (0.0)	1 (100.0)	1 (11.1)	*0.009*
Constitutional symptoms	5 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0.564
Complications						
No complication	60 (85.7)	0 (0.0)	0 (0.0)	1 (100.0)	6 (66.7)	0.298
Vascular events	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	*0.005*
Secondary myelofibrosis	6 (8.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Leukemic transformation	3 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Essential Thrombocythaemia(n=153)						
Hemoglobin (g/L)*	131 ± 25	120± 27	110	-	132 ± 16	0.176
WCC count (x10⁹/L)*	13.9 ± 8.0	13.8 ± 10.5	8.1	-	11.6± 5.5	0.555
Platelet count (x10⁹/L)*	882 ± 306	1128 ± 530	783	-	1050 ± 483	*0.022*
Clinical presentation						
Asymptomatic	88 (84.6)	17 (73.9)	1 (100.0)	0 (0.0)	22 (88.0)	0.478
Thrombotic events	9 (8.7)	5 (21.7)	0 (0.0)	0 (0.0)	3 (12.0)	0.284
Bleeding events	4 (3.8)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.824
Constitutional symptoms	3 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Complications						
No complication	89 (85.6)	20 (87.0)	1 (100.0)	0 (0.0)	19 (76.0)	0.547
Vascular events	2 (1.9)	1 (4.3)	0 (0.0)	0 (0.0)	2 (8.0)	0.208
Secondary myelofibrosis	9 (8.7)	2 (8.7)	0 (0.0)	0 (0.0)	2 (8.0)	1.000
Leukemic transformation	4 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.0)	0.468
Primary Myelofibrosis (n=34)						
Hemoglobin (g/L)*	104± 31	107 ± 44	109± 1	-	87± 22	0.636
WCC count (x10⁹/L)*	23.9± 21.2	15.5 ±5.0	15.5±9.0	-	16.2±14.0	0.733
Platelet count (x10⁹/L)*	466 ± 353	1090 ± 1394	830 + 684	-	304 + 360	0.142
Clinical presentation						
Asymptomatic	12 (52.2)	2 (66.7)	2 (100.0)	0 (0.0)	4 (66.7)	0.753
Thrombotic events	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Bleeding events	3 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1.000
Constitutional symptoms	7 (30.4)	1 (33.3)	0 (0.0)	0 (0.0)	1 (16.7)	0.913
Complications						
No complication	21 (91.3)	3 (100.0)	2 (100.0)	0 (0.0)	4 (66.7)	0.367
Vascular events	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0.549
Leukemic transformation	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0.549

Abbreviations: WCC, white cell count
P<0.05 is statistically significant.
* Mean ± Standard Deviation

PV patients with *JAK2V617F* mutation presented with higher platelet count (544±222x10^9/L, p<0.001), whereas ET patients with CALR mutation was associated with significant thrombocytosis (1128 ±530 x10^9/L, p=0.022) compared to other mutations. (Table II).

There was no significant difference in clinical presentation among classical MPN patients with various mutations. Among patients with ET, *CALR* mutated patients were less likely to develop vascular events compared to *JAK2V617F* mutated patients (Odds ratio [OR] 0.301, 95% confidence interval [95% CI] 0.097–0.939, p=0.039). Disease progression to secondary myelofibrosis from PV occurred in 8.6% of patients with *JAK2V617F* mutation, at mean duration of 66.3 months from diagnosis. In comparison, mean time to progression to secondary myelofibrosis from ET occurred later at 72.7 months, 154.5 months and 114.5 months, for *JAK2V617F*, *CALR* and triple negative ET respectively (p=0.440).

Survival outcomes of classical MPNs

Among all patients with classical MPNs, PMF had the shortest median overall survival (66.0 months) compared to patients with ET and PV (median OS not reached, p<0.001) (Figure 1a). Further analyses among patients with ET and PV showed no difference in OS across various gene mutations. Among PMF patients, however, triple negative PMF patients had shorter median OS compared to those with *JAK2V617F* mutation (24.0 months vs. 161.0 months, p=0.017) (Figure 1b). There was no significant difference in OS among patients with various DIPSS risk scores.

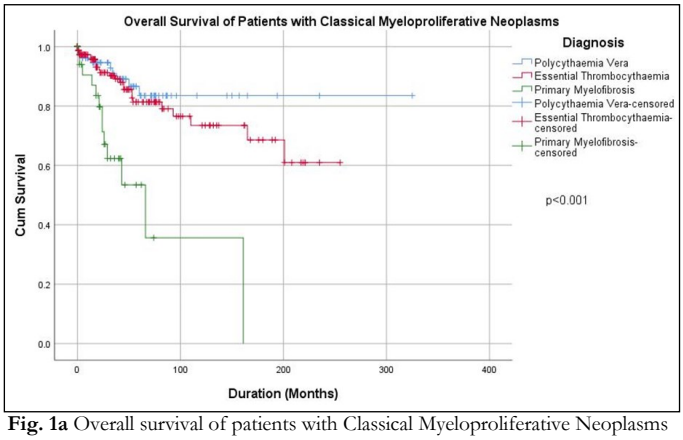

Fig. 1a Overall survival of patients with Classical Myeloproliferative Neoplasms

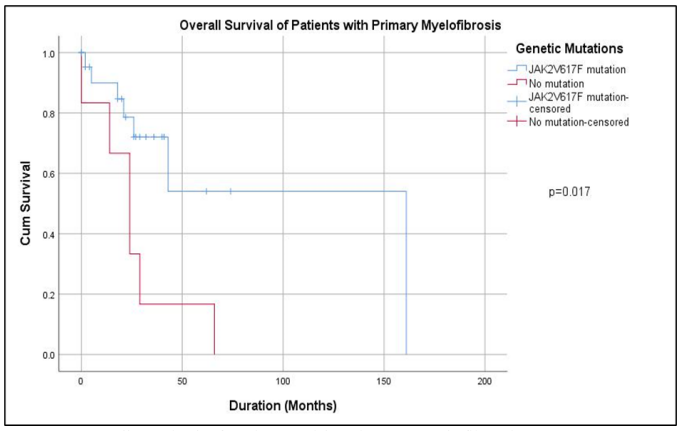

Fig 1b Overall survival of patients with Primary Myelofibrosis

DISCUSSION

Classical MPN is a group of diseases associated with several genetic alterations that activate the JAK/STAT pathway. It is caused by somatic mutations in the tyrosine kinase *JAK2*, the chaperone protein *CALR* or the thrombopoietin receptor *MPL* in majority of the patients.[19] Somatic mutations in myeloid cancer genes are often also mutated in MPN, such as *DNMT3A* and *TET2* mutations, among others. The occurrence of these concomitant mutations is found to affect the prognosis of patients with MPN.[20]

In our study, classical MPN is more prevalent in the Chinese ethnic group compared to Malay and Indian. The ethnic distribution is comparable with other studies from Malaysia as well as Singapore (between 43.2% and 65.8%), where the population comprise of multiple ethnicities.[15, 21] As pointed out by *Yap et al*, the inheritance of *JAK2* 46/1 haplotype that is linked to development of *JAK2V617F* mutation, has been found to be present among the populations in China and Japan. In fact, most Malaysian Chinese are originated from Southern China and its surrounding geographical regions, this may be the explanation for the higher prevalence of MPN compared to other ethnic groups. [15]

Among all classical MPNs, we found that ET was the most common classical MPN (57.3%) and majority of the patients were females. Although this is in contrast to reports from the USA where the most frequent MPN subtype was PV, our result is consistent with epidemiologic studies from this region, where ET

predominates (between 49.1 to 58.4%).[22-25] This observation can be explained by the distinct genetic makeup among Han Chinese, Japanese and Korean populations based on their genome wide data or ancestry informative markers.[26] The homogeneity in their ancestry genetic makeup could have translated into similarity in disease patterns in these nations and in our Chinese populations.

In contrast to Caucasian patients where most of the MPN patients were diagnosed in the elderly population (>70 years), the mean age at diagnosis in our cohort was 59.5 years, likely due to a generally younger population in our nation. Similarly, MPN patients from Japan and Korea also present at their late fifties,[24,27] and this observation again could be attributed to the analogous genetic makeup among the East Asian populations.[26]

Notably, 85% of our MPN population harboured at least one molecular mutation, with *JAK2V617F* mutation being the most common (73.8%). The finding is consistent with other studies where approximately 80% of their patients had at least one mutation identified.[16,28] However, this is contradictory to the study by Yap *et al* where only 63.7% of their MPN patients had detectable mutation.[15] The different findings could be due to the relatively high number of their patients did not have mutation study performed.

In another study with a smaller sample size conducted in Malaysia, 10.2% of their MPN cohorts harbored *CALR* mutation, similar to our findings.[17] Interestingly, the frequencies of *CALR* mutation (15.1% in ET and 8.8% in PMF) reported in our cohort were lower when compared to other Asian studies where the prevalence in their ET and PMF patients were 23.0% and 21.0% respectively. However, our finding is consistent with what was reported in the western countries where their prevalence was also at approximately 16.0%.[29] Similar to previous reports, our *CALR* mutated ET patients had significant higher platelet counts but lower thrombotic risk.[10,12] Although patients with *CALR* mutated PMF have been reported to have survival advantage, this was not seen in our study.[13] The relatively small sample size in this study may be the possible reason.

We reported a lower prevalence of *MPL* mutations among our ET patients (0.7%), compared to other countries where the prevalence was reported to be 2.7% to 4.3%.[30,31] In comparison, the prevalence of *MPL* mutated PMF in our cohort (5.9%) is similar to those in Argentina (6.1%), but lower compared to those reported in USA and Italy (8.1%).[32,33] *MPL* mutations have been shown to be associated with higher risk of transformation to secondary myelofibrosis among patients with ET, and those *MPL* mutated PMF were associated with low leukocytes counts, less cellular bone marrow (BM) and a higher number of BM megakaryocytes compared to those with *JAK2V617F* mutation.[34,35] We were not able to demonstrate these findings, again due to the relatively small sample size.

Previous literatures had reported lower vascular related event and lower risk of secondary myelofibrosis among triple negative ET patients.[36,37] In contrast, triple negative PMF patients have an aggressive clinical course and poor survival outcome. Our triple negative PMF cohort has significantly shorter median OS compared to those *JAK2*-mutated PMF. The median OS in triple negative PMF in this study was at a dismal 2 years compared to those with *JAK2*-mutated PMF, 13.4 years. This is consistent with the report by Rumi *et al.* where median OS was also at 3.2 years for triple negative PMF and 9.2 years for *JAK2*-mutated PMF.[13] Even with the availability of new therapeutic options such as *JAK2* inhibitors, it has thus far not shown to reduce the risk of mortality or disease transformation. At present, allogeneic haematopoietic stem cell transplant is the only curative treatment for PMF. In view of this, this group of patients may benefit from allogeneic stem cell transplant rather than *JAK2* inhibitor.

This study has several limitations. One of them was the relatively small sample size. In addition, this was a retrospective single centre study and hence may not truly be reflective of the Malaysian population. However, the strength of this study is the availability of the *CALR* and *MPL* mutations results where such information is scarce especially in this region, thus providing a more comprehensive overview of the epidemiological findings.

Secondly, the relatively long follow up allowed us to report on related complications and survival of the three MPNs.

CONCLUSION

In summary, our study showed that majority of classical MPN patients were Chinese, ET being the most common MPN subtype. The mutation profiles of these patients and their clinical features were comparable with previous reports. Among all mutations, triple negative PMF had the worst clinical outcome. Therefore, mutation studies should be incorporated as part of the routine diagnostic investigations for patients who are suspected to have MPNs even in a resource-limited nations such as Malaysia. This may allow one to have better understanding of the mutation landscape, aid in making the right diagnosis as well as to prognosticate patients.

CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interest to disclose.

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ORIGINAL ARTICLE

Evaluating the Resilience Level among Medical and Health Science Lecturers in Higher Education

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ABSTRACT

INTRODUCTION: The use of resilience in higher education involves recognizing and implementing adaptive mechanisms during periods of adversity or transition. The present study aims to conduct an evaluation of the resilience levels of lecturers and investigate the association between socio-demographic factors that are linked to resilience among medical and health science lecturers in Malaysia. **MATERIALS AND METHODS:** A cross-sectional online questionnaire was conducted between October and November 2023. This study employed the validated Medical Professionals Resilience Scale (MeRS) for all lecturers in medical and health science fields at Malaysian institutions, which consists of 37 items designed to assess the resilience level of the lecturers. Socio-demographic data were also collected to identify resilience characteristics. The independent sample T-test, Pearson correlation, and one-way ANOVA were used to analyze the data. **RESULTS:** The study encompassed a collective of 127 lecturers. A mean score of 123.66 and a standard deviation of 16.7 show that the lecturers have a high level of resilience. Resilience was observed more in lecturers with a non-clinical background compared to fellow clinical background (p=0.018). The other socio-demographic factors, including gender, age, marital status, years of experience as an educator, and designation of administration role, were not shown to have a significant impact. **CONCLUSION:** This study has the potential to yield valuable insights and may improve the effectiveness of university management frameworks in supporting lecturers during difficult times; this could be accomplished by advocating for leisure and sports activities and instituting healthy habits.

Keywords
resilience, lecturer, medical, health science, higher education

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INTRODUCTION

Resilience refers to the ability to cope with difficult situations, which involves mental, emotional, and behavioral flexibility and adaptation to internal and external demands.[1] It is a multifaceted process that can focus on the outcome or the process itself.[2] Resilience is dynamic and not a fixed personal attribute.[3] To better understand resilience, we need to recognize its dynamic nature. In their 2020 study, Wadi et al. introduced a resilience model for medical professionals, comprising four domains. Growth domain emphasizes psychological processes enabling positive adaptation, while Control domain involves emotion regulation and self-esteem maintenance. The involvement domain highlights dedication and persistence, and the Resourceful domain underscores leveraging available resources. These domains collectively offer insights into how medical professionals manage adversity, grow, and utilize resources effectively.[4]

Resilience has become an important area of study in education, particularly in understanding how teachers can sustain their effectiveness and well-being despite the many demands and constraints of their jobs.[5] Several studies have examined the level of resilience among medical and health science lecturers, but the results have been inconsistent, especially concerning the impact of socio-demographic factors.[6,7] In Malaysia, few studies have evaluated the resilience level of lecturers and its relationship with socio-demographic factors in general

education and healthcare, but not specifically in medical and healthcare education.[8,9] Resilience is essential in medical and health profession education evaluation since the current process prioritizes objectivity and stakeholder expectations over humanism.[4] Therefore, this study aims to conduct a comprehensive assessment of the resilience levels of lecturers and investigate the association between socio-demographic factors that are linked to resilience among medical and health science lecturers in Malaysia.

MATERIALS AND METHODS

SUBJECT'S REQUIREMENT

It was a cross-sectional study conducted from October to November 2023 among all medical (clinical and non-clinical) and health science lecturers (pharmacy, dental, nursing, allied health, and others) from 10 public universities in Malaysia. The sample size calculation was based on G*Power version 3.1.9.7.[10] The criteria used for sample size calculation are a medium effect size of 0.15,[11] a minimum level of power of 0.8,[12] a significance level of 0.05, and the number of variables was four. According to this G*Power software calculation, a minimum sample size of 85 participants is required for this study. A convenience sampling technique was used to select the lecturers.

DATA COLLECTION

The questionnaire was distributed as an online survey to all participants through Google Forms, with English being the language utilised. The rationale for choosing this method is its ease of use, efficiency in terms of respondent time, and widespread adoption as a platform for both data collection and management. The distribution occurred via email and communication platforms such as WhatsApp. The lecturers who have provided their agreement and consent to participate in the research will be responsible for responding to all inquiries.

The study evaluated the participants' level of resilience using an adopted tool, the Medical Professionals' Resilience Level (MeRS).[13] The questionnaire contained 37 items, divided into four domains: control, resourcefulness, involvement, and growth. All 37 items of the MeRS had content validity indexes (CVI) higher than 0.80, indicating a satisfactory level of content validity. To calculate the resilience score, a maximum score of four was assigned to each question, resulting in a total maximum score of 148 for all 37 items per respondent. A higher score on the MeRS indicates a stronger level of resilience, while a lower score suggests the opposite (Table I).

Table I: The total score for MeRS with a corresponding level of resilience competency*

MeRS domain (n item)	Level of resilience competency (total score)		
	Developing (low)	Established (moderate)	Exceptional (high)
Growth (15)	15-27	28-27	48-60
Control (12)	12-21	22-38	39-48
Involvement (6)	6-11	12-18	19-24
Resourceful (4)	4-7	8-12	13-16
Global score (37)	37-66	67-118	119-148

*Reproduced [13]

Sociodemographic details were collected to characterize our sample as well as to explore whether any relationships existed between them and resilience. These included gender, age, marital status, professional background, years of experience as an educator, and designation to an administration position.

Descriptive statistics were employed to provide an overview of the samples, and the normality of the data was assessed. The mean and standard deviation for the MeRS scores of the sample were calculated, along with the mean differences in the resilience level domain, as an indication of the respondents' resilience. Independent sample t-test, a one-way ANOVA, and a Pearson correlation were used to look into the link between the MeRS score and six socio-demographic variables. IBM SPSS Statistics for Windows Version 29.0 was used to conduct the statistical analyses.[14]

RESULTS

The invitations were sent to the medical and health science faculty lecturers of universities in Malaysia. Response rates ranged from 5 to 15 lecturers per university, depending on the institution's size. In this study, three out of four domains in MeRS received high scores while one domain (Involvement) showed a moderate score. As shown in Table II, the mean scores

for the following domains were as follows: growth domain was 53.72 ± 6.57, control (38.75 ± 6.71), involvement (18.49 ± 3.47), and resourceful (12.70 ± 2.61).

Table II: Descriptive statistics of resilience domain scores

	MeRS Score			
Resilience Domain	**Mean**	**Standard deviation**	**Minimum**	**Maximum**
Growth	53.72	6.57	21	60
Control	38.75	6.71	16	48
Involvement	18.49	3.47	8	24
Resourceful	12.70	2.61	4	16

The study involved a total of 127 participants. Most of the participants were women (n=87, 68.5%) with ages 40-49 (n=54, 42.5%). The majority of them were married (n=111, 87.4%), had a professional background as clinicians (n=55, 43.41%), and had 1–5 years of experience as educators (n-32, 25.2%). More than half of the participants had a position in administrative posts (n=64, 50.4%). The mean resilience score of the participants in the study was high (123.66 ± 16.70) (Table III).

Table III: Characteristic respondent and resilience score

Participants (N = 127)	**N (%)**	**Mean ± SD**	***p*-value**	**Post-hoc**
Gender				
Male	40 (31.5)	123.38 ± 17.85	0.896[a]	
Female	87 (68.5)	123.80 ± 16.25		
Age				
20-29	1 (0.8)	114.00 ± -	0.054[b]	
30-39	42 (33.1)	120.14 ± 17.66		
40-49	54 (42.5)	124.15 ± 16.48		
50-59	25 (19.7)	128.64 ± 15.20		
≥ 60	5 (3.9)	125.00 ± 17.03		
Marital Status				
Married	111(87.4)	123.64 ± 16.60	0.969[a]	
Other (widowed/divorced & single)	16 (12.6)	123.81 ± 17.90		
Professional Background				
Medical (Clinical)*	55 (43.31)	119.11 ± 18.31	0.018[c]	0.022*
Medical (Non/ pre-clinical)*	30 (23.62)	129.07 ± 13.77		
Others (Nursing, Pharmacy, Dental, Allied health)	42 (33.07)	125.76 ± 15.09		
Years of Experience as an Educator				
1-5	32 (25.2)	118.81 ± 17.38	0.077[b]	
6-10	29 (22.8)	125.10 ± 17.49		
11-15	24 (18.9)	124.92 ± 16.19		
16-20	26 (20.5)	122.92 ± 16.56		
> 20	16 (12.6)	130.06 ± 13.67		
Designation to Administrative Post				
Yes	63 (49.6)	123.21 ± 17.54	0.762[a]	
No	64 (50.4)	124.11 ± 15.96		
MeRS Total Score (n = 127), Mean = 123.66, Standard Deviation = 16.7				

Note: [a] Independent samples T-Test. [b] Pearson correlation, [c] One-way ANOVA test, $p<0.05$ taken as the level of significance. Normality and equal assumptions were met
*Tukey HSD test

The study discovered no significant difference in resilience level between gender, administrative roles, marital status, age, and years of experience as educators, as given by the *p*-values of 0.896, 0.762, 0.969, 0.054, and 0.077 respectively (Table III). However, it is worth noting that there was a significant difference in the resilience level for professional backgrounds (p= 0.018). The mean score for medical (clinical) background differed significantly from that for medical (non-pre-clinical) background, as determined by post hoc comparisons with the Tukey HSD test (p=0.022).

DISCUSSION

RESILIENCE LEVEL

This study was conducted based on the consideration of the lecturer's humanity to reach a quality standard of medical education which is rarely emphasized in conjunction with the current methodology employed in medical and health profession education. The study revealed that medical and health science lecturers in Malaysia exhibit a high level of resilience. Almost all domains of resilience were high among medical and health science lecturers, suggesting a well-rounded ability of the lecturers to navigate life's challenges, maintain well-being, and bounce back from adversity. This finding is consistent with other studies on medical educators in the United Kingdom in 2019 and a study conducted on faculty members at Malaysia's training institutes.[6,8]

Medical lecturers have numerous challenges in their employment within the field of medical education due to the intricate nature of the subject matter, the requirements of medical education, and the ever-changing healthcare environment. One of the difficulties is that medical lecturers are not only responsible for teaching in a classroom context but also for overseeing clinical teaching. This includes tasks such as organizing clinical placements, ensuring that students have enough opportunities to interact with patients, and creating valuable learning experiences in actual healthcare environments. In addition, they are required to engage in research, clinical practice, and administrative responsibilities. One potential reason for the strong resilience displayed by medical and health science

lecturers is their adeptness at handling the various challenges associated with teaching intricate subjects, managing a wide range of responsibilities, adapting to frequent changes in the medical field, and sustaining a sense of purpose in their positions.

Another crucial factor that influences the high level of lecturers' resilience is the association between coping strategies and level of education. People with lower educational attainment exhibit lower resilience and are more likely to use maladaptive coping mechanisms.[15] Prior studies suggest that higher levels of education are associated with higher resilience.[16,17] Typically, lecturers in the field of medical and health science in Malaysia are required to possess a minimum of a master's degree, with a significant number of them holding doctoral (PhD) degrees. However, it is crucial to recognize that one's level of educational achievement does not solely determine resilience. Personal characteristics, strategies for dealing with stress, past events, and sources of assistance from others also have important influences.

SOCIO-DEMOGRAPHIC

In our study, we found that gender, age, marital status, years of experience as educators, and administrative position did not influence the resilience level of lecturers. In relation to gender, this is consistent with a previous study conducted in the UK for medical educators[6] and also a study in the US for physicians,[18] despite using a different measurement instrument (CD-RISC-25), gender did not significantly impact the mean score. Such gender differences across studies vary among different populations and are inconsistent. Lecturers of different genders possess distinct talents, strengths, needs, and vulnerabilities, all of which might influence their resilience. Several studies have identified a greater level of resilience in men compared to women.[9,19,20] Some discovered that women exhibited greater resilience.[17] Nevertheless, both male and female lecturers face similar challenges related to teaching, research, professional development, and institutional dynamics. The academic environment's demands and stressors can affect individuals in comparable ways, regardless of gender.

No correlation was found between age and level of resilience. This finding aligns with studies in several Malaysia hospitals for healthcare workers,[9] Malaysia lecturers from training institutes,[8] and a study in Germany.[17] This finding highlight that among medical and health science lecturers in Malaysia, resilience tends to remain consistent regardless of age. One possible explanation for why there is no significant link between age and resilience in this study is due to a combination of individuals such as intrinsic motivation; driven by a passion for teaching and contributing to medical education, which can enhance resilience. Additionally, environmental and developmental factors may also play a role.

There was no significant difference found in the association between marital status and resilience. This conclusion aligns with findings from research carried out in the United Kingdom and the United States.[6,20] However, other studies have found that married people are more resilient than single or divorced people.[16,17] Social support from a spouse may help people overcome problems and grow. A study discovered that the loss of a spouse can decrease mental well-being but does not affect resilience.[17] The lack of a significant association between marital status and resilience in lecturers could be attributed to various factors that influence resilience. The presence of larger support systems beyond marriage partnerships often has a significant impact on resilience, such as supportive friendships, professional networks, including receiving the level of support from colleagues, and the satisfaction derived from professional accomplishments, as well as family relationships. These factors have the potential to outweigh the influence of married status alone.

Our study revealed no significant correlations between the level of resilience and the number of years of teaching experience. This finding is consistent with prior research.[6,8] The study's findings suggest that while years of teaching experience may increase resilience due to exposure and adaptability to the profession, this relationship may not be linear. Personal circumstances, occupational obstacles, and other factors can affect resilience over time.

There was no statistically significant difference regarding the designation of individuals to administrative positions. This finding is consistent with other studies undertaken.[8] The level of work satisfaction and sense of purpose that one feels at work can have a significant impact on their resilience. Some lecturers seek and succeed in administrative posts, harmonizing their professional ambitions. Finding their jobs personally enjoyable and meaningful may help them overcome problems. Others may prefer teaching and research, where resilience is more related to success.

An interesting finding of our study was that, although all lecturers exhibited high resilience levels, there was a significant difference between clinical and pre-clinical lecturers, with pre-clinical lecturers displaying higher resilience. This finding is consistent with another study that assessed the resilience of hospital-based doctors in clinical and pre-clinical departments, revealing that pre-clinical doctors demonstrate greater resilience compared to clinical doctors which is associated with more compassion satisfaction.[21] Resilience had a positive correlation with elevated levels of compassion satisfaction, reduced burnout, and an increased capacity to tolerate both general and clinical ambiguity. A study done in Malaysia examined the levels of burnout among clinical and non-clinical lecturers, where clinical lecturers reported significantly higher burnout compared to fellow non-clinical lecturers.[22] This study supports previous study's findings that clinical lecturers experienced a notable increase in burnout where the primary cause of this burnout was their involvement with administration, as they viewed administrative tasks to be the least important part of their work.[23,24] Even before the pandemic, clinical lecturers had been observed facing this issue.[25] During the COVID-19 pandemic, clinical lecturers faced challenges in delivering medical education and clinical teaching. This required them to acquire additional skills, put in more effort, and make greater commitments.[26] There is no significant difference in the level of resilience between medical lecturers (both clinical and non-clinical) and lecturers from other disciplines such as nursing, dentistry, pharmacy, or allied health.

LIMITATION

While the findings of this study provide valuable insights into the resilience among medical and health science lecturers in Malaysia, several limitations must be acknowledged regarding the generalizability of the results. First, due to the uncertain generalizability of convenience samples, the estimates obtained from such samples are frequently biased. This means that the sample estimates do not accurately reflect the true effects within the target population, as the sample poorly represents the target population. Second, utilising email (assuming that the email provided on the official university website is their most up-to-date official email address) and WhatsApp for data collection may not guarantee equitable gender representation. Although the survey is distributed to both genders, the rates at which they respond may vary. Hence, it is crucial to carefully assess the generality of the findings for all medical and health science lecturers in Malaysian educational institutions. Finally, this study has a cross-sectional design, providing a short-term perspective on a constantly changing phenomenon. Therefore, definitive conclusions about the cause-and-effect connection between each aspect cannot be drawn.

CONCLUSION

This study investigated the resilience of medical and health science lecturers at Malaysian higher institutions. The study found that lecturers exhibited a high level of resilience with individuals possessing non/pre-clinical backgrounds demonstrating higher resilience compared to those with clinical backgrounds. Meanwhile, the other group (Nursing, Pharmacy, Dental, and Allied Health) did not have significant differences compared to medical lecturers (clinical and non/pre-clinical). Moreover, socio-demographic parameters such as gender, age, marital status, years of experience as an educator, and designation of administration position didn't influence the level of resilience. Identifying less resilient groups and traits could help university management systems to have better support for lecturers. While this study might provide insights into policy-specific domains that require interventions, to ascertain the efficacy of solutions and

assess their impact on enhancing the resilience of lecturers, more extensive and interventional study is necessary.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Prevalence of Variations in the Anterior Communicating Artery Complex of the Circle of Willis: A CT Angiography Study in Malaysia

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ABSTRACT

INTRODUCTION: The anterior communicating artery complex (ACoA complex) within the circle of Willis, contributing to communicating arterial supply to the brain, exhibits significant anatomical diversity. Given the vulnerability of brain tissues to cell death resulting from poor blood supply, knowledge on this variability becomes crucial for diagnosing and managing diseases affecting the arterial supply to the brain. **MATERIALS AND METHODS:** A cross-sectional study was conducted to determine the prevalence and to give a description of these variations based on reconstructed CT angiographic (CTA) images. We included all individuals who underwent head CT angiography at a hospital in Kuantan, Pahang, Malaysia for various reasons between January 2009 and August 2015. A total of 81 CT angiographic images were analyzed for different variations, encompassing hypoplasia, aplasia, and duplication of the anterior communicating artery, as well as hypoplasia and aplasia of the A1 and A2 segments of the anterior cerebral artery, the A2 segments arising from a common trunk, and the third A2 segment. **RESULTS:** Ten distinct variation types were identified, with the typical pattern observed in 35.8% of cases. Vascular variations accounted for 64.2%, signifying a higher prevalence compared to previous studies. The cases presenting variations in the anterior communicating artery constituted 43.2%, with the aplasia being the most prevalent anatomical variation at 28.4%. **CONCLUSION:** The study highlights a higher prevalence of anatomical variations in the ACoA complex than the typical pattern.

Keywords
Anterior communicating artery complex, Circle of Willis, Computed tomography angiogram, Anatomical Variations, Cerebral circulation.

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INTRODUCTION

The brain relies on a continuous supply of blood to ensure a consistent supply of oxygen and nutrients.[1] Brain cells are highly dependent on a constant supply of oxygen and glucose due to their high metabolic rate and their lack of capacity to store oxygen or glucose. They are exceptionally vulnerable to insufficient oxygen, and the absence thereof can lead to rapid death of brain tissue within minutes. In situations where blood supply to one side of the brain is compromised, the establishment of an effective collateral blood supply from the contralateral side becomes essential. The Circle of Willis serves as a mechanism to facilitate this collateral supply.

Stroke is the second leading cause of death, with 1 in 4 people estimated to have a stroke in their lifetime.[1] Variations of intracranial vessels is one of the non-modifiable risk factors of stroke,[2] and are common in patients with ischaemic or haemorrhagic strokes.[3]

The anterior communicating artery complex consists of two anterior cerebral arteries (ACA), and an anterior communicating artery (ACoA). The ACA is divided into two parts. The proximal part is called the A1 segment, which is the pre-communicating segment, the part between its origin and ACoA, which usually passes over the optic nerve. The A2 segment of the ACA is the distal part of the anterior cerebral artery, starting from the anterior communicating artery to the junction between the rostrum and the genu of the corpus callosum.

ACoA complex is an area of high anatomical variability. The vessels in the circle of Willis showed high anatomical variability in both postmortem studies[4,5] and imaging studies.[6] Variations in cerebral arteries can be effectively detected by multi-detector CT angiographic study.[7] The anterior communicating artery is regarded as a common location of aneurysms.[8] There is a significant association between the incidence of aneurysms and the circle of Willis anatomical variations in some studies.[9,10] This study aimed to determine the prevalence and to give a description of these variations based on reconstructed CT angiographic (CTA) images.

MATERIALS AND METHODS

This is a retrospective study observing the arterial variations of the anterior communicating artery complex in reconstructed CT angiographic images. The International Islamic University Malaysia Research Ethics Committee (IREC) approved the study and the National Medical Research Registry registration number is (NMRR ID: NMRR-15-2101-27218).

SAMPLES

The study population comprised patients who underwent CTA (head) for various reasons in Hospital Tengku Ampuan Afzan (HTAA) from January, 2009 to August, 2015. The nonionic iodinated contrast materials used were Iopamiro [(Iopamidol, 300); Bracco Dexxon Ltd, Ferentino, Italy] injected at a rate of 3 mL/s (for cases done before 2014) and Omnipaque, [(Iohexol 370); GE Healthcare Inc., Princeton, NJ] injected at a rate of 5 mL/s (for cases done in 2014 onwards) with the use of a power injector (Medrad, Pittsburgh, PA) and an 18- or 20- gauge needle inserted in the antecubital vein. The volume of iodinated contrast material in each case was typically 90 to 100 mL. According to literature, the prevalence of anatomical variants in the anterior communicating artery complex ranges from 26-95.2%.[11,12,13,14] Assuming the expected prevalence of 30%, and the confidence limit (the precision) of 10%, by using the formula for sample size, n = [DEFF*Np(1-p)]/ [(d2/ Z21-α/2*(N-1)+p*(1-p)] from OpenEpi, version 3,[15] (p: the expected prevalence, d: the precision, alpha: the type 1 error and DEFF (design effect) as 1, with infinite population, and 95% confidence level), the sample size calculated was 81. Anticipating the rejection rate of images as 20%, the number of samples required was 97 (81+16).

DATA COLLECTION

A total of 112 cases for CT angiography of the cerebral vessels performed in HTAA from 1st January 2009 to 31st December 2015 were traced from Radiology Information System (RIS). The images were retrieved from Picture Archiving and Communication System (PACS), saved in Digital Imaging and Communication in Medicine (DICOM) format and transferred to iMAc for reconstruction using OsiriX software by using preset volume-rendered and maximum intensity projection display algorithms. Subsequently, the images were manipulated in any projections with varying amounts of time needed for review. Images degraded by motion or metallic artefacts, and images from diseases that obscure or significantly distorted the vascular anatomy were excluded from the study (Fig. 1). The number of images which could be retrieved for assessment was 81.

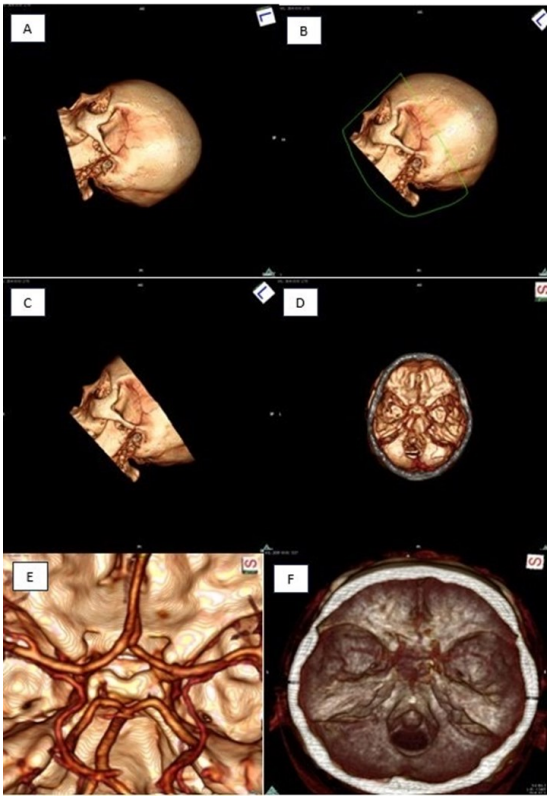

Figure (1). A: The 3D image after reconstruction. B: The direction of cutting the image. C: The image obtained after cutting. D: The image rotated to visualize the circle of Willis. E: An example of the zoomed image. F: An example of excluded images of the suboptimal CTA due to poor contrast.

CT Scanners

Multi-section CT angiograms were obtained with two different CT scanners. The cases before 2014 were performed using a 4-slice CT scanner (Somatom Volume Zoom CT scanner, Siemens Medical Systems, Forchheim, Germany). The cases done in 2014 onward used a 256 multi-row detector CT scanner (Somatom Definition Flash, dual source CT scanner; Siemens Medical Systems, Forchheim, Germany).

ASSESSMENT

Two independent radiologists validated and finalized the assessment of types of variations for every step. The source images and multi-planar reformations also were reviewed on the workstations by the radiologist. The selected images were reviewed for any type of variation in the anterior communicating artery complex and no interobserver difference was noted.

The 3D images generated by 3D reconstruction were cut, and orientated to get a view of the intracranial fossa of the skull, and zoomed in to visualize the circle of Willis (Fig. 1). The contrast was adjusted to get the best reconstructed image. The presence or absence of the anterior communicating artery, the common trunk of anterior cerebral arteries with the absence of the anterior communicating artery, the second anterior communicating artery, the A1 and A2 segments of right and left anterior cerebral arteries, and the presence of the third A2 segment of the anterior cerebral artery were observed in each case. The minimum and maximum diameters of each found artery in the anterior communicating artery complex were measured. A vessel with a maximal diameter of less than 1mm was regarded as hypoplasia. The radiologists reviewed the source images and multi-planar reformations on the workstations. A biostatistician analysed the outcomes by descriptive statistics. The types of variations were classified as illustrated in Fig. 2 (A).

RESULTS

The age of the subjects ranged from 11 to 87 years old of which the majority (78%) were 31 to 70 years old and 42% of the total cases were male. No statistical significance was noted in comparing the percentages of having variations in male and female subjects (Table I). The typical pattern, type 1 (Fig. 2B), of the anterior communicating artery complex was seen in 29 out of 81 cases, accounting for 35.8% (Fig.3). The prevalence of variations is shown in Table II. Among the variations, ACoA aplasia is the commonest type (Fig. 2C), while A1 segment aplasia is the second commonest (Fig. 2D). The third commonest variant which was found in 10 cases, accounting for 12.3%, is the duplication of ACoA (Fig. 2E). The MACC or the third A2 segment was found in 1 case (Fig. 2F).

Table I: Proportion of cases with the typical pattern in male and female subjects

	Male		Female		P value
	N	%	N	%	
Type 1	11	32.4	18	38.3	0.582[a]
Other Types	23	67.6	29	61.7	
Total	34	100	47	100	

Note. a = Pearson Chi-Square

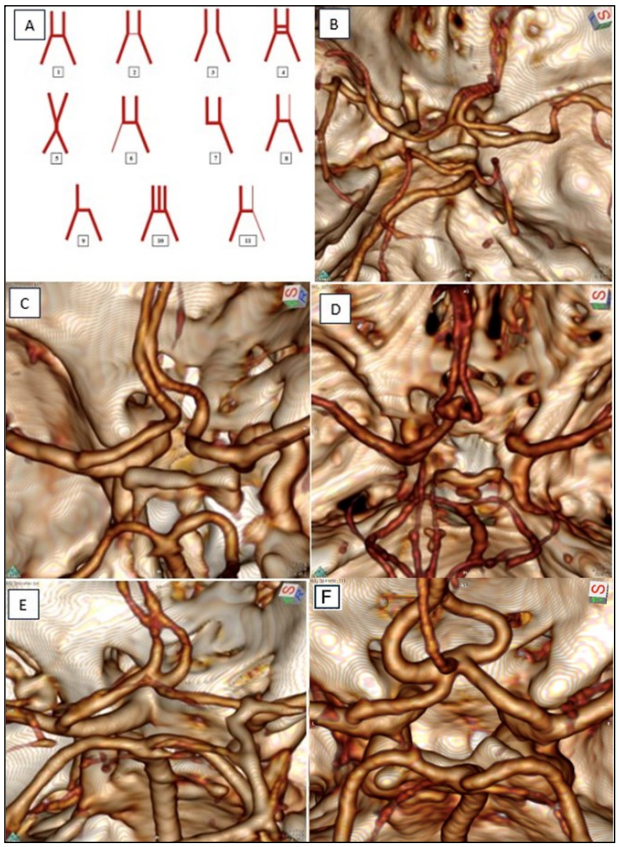

Figure (2). The anterior communicating artery complex (ACoA complex) of the circle of Willis. A. Variations in the anterior communicating artery complex. B. The typical pattern of the anterior communicating artery complex. C. Aplasia of the anterior communicating artery. D. Aplasia of the A1 segment E. Duplication of the anterior communicating artery F. Median artery of the corpus callosum or 3rd A2 segment.

Table II: Prevalence of the types of variations in the anterior communicating artery complex

Type	n	%	95% CI
1. (Typical pattern)	29	35.8	25.4, 46.2
2. (ACoA Hypoplasia)	3	3.7	-0.4, 7.8
3. (ACoA Aplasia)	23	28.4	18.6, 38.2
4. (ACoA Duplication)	10	12.3	5.2, 19.5
5. (Common trunk of ACA with no ACoA)	1	1.2	-1.2, 3.6
6. (A1 Hypoplasia)	1	1.2	-1.2, 3.6
7. (A1 Aplasia)	14	17.3	9.1, 25.6
8. (A2 Hypoplasia)	0	0	-
9. (Unilateral Aplasia of A2)	0	0	-
10. (MACC)	1	1.2	-1.2, 3.6
11. (Unilateral hypoplasia of A1 and A2)	0	0	-

Note. ACA = The anterior cerebral artery; MACC = The median artery of the corpus callosum

DISCUSSION

In this study, about two-thirds of the cases showed variations in the anterior communicating artery complex (Fig. 3). The percentage of cases having variations was 64.2%, which is the highest compared to previous different studies in different countries as stated in Table III. Further elaboration such as determining the association between the aneurysm and the variation is needed to discuss why the prevalence in this study was found to be higher than reported in other publications. Each of 62.4% of the cases in this study had one type of variation, and none of the cases had more than one type of variation. Types of variations found and their percentages are shown in Table II.

Table III: Percentages of variations in the anterior communicating artery complex in different studies

Country	Method	Percentage of variations
Serbia[16]	MRA	11.3%
Iran[17]	MRA	19.05%
India[13]	Autopsy	31.3%
Taiwan[18]	MRA	32.74%
Poland[19]	CTA	52.8%
Present study	CTA	62.4%

Note. MRA = Magnetic resonance imaging. 3D TOF MRA = Three-dimensional time-of-flight magnetic resonance angiography. CTA = Computed tomography angiography.

In this study, the most common type of anatomical variation in anterior communicating artery complex, as well as the most common variant of anterior communicating artery (ACoA), was ACoA aplasia (Fig. 2C, Table II). Absence or fenestration of ACoA has also been found to be the commonest variation (12 to 21%) in the anterior communicating artery complex in other studies.[20] The anterior communicating artery plays a crucial role in supplying blood to the side in need. This finding of the high prevalence of ACoA aplasia is important to be noted for surgeons since collateral supply from the other side can be inadequate in cases of anatomical variants such as ACoA aplasia.

CONCLUSION

It is important to note that the types and prevalence of anatomical variations in human as the knowledge of different variants is important for surgeons, physicians, and for radiologists in providing differential diagnosis, and in management of diseases. In addition, variations such as hypoplasia and aplasia can cause reduced blood supply to the supplied area of the brain. The anterior communicating artery complex (ACoA complex) of the circle of Willis is an area with great anatomical diversity, and it forms part of the communicating arterial supply to the brain. As brain tissues are susceptible to cell death due to insufficient blood supply, knowledge on this variability is important in diagnosis and management of any diseases that affect brain circulation, and can be useful to avoid accidental trauma to the vessels during surgeries4.

FUTURE RECOMMENDATION

This study has shown that the prevalence of anatomical variations in the anterior communicating artery complex is high probably because the sample were the CTA images of patients with pathology. There can probably be the difference of this figure in different populations. Studies should be done to define hypoplasia, and to describe if there is any difference in defining hypoplasia between the autopsy and imaging studies.

LIMITATIONS OF THIS STUDY

This research collected and analysed data from patients in whom CTA was done as part of investigation and management. Therefore, if the outcome representing the general population is needed, the healthy subjects have to be included.

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ORIGINAL ARTICLE

Hypolipidaemic and Cardioprotective Effects of Bee Bread Harvested from Stingless Bee (*Heterotrigona itama*) in High-Fat Diet-Induced Obese Animal Model

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Keywords
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ABSTRACT

INTRODUCTION: Bee bread has reached its research interest because of its high antioxidant and nutritional values. Our study aimed to characterize hypolipidaemic and cardioprotective effects of high-fat (F) diet-induced obese rats co-administered with bee bread. **MATERIALS AND METHODS:** Male Sprague-Dawley rats were randomly assigned as N group (rats fed with normal diet), F group (rats fed with F diet), FB group (rats fed with F diet and 0.5 g/kg/day bee bread), and FO group (rats fed with F diet and 10 mg/kg/day orlistat for 6 weeks). **RESULTS:** The FB group significantly had decreased levels of Lee obesity index, total fat pad, total cholesterol and low-density lipoprotein, and significantly had increased cardiac superoxide dismutase, glutathione peroxidase and catalase activities compared to the F group. Furthermore, the FB group demonstrated significant decreases in the levels of cardiac lipid peroxidation marker and fatty acid synthase activity with improvement in histological findings of heart and adipose tissues. **CONCLUSION:** These findings suggested that bee bread exerted hypolipidaemic and cardioprotective effects owing to its modulatory action on *de novo* synthesis of fatty acid.

INTRODUCTION

Obesity has gained primary attention among healthcare professionals as it complicates serious health issues. More than 115 million people had obesity-related conditions that were linked to cardiovascular disease (CVD), stroke, diabetes mellitus, and certain types of cancer.[1] Obesity appears to be left untreated in some individuals probably due to lack of awareness and safety issues related to medication.[2] Prolonged high-fat diet consumption promotes detrimental effects on metabolic health due to the risk of development of oxidative stress, redox imbalance, lipid dysregulation, and pro-inflammatory cytokines.[3] Inhibition of fatty acid synthase (FAS) has been shown to promote weight loss and a positive therapeutic approach against hyperlipidaemia.[4] Although excess adipose tissue accumulation is clearly described as the determinant of obesity, there is still a lack of scientific evidence supporting the treatments or interventions to reduce the accumulation of adipose tissue.

Major attention has been spared on the naturally derived products, which have a high potential to directly modulate the antioxidant defense system and a cascade of lipid metabolism. Stingless bee *Heterotrigona itama* (*H. itama*) produces bee bread from a combination of bee pollen, bee's digestive enzyme, and honey. It is stored in the bee comb or pot, allowing for a fermentation process that catalyses the metabolic content into active bio-ingredients.[5] It is rich in antioxidant activity and contains multinutrients, including carbohydrates, fats, proteins, minerals, and vitamins.[6,7,8,9] Multibiological activities of bee bread have been reported such as antibacterial,[10] anticancer,[11] and hepatoprotective properties.[12] However, there is still a lack of scientific-based evidence focusing on bee bread specifically to define its role in obesity and its related cardiovascular complications. To date, no study has been conducted on the cardioprotective effects of bee bread and its potential benefits towards oxidative stress

and lipid metabolism. This study intended to determine the possible hypolipidemic and cardioprotective effects of bee bread in high-fat diet (F)-induced obese rats by evaluating the levels of Lee obesity and adiposity indexes, serum lipid profile, cardiac oxidant/antioxidant status, total fat pad (TFP), FAS, as well as the changes on histology of heart and adipose tissues.

MATERIALS AND METHODS

Preparation of bee bread

Bee bread sample harvested from *H. itama* was acquired from a local beekeeper farm, Mentari Technobee PLT, Kelantan, Malaysia. The received fresh sample was dried in a laboratory dehydrator at 35 °C for 2-3 hours until a consistent weight was reached. The dried bee bread was kept frozen at –21 °C, and it was blended into powder form.

Animals and diets

Thirty-two male *Sprague-Dawley* rats aged 8-10 weeks with weights ranging from 180-230 g were obtained from the Animal Research and Service Centre (ARASC), Universiti Sains Malaysia, Kelantan. The animals were acclimatised for a week with food and water *ad libitum*. They were housed in a well-controlled room adapted to a ventilation setting of 22-24 °C, humidity setting of 52-54%, and maintained under a 12-hour light/dark cycle. The experimental protocol was approved by Animal Ethics [USM/Animal Ethics Approval/ 2016/ (98) (744)] and conformed to the Guidelines for the Care and Use of Laboratory Animals by the National Institute of Health.

Normal chow consisted of Altromin pellet (Altromin Spezialfutter GmbH & Co. KG, Lage) (P1324) imported from Germany. A high-fat (F) diet with 31% fat was used to induce a rapid increase in adipose tissue accumulation. It was freshly prepared and modified from the previous study.[13] It consisted of 64 g ground normal chow pellet, 32 g animal ghee, 300 mg calcium and 100UI vitamin D, and 12% of cholesterol powder. The regular chow diet consisted of 64% carbohydrate, 12% fat, and 24% protein (318.8 kcal/100 g), whereas the F diet had 46% carbohydrate, 31% fat, and 12% protein (516.5 kcal/ 100 g). Our preliminary study has shown that rats that received F diet for 6 weeks had higher Lee obesity index and fat adiposity index in comparison to rats that received a normal chow diet showing that this F diet could induce obesity in rats (unpublished data).

Experimental design

In the present study, four groups of animals (n=8/group) were randomly assigned as N group (rats fed with normal diet), F group (rats fed with F diet), FB group (rats fed with F diet and 0.5g/kg/day bee bread), and FO group (rats fed with F diet and 10 mg/kg/day orlistat for 6 weeks). The daily dosage of orlistat used in the present study was consistent with the earlier study.[14] The dose of bee bread was based on our preliminary dose study in which rats that received F diet+0.5g/kg/day bee bread had decreased Lee obesity index, total cholesterol (TC), triglyceride (TG) and low-density lipoprotein (LDL) in comparison with rats that received F diet only, F diet+1.0 mg/kg/day bee bread and F diet+1.5mg/kg/day bee bread for 6 weeks (unpublished data). The doses of bee bread and orlistat were determined based on the rat's body weight and separately suspended in distilled water to make the end suspension volume of 1 mL. Bee bread and orlistat were administered via oral gavage for 6 weeks on a daily basis (8.00 to 9.00 am). After 6 weeks, all rats were anesthetised with intraperitoneal injections of 90 mg/kg ketamine and 5mg/kg xylazine. The thoracic and abdominal cavities of the rats were explored. Blood was obtained from the posterior vena cava. The heart was transversely cut at the base of the aortic and pulmonary branches.

Measurement of anthropometrical and nutritional parameters

The body weight and food consumption of rats were measured daily. Obesity was considered when the Lee obesity index rises beyond the level of 315.[15] The Lee obesity index was calculated using the formula below:

$$\text{Lee obesity index} = \frac{\sqrt[3]{Body\ weight\ (g)}}{\text{Nasoanal length(cm)}} \times 1000$$

Measurement of serum lipid profile

Blood was centrifuged (10 min, 4000 rpm) and allowed to coagulate for two hours. The supernatant was collected, aliquoted, and kept at –80 °C for the next analysis. The TC and TG levels were determined by enzyme-linked immunoassay using available commercial kits (ARCHITECT-c Cholesterol and Triglyceride Reagent, Abbott, USA). The high-density lipoprotein (HDL) level was ascertained using the Biosino Direct HDL reagent kit (Biosino Bio-Technology and Science Inc, Beijing, China). The formula used to calculate LDL was described as follows;[16]

$$\text{LDL}\left(\frac{\text{mmol}}{\text{L}}\right) = Total\ cholesterol - HDL - \frac{Triglyceride}{5}$$

Biochemical measurement

Dissected heart was carefully separated from adjacent blood and fat, and washed with ice-cold normal saline. The heart was weighed and homogenized (15 min, 4 000 rpm) in cold phosphate buffer solution (10% w:v). The obtained supernatant was aliquoted for the measurement of cardiac antioxidant enzymes and malondialdehyde (MDA) as well as FAS. Enzymatic activities of cardiac superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) were analyzed using commercially available kits from Bioassay (San Francisco, CA, USA). Commercial kits from Northwest (Vancouver, WA, USA) and Cloud-Clone (Houstan, TX, USA) were used to measure cardiac MDA level and FAS activity, respectively. The protein level was determined by the Lowry method, which was used to standardise all the results.[17]

Fat pad and adiposity index measurement

Subcutaneous fat was removed from the abdominal and epididymal regions. The total of these regional fats was used to calculate the total fat pad (TFP). The following formula was used to calculate the adiposity index: AI= (total fat pad/final body weight) × 100.

Histology of heart and adipose tissue

The heart and adipose tissues were preserved in 10% formalin. The tissues were submerged in various ethanol concentrations before being embedded into paraffin blocks. The blocks were sectioned at 5 μm and stained with haematoxylin-eosin. Slides were examined under a light microscope at ×100 magnification. The mean surface area of the adipose tissue was determined from 10 adipocyte cells per section using Image J software (ImageJ, NIH-Bethesda, MD, USA).

Statistical analysis

One-way analysis of variance (ANOVA) was used to determine the statistical differences, and post-hoc Tukey test was used to analyse the multiple comparisons. All the results were analysed using Statistical Package for Social Science (SPSS) version 24.0. and were reported as means, and standard deviations. The P values were considered statistically significant if the values were less than 0.05.

RESULTS

Effects of bee bread on anthropometrical and nutritional parameters

The baseline body weight was almost similar in all the experimental groups. After 6 weeks of the experimental period, the F group showed a significant increase in Lee obesity index in comparison to the N group. Whereas the group supplemented with bee bread showed a significant decline in Lee obesity index in comparison to the F group. There was no discernible variation in the amount of food consumed across all the experimental groups. Additionally, the F, FB, and FO rats consumed more calories than the rats in the N group (Table 1).

Effects of bee bread on lipid profile

The TC and LDL levels were significantly increased in the F group in comparison to the N group. These lipid fractions were significantly decreased in the FB group in comparison to the F group. The LDL level in the FO group was significantly lower compared to the F group. In contrast, the TG and HDL levels did not significantly differ across any of the experimental groups (Figure 1).

Table 1: Effect of bee bread on anthropometrical and nutritional parameters.

Parameters	N	F	FB	FO
Baseline body weight (g)	202.03 (24.34)	229.69 (23.10)	229.88 (22.24)	237.71 (22.81)
Final body weight (g)	322.05 (42.96)	347.55 (26.26)	335.19 (26.74)	355.35 (26.74)
Body weight gain (g)	110.23 (38.38)	120.90 (20.52)	99.54 (31.49)	105.13 (19.70)
Lee obesity index	312.59 (5.28)	336.35 (12.75)[a]	317.84 (7.68)[b]	322.50 (12.95)
Food intake (g/day)	20.32 (3.23)	18.09 (1.47)	18.86 (2.54)	20.78 (1.00)
Calorie intake (Kcal/day)	56.61 (6.57)	93.18 (7.57)[a]	97.14 (13.10)[a]	107.02 (5.14)[a,b]

Data are presented in mean (standard deviation), *n*=8 per group. N; normal, F; high-fat diet, FB; high-fat diet and bee bread at 0.5 g/kg/day, FO; high-fat diet and orlistat at 10 mg/kg/day. [a] P<0.05 compared with the normal group, [b] P<0.05 compared with the F group. Data was analysed using One-way ANOVA followed by Tukey post-hoc test.

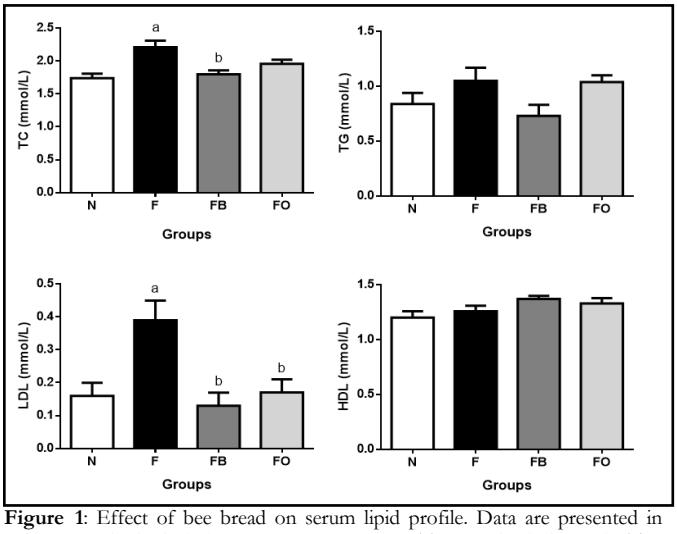

Figure 1: Effect of bee bread on serum lipid profile. Data are presented in mean (standard deviation), n=8 per group. TC; total cholesterol, TG; triglyceride, LDL; low-density lipoprotein, HDL; high-density lipoprotein. N; normal, F; high-fat diet; FB; high-fat diet and bee bread at 0.5g/kg/day, FO; high-fat diet and orlistat at 10 mg/kg/day. [a] P<0.05 compared with the normal group, [b] P<0.05 compared with the F group. Data was analysed using One-way ANOVA followed by Tukey post-hoc test.

Effects of bee bread on the levels of cardiac oxidant/ antioxidant status and fatty acid synthase

There was a significant increase in cardiac MDA level of the F group compared to the N group. Among the supplemented groups, the FB group showed a significant decrease in cardiac MDA level, whereas, in the FO group, the cardiac MDA level showed no significant change when compared to the F group. Cardiac SOD activity was significantly decreased in the F group compared to the N group. The activities of cardiac CAT and GPx showed no differences in the F group when compared to the N group. The FB group improved these antioxidant enzyme activities, as evidenced by significant increases in cardiac SOD, GPx, and CAT activities when compared to the F group. The FAS activity was significantly increased in the F group compared to the N group, and the level was significantly decreased in the FB group when compared to the F group (Table 2).

Table 2: Effects of bee bread on cardiac oxidant/antioxidants status and fatty acid synthase activity.

Parameters	N	F	FB	FO
Malondialdehyde (nmol/mg protein)	0.09 (0.01)	0.12 (0.03)[a]	0.09 (0.01)[b]	0.11 (0.03)
Superoxide dismutase (U/mg protein)	4.79 (1.40)	2.97 (0.63)[a]	4.19 (0.89)[b]	4.79 (0.92)[b]
Catalase (U/mg protein)	0.97 (0.25)	0.72 (0.30)	1.17 (0.31)[b]	0.83 (0.28)
Glutathione peroxidase (U/mg protein)	440.40 (14.62)	431.11 (3.53)	583.57 (20.39)[a,b]	566.79 (17.48)[a,b]
Fatty acid synthase (pg/ml)	509.80 (137.95)	954.66 (393.78)[a]	524.92 (279.53)[b]	716.09 (370.65)

Data are presented in mean (standard deviation), *n*=8 per group. N; normal, F; high-fat diet; FB; high-fat diet and bee bread at 0.5 g/kg/day, FO; high-fat diet and orlistat at 10 mg/kg/day. [a] P < 0.05 compared with the normal group, [b] P < 0.05 compared with the F group. Data was analysed using One-way ANOVA followed by Tukey post-hoc test.

Effects of bee bread on total fat pad and adiposity index

The F group exhibited significant increases in abdominal fat, TFP, and adiposity index when compared to the N group. In comparison to the F group, the weight of epididymal fat was significantly lower in the FB group. Conversely, the TFP was significantly lower in the FB and FO groups in comparison to the F group. In addition, all groups that received the F diet had a significantly higher adiposity index in comparison to the N group (Table 3).

Table 3: Effects of bee bread on total fat pad and adiposity index.

Parameters	N	F	FB	FO
Abdominal fat (g)	3.31(1.54)	8.48(3.9)[a]	5.77(1.72)	6.18(1.46)
Epididymal fat (g)	3.32(0.92)	5.15(0.57)	2.97(1.28)[b]	3.89(1.29)
Total fat pad(g)	7.63(1.35)	13.63(3.87)[a]	8.74(2.37)[b]	10.07(1.30)[b]
Adiposity index	1.93(0.78)	3.66(1.47)[a]	3.35(0.88)[a]	3.20(0.60)[a]

Data are presented in mean (standard deviation), n=8 per group. N; normal, F; high-fat diet; FB; high-fat diet and bee bread at 0.5 g/kg/day, FO; high-fat diet and orlistat at 10 mg/kg/day. [a] P<0.05 compared with the normal group, [b] P<0.05 compared with the F group. Data was analysed using One-way ANOVA followed by Tukey post-hoc test.

Effects of bee bread on the histology of heart and adipose tissue

The N group exhibited a structurally arranged and well-organized pattern of the cardiac fibers. Whereas the F group demonstrated the presence of necrotic patches encircled by inflammatory cells, lipid droplets, and foam cells. The cardiac fibers in the FB and FO groups showed the presence of small cholesterol cleft in between cardiac fibers, with the absence of necrotic patches in these groups (Figure 2). Figure 3 depicts normal size and organization of adipose tissue in the N group, along with the appearance of a signet ring characterised by a thin rim of cytoplasm with the nucleus at the cell edge. The adipocyte size was larger in the F group in comparison to the N group and smaller in the FB and FO groups in comparison to the F group. Significant findings were similarly found for the mean adipocyte surface area among the groups (Table 4).

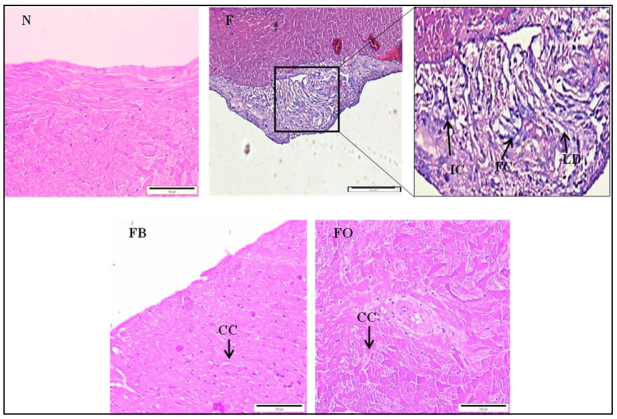

Figure 2: Histology of myocardial tissue in all groups. The N group shows a normal appearance of myocardium fibers with no pathological changes. The F group shows the presence of a necrotic patch, which consists of foam cells (FC), inflammatory cells (IC), and lipid droplets (LD) (black arrow). The dark blue staining indicates the inflammatory cells that infiltrate surrounding the necrotic area. The FB and FO groups show the presence of minimal cholesterol cleft (CC) in between the myocardium fibers. N; normal, F; high-fat diet, FB; high-fat diet and bee bread at 0.5 g/kg/day, FO; high-fat diet and orlistat at 10 mg/kg/day. (Haematoxylin and Eosin staining, magnification ×100, scale bar=100 µm).

Table 4: Effects of bee bread on surface area of adipocyte.

Parameters	N	F	FB	FO
Surface area ($\times 10^{-8}$ mm^2)	0.29 (0.09)	1.92(0.24)[a]	0.57(0.21)[a,b]	0.69(0.12)[a,b]

Data are presented in mean (standard deviation), *n*=8 per group. N; normal, F; high-fat diet; FB; high-fat diet and bee bread at 0.5 g/kg/day, FO; high-fat diet and orlistat at 10 mg/kg/day. [a] P<0.05 compared with the normal group, [b] P < 0.05 compared with the F group. Data was analysed using One-way ANOVA followed by Tukey post-hoc test.

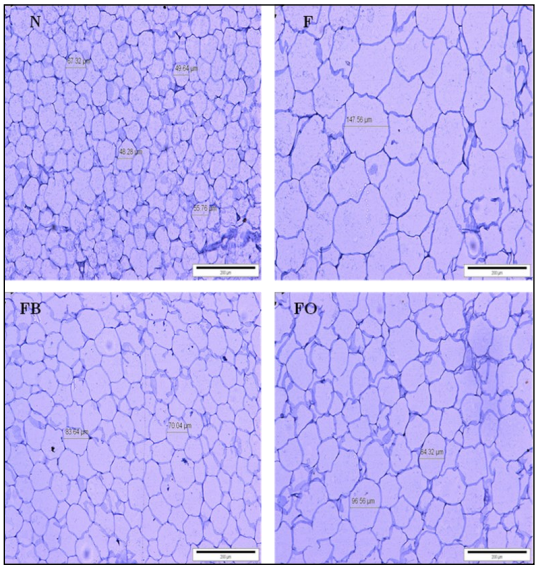

Figure 3: Photomicrograph of adipose tissue in all groups. The N group shows normal signet ring appearance of adipocyte cells. The F group shows larger adipocyte cell size. The FB and FO groups show smaller adipocyte cell size compared to the F group. N; Normal, F; high-fat diet, FB; high-fat diet and bee bread at 0.5 g/kg/day, FO; high-fat diet and orlistat at 10 mg/kg/day. (Haematoxylin and Eosin staining, Magnification = ×200, Scale bar = 200 µm).

DISCUSSION

Obesity-related cardiovascular complications such as hypertension and atherosclerosis have been implicated in the highest death rate. [18] Our study aimed to assess the hypolipidaemic and cardioprotective effects of bee bread harvested from stingless bees (*H.itama*) in high-fat diet-induced obese rats. Obesity was confirmed to be successfully established as the calculated Lee obesity index had exceeded the value of 315, reflecting a high level of body fat.[15] Our finding indicated that the Lee obesity index increased significantly in the F group compared to the N group, which was consistent with the earlier study's findings.[19] Meanwhile, the FB group demonstrated an improvement in the Lee obesity index as evidenced by a significant decline in this index when compared to the F group, and this finding was not observed in the FO group. This might indicate that bee bread had a greater ability to reduce fat buildup in comparison to orlistat. The amount of food consumed by each experimental group did not significantly vary. This might indicate that the supplementation of bee bread and orlistat did not interfere with or suppress the feeding. The present study showed a significantly higher calorie intake found in groups that received F diet (F, FB, and FO groups) in comparison to the N group. This finding might imply that

the F diet, containing 31% of total fat energy, had contributed to excessively generated energy in these groups. This, in turn, raised the need to accommodate the surplus of lipids, which in turn caused a rise in the number or size of adipocyte cells.

Hypercholesterolaemia is defined as an elevated level of cholesterol, and it is the commonest risk factor for the progression of CVD.[18] The risk of death implicated by CVD could potentially be decreased by lowering the level of circulating cholesterols. Our finding demonstrated that the F group had significantly higher levels of TC and LDL when compared to the N group. High dietary fat consumption has been found to increase the concentration of circulated free fatty acids and their uptake by hepatocytes, leading to increased TG and very low-density lipoprotein (VLDL) production.[20] The elevated amount of LDL seen in the F group of the present study might be explained by the excess VLDL in plasma, which in turn increased the catabolism of fat into LDL- and intermediate-density lipoprotein.[20] The isolated elevation of TC concentration found in the F group might also be associated with the elevation of LDL.[21] Interestingly, the FB group showed significantly lower TC and LDL levels compared to the F group, indicating that bee bread possesses hypolipidaemic property. The circulating LDL is shown to majorly contribute to the early onset of CVD, due to its strong atherogenic property. Hence, administration of bee bread and orlistat for 6 weeks in F diet-induced obese rats was able to reduce the elevated atherogenic LDL- level as a significant reduction of LDL level was found in FB and FO groups in comparison with the F group.

Obesity-related hypercholesterolaemia is thought to be a key amplifier for developing cardiac failure due to adverse cardiac remodeling, which leads to worse health outcomes.[22] Lipid peroxidation has been evoked by an increase in fat storage and circulating fatty acids. It can react with an oxygen molecule to produce a highly radical, unstable form of fatty acid.[23] Lipid peroxidation signifies an increment in the MDA level, one of the crucial markers for ROS. In the present study, the cardiac MDA level in the F group was significantly increased, with a concomitant decrease in cardiac SOD activity when compared to the N group. A significant decrease in cardiac SOD in the F group could be due to its increased utilization in scavenging free radicals or due to the destruction of the primary antioxidant system by ROS. The mismatch between oxidant and antioxidant status might also account for the development of a necrotic patch area observed in the myocardium of the F group, which was associated with the infiltration of the inflammatory cells. This could be explained by the oxidative stress environment, which could cause cellular function and structure changes, leading to cellular lipid membrane disruption.[24] Obesity-related cardiac necrosis in the present study was related to the accumulation of TC and LDL in non-adipose tissues or cells such as myocardial cells. These accumulated lipids might be transported by the fatty acid transporter proteins such as FAT/CD36, fatty acid transport proteins 1,4, and 6.[25] Our study found that bee bread might have the greater potentiality to combat lipid peroxidation or oxidative stress compared to orlistat as indicated by a significant decrease in the cardiac MDA level in the FB group. This finding was associated with significant increases in cardiac SOD, CAT, and GPx activities demonstrated in the FB group, suggesting a suppression effect of antioxidant enzymes against oxidative stress. These results could account for the improvement in the myocardium histology in the FB group, in which only minor cholesterol clefts were observed. These findings might also indicate that bee bread not only reduced TC and LDL levels by its anti-hypercholesterolaemic effect but also improved cardiac antioxidant status and decreased lipid peroxidation, thus sparing the cardiac tissue from further damage, which was comparable to orlistat.

A high level of adiposity index corresponds to increased fat accumulation.[26] This is further supported by a significant increase in TFP value concomitant to the significant increases in size and surface area of the adipocyte in the F group compared to the N group. The present study indicated that the abdominal fat was the major site for fat deposition in comparison to epididymal fat, which was remarkably increased in the F group. Significant reductions were also seen in the TFP value and

adipocyte size in the FB and FO groups, which might indicate that bee bread and orlistat could dampen the development of large adipocytes in rats fed with the F diet. The FAS catalyses the synthesis of fat by mediating the creation of *de novo* saturated long-chain fatty acids, which are the final byproduct of acetyl and malonyl-CoA.[27] In the present study, cardiac FAS was found to be significantly elevated in the F group with respect to the N group, which could be responsible for its high levels of TC, LDL, TFP and adiposity index, with concomitant larger size and surface area of adipocyte cell. The finding was consistent with the previous study, in which cardiac FAS activity was responsible for the increased TC and TG concentrations as well as the deposition of cardiac lipid in Oil-Red O-stained sections following the increased de novo long-chain fatty acids synthesis in the cardiac cells in mice fed with high-fat diet.[28] In contrast, a significant decrease in FAS activity was found in the FB group, which could explain for the lower levels of TC and LDL, and the reduced size and surface area of adipocytes that were comparable to the FO group. Therefore, in the present study, it is plausible to suggest that one of the contributing factors in lipid metabolism changes is due to the presence of the bioactive compounds in bee bread which might have an inhibitory effect against FAS. However, future study is needed to precisely determine the presence of its bioactive compounds as well as its effect on lypolytic enzyme activity.

CONCLUSIONS

Administration of bee bread at 0.5 g/kg/day for 6 weeks significantly improved the Lee obesity index, total fat pad, lipid profile, cardiac oxidant/antioxidant status as well as histology of heart and adipose tissues in F diet-induced obese rats. These findings might be related to the hypolipidaemic and cardioprotective effects of bee bread, probably due to its modulatory activity on FAS, which demands future study to determine its exact molecular mechanism of action.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Challenges in Providing Spiritual Care among Healthcare Workers: A Qualitative Study

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ABSTRACT

INTRODUCTION: Spiritual care has been identified as an integral component of holistic, culturally competent, and empathetic care. Although spiritual care offers tremendous benefits for patients, it can be challenging to implement. Despite its importance, there is a lack of literature in Malaysia on the challenges that healthcare workers encounter in providing spiritual care. Therefore, this study aimed to explore healthcare workers' challenges in providing spiritual care to the hospitalised patients. **MATERIALS AND METHODS**: A qualitative study was conducted among healthcare workers at one hospital in Malaysia. A semi-structured interview was used to collect data from May 2023 until November 2023. All interviews were meticulously recorded, transcribed, and analysed using thematic analysis. **RESULTS:** Ten participants with diverse backgrounds willingly participated in the study. Analysis reveals a few challenges in providing spiritual care among healthcare workers such as time constraints, lack of knowledge, experience shortfalls, doubts about the efficacy of spiritual care, awareness deficiency among staff, and impact of patients' conditions. **CONCLUSION:** Healthcare workers are unable to fulfil patients' spiritual care for a variety of reasons. These findings have important implications for healthcare settings, highlighting the need for ongoing awareness and training in spiritual care competencies for healthcare workers.

Keywords
Spiritual care; healthcare workers; qualitative study

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INTRODUCTION

Spiritual care is an essential aspect of healthcare, provided by health professionals to prevent illness, treat conditions, and maintain overall well-being in patients.[1] Spiritual care implies that one tries to address patients' spiritual struggles, fears, and worries, listen to their spiritual needs, and support their underlying spirituality, whatever this may mean to them.[2] Puchalski[3] believed that exploring spiritual care such as what provides meaning to a patient's life and how they cope with illness can foster a more trusting and profound relationship. Studies have recognised that spiritual distress could occur at any time during the patient's journey, and good nurses should be adequately prepared to provide spiritual care whenever needed.[4] Kurniawati et al.[5] also revealed that patients attended by healthcare workers for spiritual care were motivated to be positive and took meaning in sick conditions to get a better life.

Spiritual care in medical settings encompasses a range of practices aimed at addressing the spiritual or religious needs of patients, which can significantly impact their overall well-being and satisfaction with their care. Despite its recognised importance, healthcare workers face numerous challenges when it comes to integrating spiritual care into clinical practice such as lack of staff, heavy workload of the

staff, heavy shifts, the non-standard nurse-to-patient ratio, lack of time, burnout,[6] fear of criticism from others, lack of education, space constraints, and absence of a recording system.[7] Understanding the perspectives of healthcare workers on these issues is crucial for developing strategies that enhance the capacity of clinical settings to provide meaningful spiritual care.

The theoretical framework for this study is based on the T.R.U.S.T. Model for Inclusive Spiritual Care, which is nonlinear, allowing spiritual exploration to begin in any of its five interconnected dimensions.[8] The first "T" stands for "traditions," focusing on how clients' past and present spiritual, religious, cultural, and healing traditions impact their well-being.[9] "R" represents "reconciliation," involving the exploration of unresolved issues to promote peacefulness and trust.[9] "U" stands for "understanding," addressing how an individual's worldview and personal beliefs influence their well-being.[9] "S" denotes "searching," which involves exploring existential or faith-based questions prompted by suffering.[9] The final "T" signifies "teachers," encompassing spiritual, religious, and personal mentors, as well as trusted resources that help individuals navigate relevant spiritual issues.[9] This model was designed to help healthcare professionals address the spiritual dimension of health as an integral part of holistic care.[10]

In the complex landscape of healthcare, the provision of spiritual care is a critical yet often overlooked component of holistic patient treatment. While a few hospitals in Malaysia have begun incorporating spiritual care into their services, this aspect is still in its nascent stages. Even healthcare workers seldom include spiritual care in their routine clinical practice.[11] Therefore, this study aimed to explore the challenges faced by healthcare workers' and their expectations in providing spiritual care to patients in the hospital setting. Healthcare workers, for the purpose of this paper, are defined as individuals who provide medical and nursing care, specifically including physicians and nurses.

MATERIALS AND METHODS

DESIGN AND SAMPLE

This study used a phenomenology design, a research approach that aims to describe the essence of a phenomenon by exploring it from the perspective of those who have experienced it,[12] or an individual's lived experiences within the world.[13] Participants were purposefully selected from one teaching hospital in East Coast Malaysia based on specific criteria: male/female, professional (nurse, physician), a minimum of six months' employment at the hospital, age 18 or older, and proficiency in either Malay or English. In a qualitative study, LoBiondo-Wood and Haber[14] agree and suggest that there is no fixed rule to establish the most appropriate sample size in qualitative research. The sampling continued until data saturation was reached, meaning the process was stopped once interviews ceased to yield new information or contribute additional codes for analysis.[15] A total of 10 participants were interviewed which had reached the level of data saturation.

DATA COLLECTION

Participants were recruited between May 2023 and November 2023. Prior to the interviews, the researcher took time to build rapport with the participants. The interview was conducted to gain the participant's responses using a piloted interview guide. The data collection involved both informal and semi-structured face-to-face interviews. Example of the main questions: What are the main problems or challenges that you faced while delivering spiritual care to the patient? How do you encounter the

challenges? Explain the situation or event. Voice recorders were used with the participants' consent in addition to taking notes, ensuring comprehensive capture of the conversation for accurate transcription and subsequent data analysis. The interviews were lasted between 30 and 45 minutes and conveniently held in the offices of the participants.

DATA ANALYSIS

Thematic analysis was applied to analyse the data. Thematic analysis is a technique that identifies themes within the data, with the themes forming the basis of categorisation.[16] This method entails a detailed examination of the data, in which the researcher meticulously codes the data to uncover meaningful themes. The codes and themes that are generated serve to integrate data gathered by different methods.[17] The first step involved a thorough transcription of the data from the notes and audio recordings. The researchers then scrutinised the transcripts, actively searching for significant meanings and patterns. The second step involved generating initial codes that represent the meanings and patterns in the data. This phase included discussions within the research team, composed of qualitative research experts, to identify pertinent text segments and assign appropriate codes. Similar meanings were aggregated under unified codes. The next step was to sift through these codes to identify potential themes, ensuring each theme was cohesive and relevant. Finally, the themes were defined and named. The reporting phase included a detailed presentation of the findings, enriched with examples for clarity. NVivo software facilitated the organisation of data into these defined themes, streamlining the reporting process.

TRUSTWORTHINESS

Tobin and Begley[18] suggest that dependability and confirmability in research can be achieved by maintaining an audit trail. In this study, an audit trail was meticulously kept to record every step and any modifications made during the data collection, analysis, interpretation, and reporting phases. The researcher extensively recorded observations about the research process, interactions with participants, thoughts, emotions, and analytical interpretations in a research diary, which accompanied the audit trail. Additionally, engaging in discussions with the research team, comprised of experts in qualitative research, indirectly enhanced the study's rigour by providing critical insights and feedback, further ensuring the integrity and reliability of the research findings.

RESULT

Ten participants consented to participate in this study, and their backgrounds are summarised in Table I. The analysis revealed six themes related to healthcare workers' challenges in providing spiritual care: 1) Time constraints, 2) Lack of knowledge, 3) Experience shortfalls, 4) Doubts about the effectiveness of spiritual care, 5) Awareness deficiency among staff, and 6) Impact of patients' conditions.

Table I: Socio-demographic characteristics of the participants

	Participants (n)	
Age (years old)	24-41	
Gender	Male	3
	Female	7
Marital Status	Married	9
	Single	1
Position	Staff nurse	3
	Sister/Matron	6
	Doctor	1
Working experience (years)	3-7	

Theme 1: Time constraint

Most of the healthcare workers mentioned that time limitation is the main challenge for them as they have many tasks to settled within their work shift.

"Limitation of time is one of the challenges because sometimes patients with chronic illness have a lot to share with us, so it will take me time." (P5)

"We will always have other things to do, so each of us have limitations of time." (P8)

Theme 2: Lack of knowledge

Few healthcare workers expressed their limitation of knowledge, which constrained them to deliver spiritual care to patients.

"Need to polish more…even though I am a spiritual trainer, I still feel that I do not have enough knowledge." (P5)

"Our knowledge is limited, sometimes we want to help patients, but we are not able to answer their questions, especially regarding religious practice. Some of it we will be able to answer, but there are also difficult ones." (P10)

Theme 3: Experience shortfalls

New and young staff have been found to lack experience compared to senior staff and those who have been trained.

"But for new staff, they are still in the learning phase, they do not know things to do and could not reflect on patients' problems." (P3)

"I have less experience than the senior in this ward" (P6)

Theme 4: Doubts the effectiveness of spiritual care

Healthcare workers find themselves uncertain about the effectiveness of their spiritual care practices due to the absence of a defined evaluation method.

"To ensure staff deliver suitable advice to patients, we don't know how effective is that." (P5)
"For me, we don't know the patients' acceptance about our spiritual care." (P6)

Theme 5: Awareness deficiency among staff

Awareness among healthcare workers needs improvement. While some healthcare workers possess an understanding of spiritual care, there remains a significant reluctance among certain individuals to engage with it.

"Awareness…we could say still not enough, we need more awareness among staff" (P3)

"I think for staff awareness, especially in my ward, they should practice more." (P7)

Theme 6: Impact of patients' conditions

Patients' age and critically ill patients matter as it affects healthcare workers' way of communicating with the patients. Patients' age matters, especially geriatric patients.

"For young patients it's manageable but for bedridden patients, it's quite difficult for us to deliver spiritual care" (P2)

"As you know in ICU, sometimes it's hard for us to deliver spiritual care due to patients' conditions" (P3).
"Older patients usually have their own attitude to be handled." (P6)

DISCUSSION

Healthcare workers confront several common challenges in providing spiritual care, including limited time, insufficient knowledge, lack of experience, questioning the effectiveness of spiritual care, lack of staff awareness, and the impact of patients' conditions.

Time constraints are consistent in other studies, highlighting how healthcare workers struggle to allocate time for spiritual care amidst their numerous

responsibilities, often overlooking its importance in patient care.[19-21] Many healthcare workers recognise their limitations in knowledge, particularly regarding issues pertaining to religious practices, which they find challenging. This observation aligns with findings from other studies, which note the diversity of patients' needs that must be met became a barrier for them.[6,19,22] This study highlighted the issue of inexperience, noting that newer staff members often have less experience than their senior counterparts, leading to obstruction in delivering spiritual care to patients. This gap in experience aligns with the studies by Momeni et al.[6] and de Diego-Cordero et al.[11], where healthcare workers acknowledged their limited experience in providing spiritual care.

The study further revealed that a lack of awareness among staff poses a significant challenge for them in delivering spiritual care. Notably, not all healthcare workers acknowledge the significance of integrating spiritual care into patient treatment, resulting in its underutilization. The reluctance is reflected in the findings by Karimollahi et al.[23], who suggest that some healthcare workers perceive the provision of spiritual care as complicating their workflow. Moosavi et al.[24] reported that there is a sentiment among some staff members that engaging in conversations and listening to patients' spiritual needs is energy-draining and time-consuming. These challenges highlight the need for increased awareness and a deeper understanding of the value of spiritual care within the healthcare setting.

The condition of patients has emerged as another significant challenge for healthcare workers in providing spiritual care. Notably, delivering spiritual support to geriatric or critically ill individuals poses significant hurdles. Participant P3, for instance, shared the difficulties faced when attempting to offer spiritual care within the intensive care unit (ICU) setting, where many patients are terminally ill. Despite these obstacles, healthcare workers strive to address patients' spiritual needs to the best of their ability. Moreover, the study by Giske and Cone[4] emphasised that different age groups necessitate varied communication approaches by nurses, further complicating the delivery of spiritual care across patient demographics.

The new findings that can be highlighted in this paper are the uncertainty about the effectiveness of spiritual care has been a concern among healthcare workers, who expressed doubts about the impact of their spiritual care interventions. Without a clear method to measure effectiveness, healthcare workers felt it quite challenging for them to observe or acknowledge any changes in patient's conditions as an indicator of successful spiritual care. Therefore, the importance of ensuring that patients receive and comprehend the spiritual care provided is required for effective spiritual care practices in healthcare settings.

A notable limitation of this study is its reliance on participants from a single hospital. Despite the constraint, the in-depth data gathered through face-to-face interviews compensated for the study's limited scope, enriching the findings significantly. This research could be further extended to diversify the participant base by including healthcare workers from various types of hospitals across Malaysia. Future studies should encompass public, private, and other teaching hospitals, particularly those that adhere to shariah-compliant practices. Such an approach would enhance the representativeness and generalisability of the findings, providing a more comprehensive understanding of the challenges regarding spiritual care in diverse healthcare settings.

CONCLUSION

The challenges healthcare workers encounter highlights the intricate nature of providing spiritual care to hospitalised patients. Nevertheless, the insights gleaned from these challenges offer a deeper understanding of the nuanced nature of spiritual care within healthcare environments. These findings carry significant implications for healthcare settings, underlining the critical need for continuous education, heightened awareness, and targeted training in spiritual care competencies for healthcare workers. By deepening their understanding of and respect for patients' spiritual beliefs and practices,

healthcare workers can navigate the challenges more effectively. This enables them to offer supportive spiritual care in tandem with medical treatment, facilitating a comprehensive approach to patient well-being. Such efforts are key to advancing the holistic health of patients, reflecting the essential role of spiritual care in the broader spectrum of healthcare.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

Effectiveness of Defocus Incorporated Multiple Segments (DIMS) Lens in Slowing Myopia Progression among Malay Schoolchildren

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ABSTRACT

INTRODUCTION: Defocus Incorporated Multiple Segments (DIMS) lens imposes simultaneous myopic defocus for myopia control and has been proven to be effective in controlling myopia progression in children. However, the effectiveness of the DIMS lens may vary between different ethnicity due to different retinal profiles among children. This study aims to determine the effectiveness of DIMS lens in controlling myopia progression among myopic Malay schoolchildren. **MATERIALS AND METHODS:** This is a randomized control trial and was conducted as a single-site study where forty-two myopic Malay schoolchildren, (mean age of 9.53±1.50 years old) were recruited. The effectiveness of the DIMS lens was measured via changes in spherical equivalent refraction and axial length elongation for 12 months, and findings were compared with children wearing single vision (SV) lens. Data was analysed using repeated analysis of variance (ANOVA), between-within with Bonferroni correction, and $p<0.05$ indicated a significant difference. **RESULTS:** After 12 months, 38 subjects completed the study, with 20 subjects in the DIMS group and 18 subjects in the SV group. The DIMS group showed a significantly lower myopia progression; with 0.07±0.10mm increment in axial length elongation and -0.16±0.30D in spherical equivalent refraction increment compared to the SV group. The main effect comparing the changes in axial length elongation and spherical equivalent refraction increment between the DIMS group and the SV group was significant, ($F=7.61$, $p<0.05$) and ($F=3.23$, $p<0.05$), respectively. **CONCLUSIONS:** Full time wear of the DIMS lens is significantly effective in slowing myopia progression compared to SV lens in myopic Malay schoolchildren.

Keywords
Myopia progression, DIMS lens, Myopic Malay schoolchildren

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INTRODUCTION

Myopia prevalence is rising significantly worldwide,[1,2] especially in developed Asian countries such as China, Hong Kong, Taiwan and Singapore.[3-5] This is disconcerting because of the increased risk to visual impairment and blindness including cataract, glaucoma, retinal detachment and other chorio-retinal abnormalities.[6–8] Current interventions, including low dose atropine, dual-focus contact lenses, and orthokeratology, have shown promise in mitigating myopia progression among schoolchildren.[9] However, their invasive nature and associated risks pose challenges, especially concerning their implementation in younger children.[10] Therefore, the preferred myopia control strategy for younger children should be simple and minimally invasive, which makes spectacle lenses an appealing and ideal alternative option for them.

Myopia is associated with excessive axial eye growth and disproportionately high corneal power. Animal studies have shown that myopic defocus can impede eye growth while hyperopic defocus drives eye elongation.[11,12] Observations on animal studies also showed that when

the eye was presented with equal amounts of competing defocus, myopic defocus produced a stronger effect than hyperopic defocus.[13] Nowadays, myopic defocus theory has been established and already underlaid several current myopia control strategies, such as in orthokeratology and multifocal soft contact lenses.

In 2020, a research team from The Hong Kong Polytechnic University designed a novel spectacle lens based on the myopic defocus theory for myopia control, known as Defocus Incorporated Multiple Segments (DIMS) spectacle lens. This lens provides a simultaneous myopic defocus and have shown to significantly slow myopia progression in schoolchildren by 52% over 2 years in spherical equivalent increment and 62% in axial elongation when compared to the single vision (SV) lens.[14] DIMS lens is safe and has no effect on children's binocular vision.[15] In addition, a six-years study on the effectiveness of DIMS lens showed no rebound effect, and annual increment in axial length is maintained at 0.12 mm.[16] The effectiveness of DIMS lens during COVID-19 related lockdown measures in schoolchildren were also proven to be superior to SV lens[17] as well as in the large scale or diverse clinical circumstances study on myopic children.[18]

However, previous randomized control trial[14] recruited only homogenous Hong Kong Chinese schoolchildren and not evaluated on another ethnicity. Epidemiological evidence[19] have shown major differences between ethnic groups in the prevalence of myopia even though detail analysis suggests that these differences may be mediated by environmental exposures.[20] To the best of the authors' knowledge, there is no other randomized clinical trial that study the effectiveness of DIMS lens in other ethnicity; which may limit the generalizability of its results.

Malaysia is a multi-ethnic country with a population of almost thirty-five million. The largest ethnicity is made up of Malays accounting for over half of the country's population besides Chinese and Indian. Although Chinese ethnicity has the highest prevalence of myopia among schoolchildren in Malaysia, the quadruplet increment of myopic schoolchildren in Malay is worrying.[21] This present study therefore aims to investigate if the DIMS lenses can effectively slow down the myopia progression in myopic Malays schoolchildren by comparing the change in spherical equivalent of cycloplegic autorefraction (SER) and axial length between DIMS and single-vision spectacle lenses. This study also reports the best-corrected visual acuity (BCVA) and lens performance between both groups.

MATERIALS AND METHODS

Study design

This was a prospective, randomised, double-masked clinical trial and a single site study, conducted at Optometry Clinic, Faculty of Health Science, Universiti Kebangsaan Malaysia. The subjects were randomly allocated to two groups: the treatment group (DIMS lens) and the control group (SV lens). Changes in spherical equivalent refraction (SER) and axial length were used to determine the efficacy of the DIMS lens. Each parameter was measured at baseline and every 3-months for 12 months, and the changes in SER and axial length between two groups were compared over the study period. Three months follow-up regime were designed to determine the pattern of the myopia control in shorter interval. This study adhered to the tenets of the Declaration of Helsinki and approval was obtained from the institutional ethics committee (UKM PPI/111/8/JEP-2020-667). Detailed explanation about the research was given to both parents and subjects including its potential risks and benefits before consent was obtained in this study. The subjects were free to withdraw from the clinical research at any time.

Subjects

Subjects were selected based on specific inclusion criteria, which required them to be schoolchildren aged 7 to 12 years with a spherical refractive component ranging from -0.50D to -5.00D and astigmatism and anisometropia of less than 1.50D. They should demonstrate a monocular best-corrected visual acuity (BCVA) of 0.00 log MAR (6/6) or better. They were also required to commit to participating in multiple follow-up sessions for data collection and agree to randomized group allocation as part of a masked study design.

This study recruited only myopic Malay schoolchildren. The Malay ethnicity of the subjects was contained to at least a minimum of three tier of Malay descendants. Subjects were excluded if they have any strabismus and binocular vision abnormalities, ocular and systemic abnormalities and had prior experience with any myopia control program. The inclusion and exclusion criteria were developed from the recommendations by the International Myopia Institute to reduce bias and variability, and to maximize generalizability for easier comparison with myopia control studies elsewhere.[22,23]

Subjects were instructed to wear the spectacles during the whole waking hours, except during shower. Wearing time compliance was asserted at every follow-up appointment. The final distance prescription was determined using cycloplegic subjective refraction and the lenses were replaced with an updated prescription when the change of SER was more than 0.50D.

Intervention and control

All subjects were supplied with spectacle lenses that were made of polycarbonate. The children in the treatment group wore the DIMS spectacle lenses while those in the control group wore SV spectacle lenses. Each DIMS lens comprises a central optical zone of 9 mm in diameter and contains multiple lenslets, each lenslet with a relative positive power of +3.50D. The optical principles and designs of the DIMS lens were described in detail by Lam et al.[14]

Sample size

The sample size required in this study was calculated using statistical package G*Power version 3.1.9.4 for analysis of variance (ANOVA) between and within interaction of the two groups. With a total of 5 visits for a complete data collection, a total of 24 subjects were required in this study to achieve an 85% study strength with an alpha level of 0.05 (2-tailed). Attrition rate was initially set at 10% but was revised and increased to 25% to safeguard the subject enrolment since the unprecedented emergence of COVID -19 outbreak and prolong movement control order during the data collection phase. Therefore, with a higher attrition rate estimation, a total of 32 subjects were required in this study.

Masking and randomisation

To adhere to the double-blinded research protocol, a designated investigator who was not associated with the masking process undertook responsibilities including group allocation, dispensation, spectacle delivery, and record-keeping. Both children and parents remained unaware of the group assignments, ensuring the integrity of the blinding procedure. Block randomisations were used in this study by using the f(x)=ran() function available in the Microsoft Excel. Block randomisations were chosen to achieve a balanced subject distribution between groups, minimizing potential biases and enhancing the validity of the study results. Subsequently, eligible subjects were allocated to either the treatment or control group based on the sequence generated by Excel. Detailed instructions were provided during the spectacle delivery, emphasizing on full-time wear. Rigorous monitoring of wearing hours compliance was executed through regular face-to-face interviews during follow-up sessions and via comprehensive questionnaires.

Outcome variables

Three primary research outcomes were observed at baseline and at 3-month intervals for 12 months in this study. The primary outcome was myopia progression, which was the difference between the mean axial length at the baseline and the subsequent axial length recorded at every visit throughout the study period. The secondary outcome was the change in the SER.

In this study, axial length was measured using optical biometry (Lenstar 900, Haag-Streit, USA) while an autorefractor (Grand Seiko WAM-5100, Hiroshima, Japan) was used to measure the cycloplegic SER. Average of five measurements of axial length and autorefraction for each eye were obtained for analysis. Prior to the autorefractor measurement, two drops of cyclopentolate hydrochloride 1%, (Cyclogyl, Alcon) were instilled at five-minute intervals between each drop to achieve the cycloplegic effect. Cycloplegia was confirmed by

measuring the amplitude of accommodation via push-up method when accommodation was 2D or less.

The third outcome was the BCVA and was observed at baseline. In this third outcome, variables comprised the changes in BCVA throughout the study period including the high contrast VA (HCVA) and low contrast VA (LCVA) for both distance and near visual acuity. HCVA at distance was measured using Logarithmic 2000 series Early Treatment Diabetic Retinopathy Charts while Low Contrast Early Treatment Diabetic Retinopathy Charts at 4m (Precision Vision Inc., Woodstock IL, USA) were used to measure the LCVA at distance. HCVA and LCVA at near were measured using the Mixed Contrast European-Wide Near Vision Card (Precision Vision Inc.) All VA measurements were conducted monocularly and binocularly under standardized room illumination of 500 cd/m^2.

Statistical Analysis

Data from all subjects who completed with the 12 months follow-up were analysed. Data analyses were conducted using per-protocol without employing imputation to account for missing data or dropouts. The change in parameters was defined as the difference between baseline and corresponding follow-up measurements. Data from the right eye will be used for data analysis if high correlation was found between the two eyes. Statistical analyses were conducted using a commercial software (SPSS version 23.0; SPSS, Inc., Chicago, IL).

The distribution of the measured variables for univariate analysis was estimated by the Shapiro-Wilk test meanwhile Cook's Distance was used for multivariate analysis. Parametric tests were chosen for normally distributed data, while non-parametric tests were used if normality were breached. Baseline demographic, refractive and biometric measurements such as age, gender ratio, corneal curvature, lag of accommodation, axial length and SER between DIMS treatment group and SV group were compared using unpaired t-test. Changes in SER and axial length elongation at different time points relative to the baseline were calculated. Repeated measure ANOVA was used to compare the changes in SER and axial length elongation between DIMS group and SV group during the experimental period, with the assumption in the homogeneity of variance. Post-hoc tests were conducted by Bonferroni correction. Pearson correlations were used to analyse the relationship between age, SER and axial length elongation. P-values of less than 0.05 were considered as statistically significant.

RESULTS

Subject profile

Forty-two myopic Malay schoolchildren, mean age of 9.50±1.48 years old, were randomised and included in this study. However, at the end of the study duration, only 38 subjects completed their data collection for the final data analysis. The drop-out cases were unrelated to the study protocols. Specifically, the parents of two children opted to withdraw their children from the study due to concerns about the ongoing COVID-19 pandemic during the study duration. Two participants were counselled-out for not able to cooperate during the data collection phase. Fig. 1 provides a visual representation depicting the number of subjects screened and enrolled in this study. Even with the stringent limitations and restrictions policies during the COVID-19 pandemic, 38 subjects managed to complete the study, which yielded a study strength of more than 95% when calculated via G*Power of post-hoc statistical test for ANOVA.

In general, both groups showed an overall good compliance and were able to wear the spectacles full time. The mean daily lens-wearing time in the DIMS group and SV group was 15.85±1.62 and 15.94±1.57 hours, respectively, and the difference was not statistically significant ($p<0.05$). Preliminary analysis of the data found both eyes to be highly correlated (correlation between eyes for SER, $r=0.93$, $p<0.001$, and correlation between eyes for axial length, $r=0.97$, $p<0.001$). Therefore, only data of right eyes were used for further analysis.

Baseline characteristics

The mean SER in the DIMS group was -2.81 ± 1.25D and the mean SER in the SV group was -3.05 ± 1.32D at the baseline. Meanwhile, the mean AL in the DIMS and

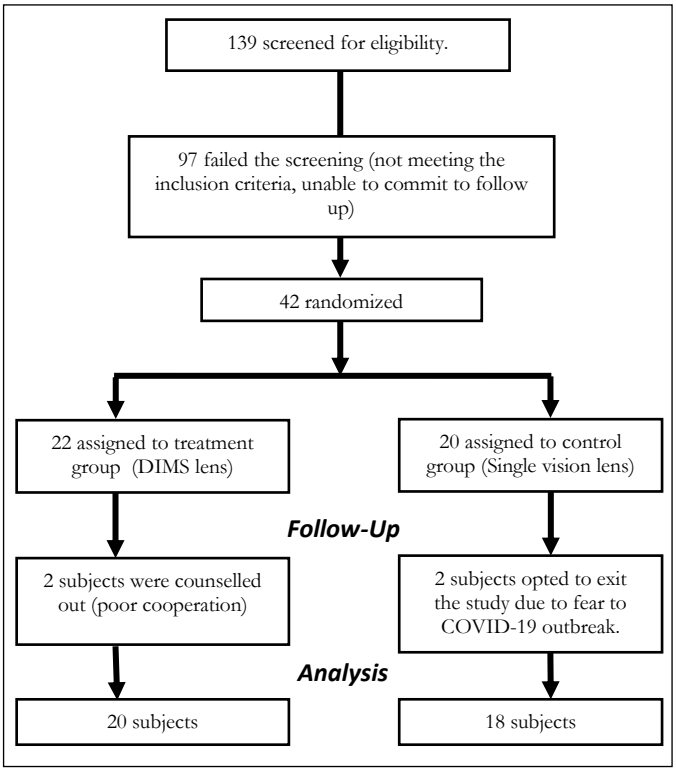

Fig. 1 A flow diagram of the subject enrolment. DIMS, Defocus Incorporated Multiple Segments spectacle lens; SV, single vision spectacle lens.

SV groups was 24.48 ± 0.98mm and 24.31 ± 0.85 mm, respectively. In this cohort, thirty-three subjects have at least one or both myopic parents. The baseline characteristics of each treatment group for all participants who completed the 12 months follow-up are shown in Table I.

Table I Baseline characteristics of participants who completed the 12 months follow-up in each treatment group.

	DIMS (n=20)	SV (n=18)	p-value
Age at enrolment (years)	9.55 (1.61)	9.50 (1.43)	0.92
Gender ; Female, % (n)	75.0% (15)	44.5% (8)	0.05
Distance High Contrast VA	0.01 (0.03)	0.00 (0.04)	0.58
Distance Low Contrast VA	0.13 (0.06)	0.13 (0.06)	0.85
Near High Contrast VA	0.02 (0.04)	0.02 (0.03)	0.73
Near Low Contrast VA	0.15 (0.07)	0.14 (0.04)	0.60
Cycloplegic Autorefraction, SER (D)	-2.81 (1.25)	-3.05 (1.32)	0.58
Axial length (mm)	24.48 (0.98)	24.31 (0.85)	0.57
Corneal power at flat meridian (D)	43.60 (1.50)	43.96 (1.31)	0.43
Distance phoria, Δ	-0.25 (1.68)	-0.67 (2.25)	0.53
Near phoria, Δ	-1.35 (1.84)	-0.56 (1.20)	0.31
Accommodation lag (D)	1.18 (0.34)	1.07 (0.32)	0.31

Note: Data are presented as Mean (Standard Deviation, SD), $p<0.05$ is considered significant (Independent paired t-test)

Abbreviation: Δ, prism dioptres; AL, axial length; D, dioptres; DIMS, Defocus Incorporated Multiple Segments; SV, Single Vision; -ve phoria indicate exophoria

Changes in SER

In general, both groups showed an increment in SER after 12 months of the observation. The mean SER progression in the SV group was statistically higher (-0.44 ± 0.36D) compared to the increment in the DIMS group (-0.16 ± 0.30D).

Repeated measure ANOVA with Bonferroni correction showed a significant main effect for time F=5.72, p=0.003, η_p^2=0.14 and significant main effect for type of lens used F=3.97, p=0.05 η_p^2 =0.01. The main effect comparing the changes in the SER in DIMS and SV groups was also significant F=3.23, p=0.038, η_p^2 =0.08. These statistical analysis findings confirming that there was significant effect of DIMS lens on SER over 12 months in myopic Malay schoolchildren. Children wearing DIMS lens had significantly less SER increment by 63.6%, with mean difference of -0.29±0.36D, $p<0.0125$ (Fig. 2). Pearson correlation analysis showed that the changes in SER was not correlated with the age of enrolment in both groups ($p>0.05$).

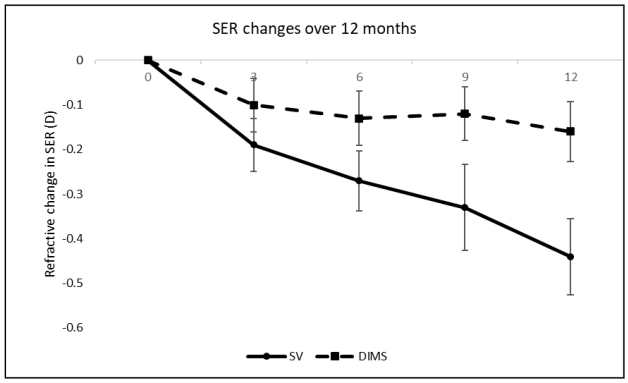

Fig. 2 SER from baseline to 12 months. Error bar denotes SEM

Changes in axial length elongation

Similarly to SER, both groups also showed an increment in axial length elongation after 12 months of the study period. The total axial length elongation over 12 months was 0.07±0.10 mm and 0.20 ± 0.13 mm in the DIMS and SV groups, respectively. Children wearing DIMS lens had significantly less axial length elongation by 65.0%, with mean difference of 0.13 ± 0.04mm, $p<0.0125$ (Fig. 3).

Repeated measure ANOVA with Bonferroni correction showed a significant main effect for time F=22.96,

$p<0.001$, $\eta p2 = 0.39$ and significant main effect for type of lens used $F=11.60$, $p=0.002$ $\eta p2=0.24$. The main effect comparing the changes in the axial length elongation between the DIMS group and SV groups was also significant $F=7.61$, $p=0.003$, $\eta p2=0.18$. These statistical analysis findings confirmed that there were significant effect of DIMS lens on axial length elongation over 12 months in myopic Malay schoolchildren. Pearson correlation analysis showed that the changes in axial length elongation was not correlated with the age of enrolment in both groups ($p>0.05$).

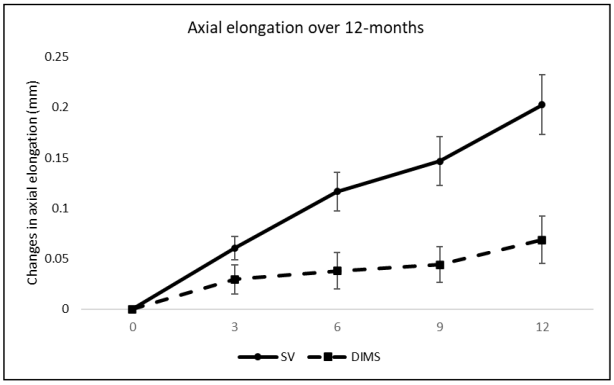

Fig. 3 Mean and SE of axial length elongation from baseline to 12 months. Error bar denotes SEM.

Changes in visual acuity performance

Both groups showed good and stable VA at both distance and near acuity measurements throughout 12 months of study duration with no significant difference noted. Details of the visual acuity performance is shown in Table II.

Table II Changes in VA between DIMS group and SV group for 12 months

	Baseline		3rd month		6th month		9th month		12th month	
	DIMS	SV	DIMS	SV	DIMS	SV	DIMS	SV	DIMS	SV
HCVA (Distance)	0.01 (0.04)	0.01 (0.03)	-0.01 (0.05)	-0.01 (0.06)	-0.02 (0.04)	-0.04 (0.05)	-0.04 (0.05)	-0.05 (0.06)	-0.04 (0.03)	-0.06 (0.05)
LCVA (Distance)	0.13 (0.06)	0.14 (0.06)	0.11 (0.06)	0.12 (0.09)	0.07 (0.05)	0.10 (0.03)	0.07 (0.05)	0.10 (0.05)	0.07 (0.05)	0.10 (0.05)
HCVA (Near)	0.02 (0.04)	0.02 (0.03)	0.00 (0.07)	0.02 (0.06)	-0.02 (0.06)	0.00 (0.02)	0.00 (0.02)	-0.01 (0.04)	-0.01 (0.04)	-0.02 (0.03)
LCVA (Near)	0.15 (0.07)	0.14 (0.06)	0.13 (0.07)	0.12 (0.06)	0.12 (0.06)	0.10 (0.04)	0.09 (0.04)	0.09 (0.04)	0.09 (0.05)	0.08 (0.04)

Note: Data is presented as Mean (Standard Deviation, SD)
No significant difference between group at all visual acuity measurements
Repeated measure ANOVA (between-within subject analysis of variance) with Bonferroni correction, $p>0.005$, $\eta p2< 0.03$)
Abbreviations: DIMS, Defocus Incorporated Multiple Segments; SV, Single Vision; HCVA, High Contrast Visual Acuity ; LCVA, Low Contrast Visual Acuity
-ve notation indicate better acuity than the Log MAR 0.00

In addition, all VA elements showed improvement towards the end of the study. This observation is possibly contributIn addition, all VA elements showed improvement towards the end of the study. This observation is possibly contributed by subjects getting more experienced with data collection techniques and better adaptation to the spectacles. Both groups also recorded about 1.5 line poorer in LCVA than the HCVA. This finding is expected as the HCVA and LCVA are usually reduced by two lines at distance for normal subjects.[24]

Lens performance

Direct information on lens performance acquired via questionnaires demonstrated that DIMS and SV gave a comparable performance. On the last question regarding subjects' feedback on the overall lens performance, the DIMS group scored only 0.1 point less than the SV group (Fig. 4). No treatment-related adverse events were reported throughout the study period from any of the group.

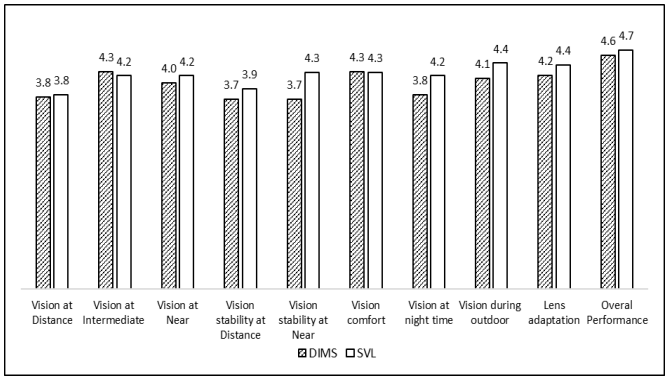

Fig. 4 Subjects' response to lens performance. (Score: 1-Poorest to 5-Excellent).

DISCUSSION

DIMS lens has been established as an effective treatment option for controlling myopia progression in Chinese population.[14–18] More reports on the effectiveness of DIMS lens in controlling myopia progression were also being established in other ethnic population.[25,26] This study hereby showed that the simultaneous myopic defocus provided by the DIMS lens was also effective in controlling myopia in myopic Malay schoolchildren and ascertained the effectiveness of DIMS lens in another ethnicity.

Myopia is a multifactorial condition, and even though ethnicity was not considered as a major risk factor for myopia as opposed to education and time spent outdoor,

ethnicity may affect the genetic determination in human. Various epidemiological evidence shows major differences between ethnic groups in the prevalence of myopia,[27,28] even though these prevalence differences are probably mediated by environmental exposures as well. In this cohort, the 12 months cumulative absolute reduction in axial length elongation was 0.07mm with the standard error of 0.03mm and comparable with result by Lam et al.,[14] which reported the 12 months cumulative absolute reduction in axial length elongation of 0.11mm with the standard error of 0.02mm. Axial length is more sensitive in monitoring myopia progression and has been recommended as a gold standard in monitoring myopia progression in clinical studies.[22,29] However, the smaller effect size noted in the interaction analysis of SER increment between the two groups observed in this study probably contributed by varied residual accommodation which may affect the final measurement of SER especially in dark-irided/pigmented children[30] like the Malays.

Another important observation in this study was the treatment effect. The treatment effect in terms of axial length elongation was greatest at the first nine months of the study with the relative efficacy of up to 73% and reduced to 65% at the end of 12th-month. Brennan et al.[29] calculated an approximately 31%-40% of the projected treatment efficacy of optical interventions to control myopia occurred in the first 6th-month of the study period and suggested one of the possible factors to this short treatment effect may attributed by transient choroidal thickening in the retina in response to simultaneous myopic defocus induced by the optical lens. Recent research has already proposed that the choroid is an important biomarker of eye growth in the human eye and prompted further research in human for better understanding in signals and pathways regulating the eye growth.[31]

In addition, study on human eye has already documented quick retinal response in the human eye and the retina can detect and response to sign of blur (defocus) within minutes.[32,33] Therefore, caution must be applied in generalizing or postulating the short-term treatment study efficacy for the long-term myopia management for every myopic child.

No treatment-related adverse events were reported during these 12 months of observation. Information acquired via questionnaire also showed a comparable score in terms of lens performance demonstrated in both group suggesting the stability and comfort of using the DIMS lens for myopia control in children.

Limitation in this study must be addressed for better research design in the future. The SER range in this cohort was limited to -5.00D with anisometropia and astigmatism of not more than 1.5D. It is then suggested that future RCT should extend the SER inclusion criteria to a higher degree of myopia. Meta regression analysis by Sarkar et al.[34] showed baseline SER having a significant impact on the treatment effect where treatment effect was larger with higher magnitude of baseline SER. This study also recruited subjects from a large age group even when many established research has established a greater risk of myopia progression in early onset myopia.[20] It is thus recommended that future studies have younger age groups in mind, preferably children less than 9 years old. Small sample size is always a concern, but as mentioned previously, the small sample size is justified with the study strength of more than 95% when recomputed again from the post-hoc statistical test for ANOVA upon the study completion.

CONCLUSION

In conclusion, full time daily wear of the DIMS lens can effectively control myopia progression and axial elongation in myopic Malay schoolchildren when compared to children wearing SV lens. DIMS lens also provides stable and good vision at both to distance and near. This intervention is straightforward, and the least invasive method compared to pharmacological or contact lens treatments. Spectacle correction using the DIMS lens would be a strategic approach to reduce myopia progression in younger schoolchildren.

FUNDING

This research received a University Research Grant (GUP -2020-054) from Universiti Kebangsaan Malaysia.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITEE)

This study adhered to the tenets of the Declaration of Helsinki, and approval was obtained from the institutional ethics committee (UKM PPI/111/8/JEP-2020-667).

CONSENT TO PARTICIPATE

All individual participants in this study provided informed consent. The parents and participants were provided with a comprehensive explanation of the research, including the potential risks and benefits, prior to giving their consent to participate in this study. Participants had the autonomy to discontinue their involvement from this study at any given moment.

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ORIGINAL ARTICLE

Antidiabetic Effects of Coffee Enriched with Maca and Marine Collagen Peptide (Blackbelt®) in a Type 2 Diabetes Mellitus Rat Model

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ABSTRACT

INTRODUCTION: The International Diabetes Federation (IDF) reported 463 million global cases of Type 2 diabetes mellitus (T2DM) in 2019. *Lepidium meyenii* (maca) and marine collagen peptide (MCP) have individually shown potential in alleviating T2DM symptoms, but their combined effects remain underexplored. This study evaluated the impact of Blackbelt® coffee, enriched with maca and MCP, on fasting blood glucose, insulin levels, and pancreatic and liver histology in a T2DM rat model. **MATERIALS AND METHODS:** Thirty-six male rats with a high-fat diet and streptozotocin-induced diabetes were treated with metformin, maca, MCP, Maca/MCP® (Blackbelt® formulation), or Blackbelt® coffee for 28 days. Fasting blood glucose (FBG) levels were monitored, and fasting serum insulin, HOMA-IR (insulin resistance), HOMA-B (ß-cell function), and QUICKI (insulin sensitivity) were assessed. Histological analysis of the pancreas and liver was performed using haematoxylin-eosin staining. **RESULTS:** After 4 weeks, treatments significantly reduced FBG levels compared to control ($p<0.05$), with Blackbelt® coffee notably increasing insulin production ($p<0.05$). All groups showed decreased HOMA-IR ($p<0.05$), and both metformin and Blackbelt® coffee groups had significant HOMA-B score increases ($p<0.05$). Histological analysis revealed improved pancreatic health in all treated groups, with significant liver histology enhancement in the Blackbelt® coffee group. **CONCLUSIONS:** Blackbelt® coffee improved FBG levels, insulin resistance, and ß-cell function more effectively than maca or MCP alone, and surpassed metformin in insulin production and hepatoprotective effects. Despite its promising potential for diabetes therapy, further research is needed to understand the synergistic effects of maca and MCP and the contribution of the coffee components.

Keywords
animal model, diabetes mellitus, Lepidium meyenii, maca, marine collagen peptide

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INTRODUCTION

Diabetes Mellitus (DM) is characterised by elevated blood sugar levels, known as hyperglycaemia. Type 2 Diabetes Mellitus (T2DM) is the most prevalent form, involving insulin resistance and insufficient insulin production.[1,2] In 2019, the International Diabetes Federation (IDF) reported 463 million cases of T2DM worldwide, with 79% originating in low and middle-income countries. Southeast Asia, particularly Malaysia, is significantly affected, with Malaysia having 3.65 million cases.[3] Projections indicate that diabetes prevalence will rise to 578 million by 2030 and 700 million by 2045.[2]

Hyperglycaemia is a major contributor to complications in organs such as the kidneys, liver, and central nervous system. Acute glucose level fluctuations increase oxidative stress, leading to tissue damage and systemic complications.[4] Insulin resistance, marked by reduced tissue responsiveness to insulin, is central to these complications.[5] Despite extensive research, there is a need for effective and affordable therapeutic interventions for T2DM. Functional foods and nutraceuticals are being explored as alternative treatments.

Epidemiological studies suggest coffee consumption offers health benefits, including a reduced incidence of T2DM, through potential regulation of glucose and lipid metabolism, and antioxidant and anti-inflammatory properties.[6,7]

Lepidium meyenii, or maca, from Peru, contains bioactive compounds called macamides. These compounds have medicinal effects, potentially benefiting hyperglycemia and providing antioxidant properties that could reduce metabolic syndrome and oxidative stress.[8,9] Marine collagen peptides (MCP) have been shown to improve glucose levels and insulin sensitivity in diabetes in both animal and human studies. These peptides enhance the insulin signaling pathway by reducing oxidative stress and inflammation, which are key contributors to insulin resistance.[10,11]

Despite these promising findings, there remains a significant gap in translating these benefits into a practical, combined therapeutic approach. The current study aims to address this gap by evaluating a novel formulation, Blackbelt® coffee, which combines maca and MCP. Using a high-fat diet/streptozotocin (STZ)-induced diabetes rat model, the study investigates the effects of this formulation on biochemical parameters and histological changes in the pancreas and liver of T2DM rats. This research seeks to provide new insights into diabetes management, potentially offering a novel and effective approach to addressing the global T2DM burden.

MATERIALS AND METHODOLOGY

Drugs, chemicals, and supplements

STZ was obtained from Sigma Aldrich Company (St. Louis, MO, USA). Metformin (GLUCOPHAGE® 500 mg tablets) was from DoctorOnCall (Malaysia), licensed by Merck Santé France. Each Metformin tablet was dissolved in a 0.5% carboxymethyl cellulose solution.[12] Citrate buffer (pH 4.5) was from Evergreen Engineering & Resources (Selangor, Malaysia). Blackbelt® coffee, maca powder, and MCP powder were obtained from TheSpecialistsFormula Sdn. Bhd. (Selangor, Malaysia). Blackbelt® coffee is approved as safe by the Ministry of Health Malaysia (FSQD 030685). Standard dry pellets were purchased from Gold Coin Sdn. Bhd. (Selangor, Malaysia). High-fat diet (HFD) comprises of commercially obtained 60% fat, 20% protein, and 20% carbohydrates.

Experimental animals

A cohort of 36 male Sprague Dawley rats, aged 7 weeks and weighing around 170 g, were obtained from A Sapphire Enterprise in Malaysia. After a one-week acclimatisation period, the rats were housed individually in polypropylene cages at the Physiology-Pharmacology Laboratory, International Islamic University Malaysia (IIUM) Kuantan Campus. The environment was controlled with a temperature of 28±2°C, 55±10% humidity, and a 12-hour light/dark cycle. The rats were fed standard commercial pellets and given water ad libitum. All procedures adhered to IIUM Institutional Animal Care and Use Committee guidelines (Ethics approval ID: IACUC-2021-008) and the National Institutes of Health Guide for the Care and Use of Laboratory Animals (2011).

Study design

Figure 1 illustrates the general experimental workflow for the study conducted with 36 rats. After a one-week acclimatisation period, T2DM was induced using a combination of HFD and STZ. Rats were categorised as

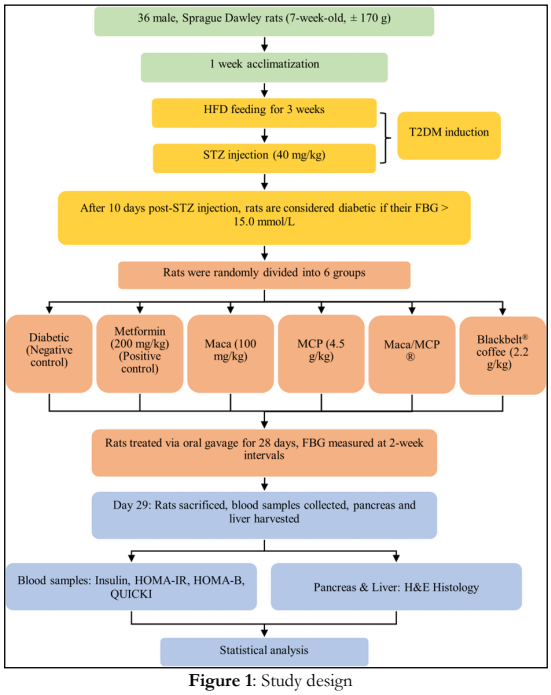

Figure 1: Study design

diabetic if their fasting blood glucose (FBG) levels exceeded 15.0 mmol/L. The rats were then randomly divided into one negative control and five treatment groups, and baseline FBG levels and weights were recorded. The treatment duration, doses of metformin, maca, and MCP were determined from previous studies with similar study designs, number of samples, and duration of study that have shown significant biochemical and histological results after 28 days of treatment.[11,12,13] Group 5 received a combination of Maca/MCP® based on the formulated dose in Blackbelt® coffee. The dose for Blackbelt® coffee in Group 6 was calculated using an empirical method.[14,15] In order to minimise the number of animals used as recommended by animal ethical guidelines, normal control (non-diabetic group) was omitted as the untreated diabetic group provided the necessary baseline for comparisons regarding the efficacy of different treatments. Extensive data on the physiological differences between non-diabetic and diabetic states is available from referenced studies.[11,12,13]

Preparation of maca, MCP, and Blackbelt® coffee

Each Metformin 500 mg tablet was crushed and mixed in a 10 mL solution of 0.5% carboxymethylcellulose, then stirred to produce a suspension of 50 mg/mL.[12] Maca, MCP, Maca/MCP®, and Blackbelt® coffee were dissolved in distilled water. A solution containing 1 g of maca powder in 100 mL of distilled water was prepared to achieve a concentration of 10 mg/mL. Additionally, 300 g of MCP powder coffee was dissolved in 1 L of distilled water to yield a suspension of 300 g/L, while 100 g of Blackbelt® coffee was dissolved in 1 L of distilled water to create a suspension of 100 g/L. The formulation of Maca/MCP® cannot be disclosed but is lower than the Maca and MCP doses in the respective treatment groups. The dosage administered to the rats was determined based on the formulated dose of both maca and MCP present in Blackbelt® coffee. A magnetic stirrer and hotplate were employed during the preparation. Once the mixture reached the desired temperature, it was administered to the rats via an oral gavage feeding tube, ensuring accurate dosing.

Induction of T2DM

T2DM induction involved feeding rats a self-prepared HFD consisting of 60% fat, 20% protein, and 20% carbohydrates for 3 weeks, followed by a low-dose injection of STZ.[12,16,17] STZ (40 mg/kg) was freshly prepared in 0.1 mM citrate buffer (pH 4.5) at a volume of 2 mL/kg and administered to rats via a single intraperitoneal injection.[12] Freshly prepared STZ was kept on ice before use.[13] Treatment commenced upon confirmation of hyperglycaemia ten days post-STZ administration in the rats characterised by a stable hyperglycaemic state of FBG levels higher than 15mmol/L.[12]

Full blood glucose measurement

FBG for diabetic confirmation was taken at day 10 post STZ administration. FBG levels were monitored fortnightly using an Accu-Chek glucometer (Roche Diagnostics (Malaysia) Sdn. Bhd.).[16] Blood samples were collected from the tail end and applied to glucometer strips.[18]

Insulin measurement

Upon completion of the treatment regimen on the 29th day, rats underwent an overnight fasting period and were subsequently anesthetised using ketamine (80 mg/kg) and xylazine (10 mg/kg) the following day for blood sample collection from the retro-orbital region. The separation of serum from blood plasma was achieved through centrifugation at 3000 rpm for 20 minutes. Fasting blood insulin (FBI) levels were quantified using a rat insulin ELISA kit (EZRMI-13K, Merck KGaA, Darmstadt, Germany).[12,17,19]

Measurement of HOMA-IR, HOMA-B, and QUICKI

Insulin resistance was assessed using HOMA-IR, calculated as [FBG (mmol/L) × FBI (μU/mL)]/22.5, with higher values indicating greater resistance.[12] ß-cell function was evaluated with HOMA-B, computed as 20×FBI(Mu/ml)/ [FBG (mmol/L)-3.5].[4] QUICKI measures insulin sensitivity, with higher values indicating better sensitivity, calculated as 1 / [log (FBI in mIU/L) + log (FBG in mg/dL)].[4]

Histological investigations

The pancreas and liver, rinsed with saline, were fixed in 10% neutral buffered formalin for 72 hours.[17] Following fixation, the tissues were embedded in paraffin and sectioned at approximately 5 μm using a semi-automated rotary microtome (Leica Biosystems RM2245, United States) before mounting on glass slides.[12] The sections were then mounted in molten paraplast at 58°C–62°C. Subsequently, they underwent H&E staining, involving dehydration with ascending grades of ethyl alcohol (100%, 90%, and 70%) followed by clearing with xylene to remove the alcohol. After staining with H&E, the samples were examined under light microscopy (Eclipse E200-LED, Tokyo, Japan) at 200× magnification.[4]

Pancreas histology

To assess the mean islet number, islets were counted in three distinct microscopic fields at 10× magnification. The average number per field was then calculated for each study group. For measuring the maximum girth, a 1000 μm ocular grid at 10× magnification was used to evaluate islet size. The maximum diameter was determined by comparing all available radii diameters for each islet and selecting the largest. This process was repeated in three separate microscopic fields, and the mean size of islets was computed for each group.[20,21] The histological evaluation of pancreatic tissues involved a thorough examination of morphological features and pathological changes by a pathologist.

Liver histology

Analysis of liver tissue involved a comprehensive assessment of various parameters by a pathologist, covering overall liver morphology and specific indicators of pathological changes. This included examining general liver architecture, identifying fatty changes, detecting hydropic alterations, quantifying inflammatory cell infiltrates and vessel congestion, observing Kupffer cell hyperplasia, identifying haemorrhagic events, and detecting hepatocyte necrosis.

Statistical analysis

The results were presented as means ± SD and analysed using SPSS Version 20 (SPSS Inc., Chicago, IL, USA). For variables measured over time, like FBG, repeated measures ANOVA with Bonferroni post hoc tests were used. For other variables such as insulin levels, HOMA-IR, and HOMA-B, one-way ANOVA was employed. Post hoc analysis (Duncan's test) followed if significant differences were detected.ws serum insulin, HOMA-IR, HOMA-B, and QUICKI values in the T2DM rat model at week 4. Blackbelt® coffee had the highest serum insulin production of 46.19±4.33 μIU/mL. It also reduced HOMA-IR (21.15±3.93) and improved HOMA-B (8.07±2.78).

RESULTS

Full blood glucose levels

Fig. 2 illustrates the mean and SD values of FBG for each group. The FBG levels consistently decreased across all groups from week 0 to week 4 following treatment administration. After 4 weeks of treatment with metformin, maca, MCP, or Blackbelt® coffee, a significant reduction in FBG levels was evident ($p<0.05$). Compared to pre-treatment levels, FBG decreased by 63.52% (metformin), 47.09% (maca), 58.78% (MCP), and 47.97% (Blackbelt® coffee) respectively.

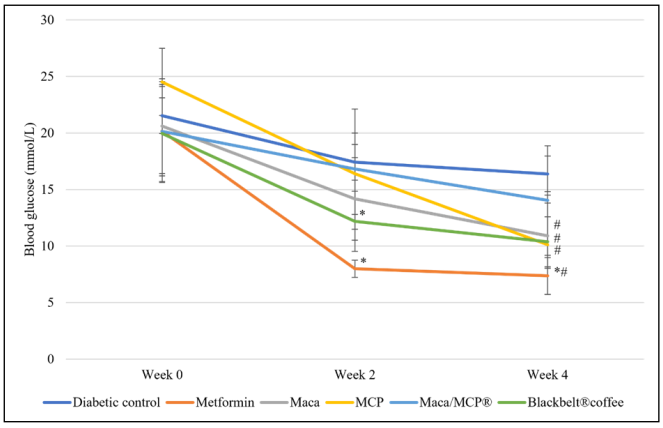

Figure 2: Changes in FBG levels in the different studied groups. The data were expressed as a mean±SD (n=6). *significantly different when compared to the diabetic control group, $p<0.05$, #significantly different when compared to week 0, $p<0.05$.

Serum insulin levels, HOMA-IR, HOMA-B, and QUICKI scores

Table I shows serum insulin, HOMA-IR, HOMA-B, and QUICKI values in the T2DM rat model at week 4.

Blackbelt® coffee had the highest serum insulin production of 46.19±4.33 µIU/mL. It also reduced HOMA-IR (21.15±3.93) and improved HOMA-B (8.07±2.78).

Table I Fasting serum insulin levels, HOMA-IR, HOMA-B and QUICKI scores of T2DM rat.

Groups	Parameters			
	Serum insulin (µIU/mL)	HOMA-IR	HOMA-B	QUICKI
Diabetic control	27.68±6.66	31.58± 4.45	2.94±2.08	0.26±0.0058
Metformin	34.47±1.44	11.27±2.50[a]	11.82±6.16[a]	0.27±0.008[a]
Maca	31.98±8.62	15.48±6.42[a]	5.62±3.48	0.27±0.011
MCP	36.75±7.50	17.23±5.72[a]	8.98±5.85	0.27±0.019
Maca/ MCP®	28.66±1.22[b]	17.88±7.40[a]	5.74±6.64	0.26±0.018
Black-belt® coffee	46.19±4.33[ab]	21.15±3.93[a]	8.07±2.78[a]	0.25±0.005[b]

The data were expressed as a mean ± SD (n=6). [a]: significantly different when compared to the diabetic control group, $p<0.05$. [b]: significantly different when compared to metformin, $p<0.05$.

Pancreas histology

Mean islet number and islet size

Table II shows a significantly higher islet count and size across all treated groups compared to the diabetic control group ($p<0.05$). While metformin showed the highest increases in both parameters, Blackbelt® coffee was a lose second.

Table II The mean number and diameter of pancreatic islets of studied groups.

Groups	Number of islets	Islet diameter (µm)
Diabetic control	9.33±0.72	48.25±1.37
Metformin	12.33±0.61[a]	80.08±1.66[a]
Maca	11.25±0.32[ab]	56.08±0.88[ab]
MCP	12±0.27[a]	58±1.36[ab]
Maca/MCP®	11±0.38[ab]	51.17±0.88[ab]
Blackbelt® coffee	12.25±0.42[a]	77±1.19[ab]

The data were expressed as a mean ± SD (n=6).[a]: significantly different when compared to the control group, $p<0.05$,[b]: significantly different when compared to the metformin, $p<0.05$.

Morphology of pancreas

Fig. 3 displays H&E-stained pancreatic images from different treatment groups, highlighting the effects of: A) Diabetic control, B) Metformin, C) Maca, D) MCP, E) Maca/MCP®, and F) Blackbelt® coffee. The pancreas of diabetic control group exhibited significant histological changes, as shown in Fig. 3A. Islet cell morphology

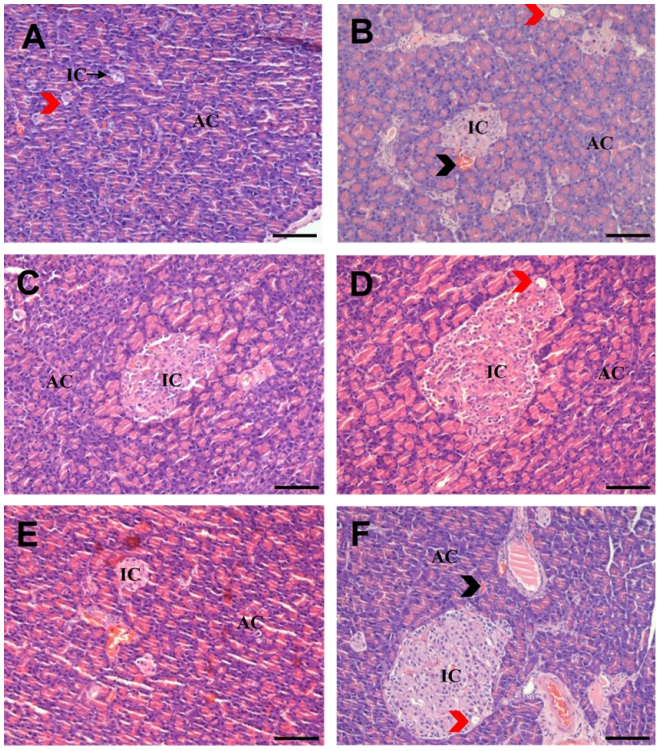

Figure 3: H&E-stained microscopic photomicrographs of the pancreas in the different studied groups at magnification: ×200. A: Diabetic control, B: Metformin, C: Maca, D: MCP, E: Maca/MCP®, F: Blackbelt® coffee, AC: acinar cells, IC: islet cells, black arrow: congested blood capillaries, red arrow: vacuolation in cells. Scale bar: 200 µm.

displayed a notable decrease in both number and diameter, indicating altered functionality and disrupted architecture. Additionally, pancreatic acinar cells showed signs of fat accumulation, along with inflammatory cell infiltrate and necrosis, suggesting tissue damage and inflammation consistent with T2DM.

In contrast to the diabetic control group, rats treated with metformin (Fig. 3B) showed distinct histological improvements in pancreatic morphology. Notably, there was an increase in the number and size of islets. Furthermore, reductions in fat accumulation and inflammatory cell infiltrate were observed in the pancreatic acinar cells, with less pronounced focal necrosis. Histological improvements were also noted in the pancreas of group receiving maca (Fig. 3C), MCP (Fig. 3D), Maca/MCP® (Fig. 3E), and Blackbelt® coffee (Fig. 3F) when compared to the diabetic control group. The pancreatic islets' morphology in rats treated with Blackbelt® coffee showed improvement comparable to those treated with metformin.

Liver histology

Morphology of liver

Fig. 4 displays H&E-stained liver images from different treatment groups, highlighting the effects of: A) Diabetic control, B) Metformin, C) Maca, D) MCP, E) Maca/MCP®, and F) Blackbelt® coffee. As shown in Fig. 4A, the liver histology of the diabetic control group displayed significant alterations, including fatty changes characterised by fat accumulation, cellular swelling indicating hydropic changes, and lymphocytic infiltration indicating inflammation. Moreover, signs of vessel congestion and Kupffer cell hyperplasia suggested a heightened immune response. Additionally, evidence of liver tissue haemorrhage and hepatocyte necrosis, reflecting cell death, were also observed. In contrast, metformin (Fig. 4B) groups did not show improvement in liver histology.

Maca (Fig. 4C) and MCP (Fig. 4D) groups exhibited improvements, displaying reduced fatty changes, hydropic changes, infiltration of lymphocytes, vessel congestion, Kupffer cell hyperplasia, and haemorrhage. Notably, MCP showed no hepatocyte necrosis. However, Maca/MCP® (Fig. 4E) groups did not show improvement in liver histology.

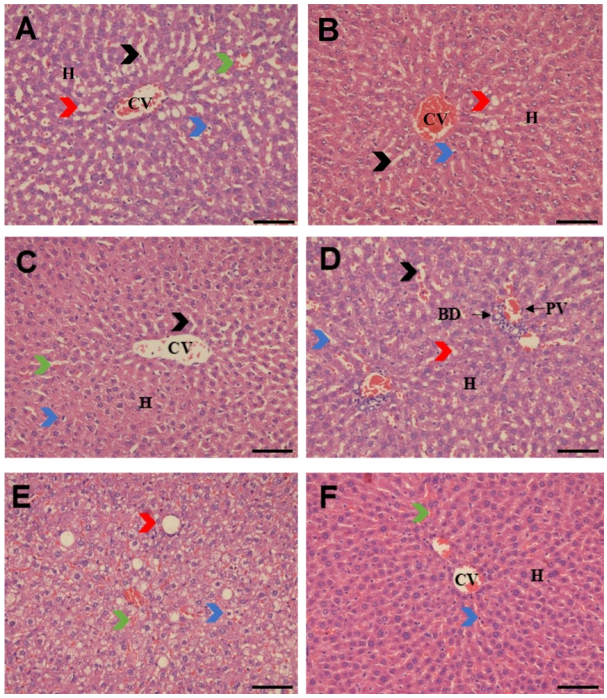

Figure 4: H&E-stained microscopic photomicrographs of the liver in the different studied groups at magnification: ×200. A: Diabetic control, B: Metformin, C: Maca, D: MCP, E: Maca/MCP®, F: Blackbelt® coffee, CV: central vein, H: hepatocytes; PV: portal vein, black arrow: hepatic sinusoids, red arrow: vacuolated hepatocytes, green arrow: congestion, and the blue arrow: Kupffer cell. Scale bar: 200 µm.

Finally, Blackbelt® coffee (Fig. 4F) administration resulted in the most significant improvement in liver histology compared to other treatment groups. These included a reduction in fatty changes, indicating decreased fat accumulation within liver tissues, as well as a decrease in hydropic changes, signifying a reduction in cellular swelling due to water retention. Moreover, there was minimal infiltration of lymphocytes, suggesting reduced inflammation, along with less vessel congestion, indicating improved blood flow within liver vessels. Notably, no hepatocyte necrosis or Kupffer cell hyperplasia was observed, indicating the absence of liver cell death and normal proliferation of immune cells in the liver, respectively. Additionally, there was no evidence of haemorrhage, reflecting the absence of bleeding within the liver tissue. The liver tissue exhibited a more organised distribution of hepatocytes and maintained a typical hepatic architecture.

DISCUSSION

Effects of Blackbelt® Coffee on Biochemical Parameters and Indices

This model of streptozotocin (STZ) and HFD was chosen to closely mimic human Type 2 Diabetes Mellitus (T2DM). STZ damages pancreatic ß-cells, reducing insulin secretion, while HFD induces insulin resistance, as validated by HOMA-IR and QUICKI assessments.[17,22] This dual approach typically results in hyperglycaemia.[23,24] The induced diabetic state in rats leads to metabolic dysregulation, including impaired glucose tolerance and altered lipid metabolism, manifesting as obesity and insulin resistance.[25]

Maca and marine collagen peptide (MCP) individually demonstrated potential in lowering hyperglycaemia, and enhancing glucose regulation in T2DM, consistent with previous studies.[12,14] However, the Maca/MCP® combination did not significantly reduce fasting blood glucose (FBG) levels in T2DM rats. In contrast, Blackbelt® coffee, which includes both maca and MCP, significantly decreased FBG levels, indicating its efficacy

in managing hyperglycaemia.

The bioactive compounds in Blackbelt® coffee, such as caffeine and polyphenols, may synergistically enhance the effects of maca and MCP on glucose metabolism.[6] The absence of coffee in the Maca/MCP® group might have impacted absorption rates and physiological responses, highlighting the importance of the delivery medium as the rich content of chlorogenic acid in coffee can enhance the absorption and bioavailability of other polyphenols.[26] Coffee consumption can also influence gut microbiota, affecting nutrient metabolism and absorption, potentially explaining the observed differences.[27] The results may also be due to the lower content of Maca and MCP in the Maca/MCP® formulation.

Blackbelt® coffee significantly increased insulin secretion and reduced fasting blood glucose (FBG) levels in rats with type 2 diabetes mellitus (T2DM), indicating enhanced insulin production. Treatments with maca, MCP, Maca/MCP®, and Blackbelt® coffee reduced HOMA-IR values from baseline, indicating decreased insulin resistance. In comparison, the HOMA-IR value in the Blackbelt® coffee group was higher than in the other treatment groups, likely due to elevated insulin levels. As this finding was not observed in the other groups, it is unlikely to be attributed to compensatory hyperinsulinaemia in response to insulin resistance. Rather, it is more likely the result of increased insulin secretion and pancreatic β-cell volume, driven by enhanced insulin signalling from caffeine, as shown in previous studies. Furthermore, caffeine's protective effects on pancreatic β-cells, through the alleviation of endoplasmic reticulum stress, may also play a role in this outcome.[28] Maca's effects on hormone modulation, antioxidant, and anti-inflammatory properties likely contribute to better glucose metabolism and reduced insulin resistance.[29,30,31] Collagen peptides, including MCP, may enhance insulin action, decreasing HOMA-IR values, possibly through structural benefits to pancreatic tissues and improvements in gut health, which can influence insulin regulation and glycaemic control.[32,33]

Blackbelt® coffee also exhibited elevated HOMA-B values compared to untreated diabetic rats, suggesting enhanced ß-cell function. This improvement might be due to the bioactive properties of macamides in maca as well as collagen peptides and amino acids in MCP .[32, 33, 34, 35]

Pancreatic protective effects

The induction of diabetes in animal models via a combination of HFD and STZ profoundly impacts the pancreas, as evidenced by histological examination. HFD contributes to increased fat accumulation and stress within the islets of Langerhans, while STZ induces diabetes by selectively destroying insulin-producing ß-cells, leading to decreased insulin production and secretion.[22,36] This combination accelerates diabetes development, resulting in significant loss of islet cells, disrupted islet architecture, and signs of inflammation and fibrosis.[22]

Maca's anti-inflammatory and antioxidant properties help mitigate diabetes-related damage to pancreatic islets by preserving and potentially regenerating islets.[37] Maca's adaptogenic nature may also influence hormonal balance, crucial for pancreatic function and insulin secretion from islets.[38,39] Similarly, marine collagen peptides (MCP) benefit connective tissues, potentially enhancing structural support for pancreatic tissues, including islets. Natural compounds in both maca and MCP may influence cellular proliferation and differentiation, targeting pancreatic progenitor cells or stimulating the growth of existing islet cells, thereby increasing islet count and size.[21] However, the specific mechanisms behind these pancreatic islet changes in the context of diabetes are not well documented.

This study found that both the Blackbelt® coffee and metformin groups exhibited higher islet counts and larger islet diameters compared to other treatment groups. This suggests potential preservation or regeneration of pancreatic islets, which are crucial for insulin production and glucose regulation. The larger islet diameter indicates enhanced structural integrity and functionality.[12,21] The comparable effectiveness of Blackbelt® coffee to

metformin further supports its potential as a natural intervention in diabetes management.

Hepatoprotective effects

Extended exposure to HFD, especially one rich in saturated fats, commonly precipitates non-alcoholic fatty liver disease (NAFLD), characterised by intracellular fat accumulation. This condition may advance to non-alcoholic steatohepatitis (NASH), which involves liver inflammation and cellular injury.[39] Streptozotocin (STZ), known for its toxic impact on pancreatic ß-cells, can also indirectly influence the liver, causing systemic disruptions. The combination of HFD and STZ exacerbates liver-related issues, potentially leading to heightened hepatic steatosis, inflammation, and even fibrosis or cirrhosis.[22,36]

This study revealed that metformin treatment did not yield significant improvement in liver histology, indicating its limitations in addressing the multifaceted nature of liver damage in diabetic rats. This result contradicts a previous study where metformin improved NAFLD.[41] However, Blackbelt® coffee exhibited notable hepatoprotective effects, surpassing those of metformin. Hepatocytes exhibited a more organised distribution, indicative of typical hepatic architecture, and improvements were observed in hepatic sinusoids, suggesting enhanced vascular function.[42,43,44] These findings collectively suggest that the unique components in Blackbelt® coffee including macamides and collagen peptides contribute to its hepatoprotective effects, potentially including anti-inflammatory or antioxidant properties. This is supported by previous studies that concluded treatment with maca improves liver enzyme levels and reduces malondialdehyde (MDA) levels in hepatotoxicity. [45] Additionally, a separate study found that MCP supplementation enhances hepatocyte viability and mitigates alcohol-induced hepatic steatosis.[46]

CONCLUSION

In summary, Blackbelt® coffee has shown promising effects on various aspects of diabetes management, including lowering FBG levels, enhancing ß-cell function, and potentially improving insulin resistance. In this study, Blackbelt® coffee outperformed metformin in terms of insulin production and demonstrated additional hepatoprotective effects. However, further research is needed to understand the specific contributions of all its components.

LIMITATIONS OF STUDY

The limitations of this study include the absence of a normal (non-diabetic) control group. However, since the study focuses on the effects of maca, MCP, Blackbelt® coffee on a diabetic rat model, the untreated diabetic group served as the negative control, and the group treated with metformin served as the positive control. Another limitation is the absence of a group receiving coffee only. Including a coffee-only group in future studies could help distinguish the effects of the added ingredients from those of the coffee itself.

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ORIGINAL ARTICLE

The CAPE will Influence the Angiogenesis in Traumatic Brain Injury

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ABSTRACT

INTRODUCTION: Traumatic brain injury (TBI) is a frequent and highly heterogeneous neurological disorder which has the potential to cause major social and economic consequences. However, Caffeic Acid Phenethyl Ester (CAPE), obtained from propolis through extraction from honey bees, has long been known as a folk medicine. This study identifies the predictor factors for angiogenesis in a TBI rat model following the provision of CAPE. **MATERIALS AND METHODS**: This experimental control treatment and randomization study used fifteen male Sprague-Dawley rats with surgically induced brain injury. The rats were treated with CAPE. We measured vascular endothelial growth factor (VEGF) levels as an indicator and Myeloperoxidase (MPO) as a polymorphonuclear activity marker. The gauges for brain edema and oxidative stress were mRNA, AQP4, and F2 Isoprostane, respectively. The correlation test of TBI parameters in the form of MPO, mRNA AQP4, and F2 isoprostane against VEGF as an angiogenesis process indicator was performed to identify the factors associated with post-TBI angiogenesis. **RESULTS:** Mean values were obtained using a descriptive tests, while the correlation test results were VEGF (938274.352), AQP4 mRNA (10099.00), MPO (9284222.028), and F2-Isoprostane (307346.562). The findings suggested a strong correlation between all TBI parameters and VEGF as an angiogenesis indicator ($p<0.001$). In addition, polymorphonuclear activity (MPO) and the presence of brain edema, as indicated by mRNA AQP4 expression, were identified as the most significant influences. **CONCLUSION:** The post-TBI angiogenesis (VEGF) process, conducted by administering CAPE, was influenced by polymorphonuclear activity (MPO) and increased water content in the brain (mRNA AQP4).

Keywords
Traumatic brain injury; Angiogenesis; Caffeic Acid Phenethyl Ester; Predictors.

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INTRODUCTION

Angiogenesis is the growth of new blood vessels from existing ones. This process is initiated by the secretion of endothelial cell proteases, followed by cellular movement to the place of formation.[1,2] Therefore, proliferation and differentiation occur to form a new lumen. The secretion of growth factors by the endothelial cells attracts supporting cells, including the pericytes and smooth muscles, thus forming a basement membrane.[3] These components ensure function and stability. The final stage involves specific development according to the tissue or organ being supplied.[1–5]

Vascular endothelial growth factor (VEGF) is an indicator of blood vessel permeability and functions as a regulator for angiogenesis.[6] This triggers cerebral edema through the synthesis and release of NO, as a GMP-dependent cyclic activator.[5,6] In addition, VEGF phosphorylates occludin is one of the VEGF metabolites

capable of interfering with occludin function, instigating the opening of tight junctions and edema formation.[5–7]

Myeloperoxidase (MPO) is an enzyme secreted by neutrophils and active macrophages or microglia.[8,9] Higher amounts of the enzyme have been implicated in impaired endothelial function, as well as increased nitrite oxide formation and damage to active lipoproteins.[8,10] It is also known to trigger the development of ROS, which initiates ischemia processes.[10,11]

Aquaporin (AQP) is a protein compound that is essential for water transport across the plasma membrane. It is widely expressed from tissues, including the renal epithelium and erythrocytes, to various cells of the central nervous system. In addition, the main aquaporin molecules comprised of AQP1 and AQP4 play a role in regulating brain fluid and CSF movement. These also contribute to cytotoxic and vasogenic edema, which are implicated in the control of intracellular and extracellular fluid volume.[12,13] Specifically, AQP4 is a dysfunction center in glutamate metabolism, synaptogenesis, and memory consolidation. The expression is essential for cellular migration and angiogenesis in tumor growth.[12–15]

Caffeic Acid Phenethyl Ester (CAPE) therapy is obtained from propolis, which has an extensive history as a folk medicine.[16] The drug structure comprises a known powerful anti-oxidant, known as catechol. Furthermore, CAPE has been shown to decrease inflammatory initiation, brain lipid preoxidation, and free radical damage.[17] Previous reports have demonstrated the effect on xanthine/xanthine oxidase, nuclear factor-kB (NF kB), cyclooxygenase 2 (COX-2), 5-li-poxygenase (5-LOX), alongside the production of inflammatory cytokines and the release of cytochrome c from mitochondria.[16–18]

This study examines the relationship between the process of post-trauma angiogenesis in the brain, as characterized by the expression of VEGF with AQP4 mRNA and Myeloperoxidase (MPO) levels in the blood after the provision of CAPE.

MATERIALS AND METHODS

Animal

Fifteen male Sprague-Dawley rats weighing 200–300g were used in this study. All animal procedures received approval from the Health Research Ethical Committee of the Faculty of Medicine, Hasanuddin University, Makassar, Indonesia, number: 771/UN4.6.4.5.31/ PP36/2019.

Examination of the mRNA AQP4 gene expression and the levels of MPO, VEGF, and F2-IsoProstane

The mRNA expression of the AQP4 gene was examined by extracting RNA in alignment with the guanidium thiocyanate method.[19–22] 100 µl of fresh blood was mixed with L6 buffer containing guanidium thiocyanate. A quantitative real-time PCR was performed with HPRT as a housekeeping gene (internal control). In addition, the AQP4 gene was the Sequence Nucleotide used, with the primary sequence of sense 5-CCA-CTG-GA T-ATA-TTG-GGT-TGG-A-3; antisense 5-CCA-CGT-CAG-GAC-AGA-AGA-CAT-A-3. However, the primer sequences included HPRT sense 5-GGA-CCT-CTC-GAA-GTG-TTG-GAT-3 and HPRT antisense 5-CCA-ACA-ACA-AAC-TTG-TCT-GGA-A-3. The PCR cycle was initiated at 94^{o}C for 5 minutes, which was sustained for another 20 seconds, followed by a decline and maintenance at 54^{o}C for 30 seconds. This rotation was repeated 25 times. The procedure was carried out according to the Tomomi Yajima protocol, and the oligonucleotide primers used were obtained from Macrogen Laboratory, Korea, with NO. DG 190726.

A total of 12.5 µl from 2 x SYBR Green QRT-PCR master mix was added to 10 µl of the initial primer (concentration optimized), Nuclease - PCR free - H2 level x µl of final primer (concentration optimized) as well as 0.375 µl of the reference dye solution collected from step 1 (optional), and 1.0 µl of the RT/Rnase enzyme block mixture with 25 µl of total reaction volume. This combination was mixed slowly (not rotated) to avoid bubble formation. Then, the mixture was distributed to test tubes containing 10 µl of experimental RNA. The reaction was briefly centrifuged and placed in the

instrument before running the PCR program using a Real -Time PCR machine (CFX Connect system, Biorad Laboratories, Real-Time PCR 96 well 0.1 ml, USA).[23–26]

Meanwhile, the other 3 parameters were evaluated using the sandwich ELISA method, Myeloperoxidase (MPO) Catalog No. Ls-F24875, VEGF Catalog No. Ls-F978 was purchased from Life Span BioSciences, Inc., while the 8-iso-PGF2 (8-isoprostane) Catalog No. MBS7606827 was obtained from MyBioSource Inc.

CAPE provision

CAPE powder was diluted with saline solution and administered through intraperitoneal injection (IP) 30 minutes after trauma. This required a dose of 10mg/kg,[8] repeated daily for 7 days.

Preparation for surgery

Five virus-free male Sprague-Dawley rats were used in the study. These rats, weighing 280–300 g, were adapted and reared for approximately 2 months, with unrestricted access to food and drink. The trauma model was performed according to the marmourou journal model for developing countries with modification to Nasution et al..[26,27]

Statistical analysis

Basic data were presented in terms of mean ± SD. The angiogenesis predictor factors in the experimental animals after administering CAPE were evaluated by performing a correlation test on the initial analysis, using the Pearson correlation, resulting in normally distributed data. Furthermore, multivariate linear regression analysis was conducted for all examined parameters in instances where p-value was statistically significant at <0.05. All data were processed and analyzed using Excel 2013 and SPSS version 23 software (Armonk, NY: IBM Corp.).

RESULTS

All rats survived after trauma up to a predetermined experimental time point.

Table I: Average TBI parameters after CAPE provision

Parameter	Mean	Standard Deviation
VEGF	938274.352	96049.339
mRNA AQP4	10099.00	531.490
MPO	9284222.028	953098.093
F2 isoprostane	307346.562	31119.798

The average weight of Sprague-Dawley rats in this experiment was 290.07 grams. Table I shows each TBI parameter tested by descriptive analysis to determine the average following the administration of CAPE.

Table II: Correlation test results between VEGF and parameters mRNA AQP4, MPO, and F2 isoprostane

Variable		R value			
		mRNA	sAQP4	sMPO	F2iso
VEGF	Pearson Correlation	0.957	0.910	0.957	0.917
	Sig. (2-tailed)	<0.001*	<0.001*	<0.001*	<0.001*

Note: * p <0.05 is significant

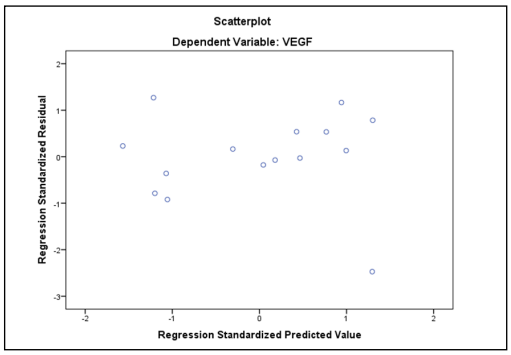

Figure 1. VEGF variable scatterplot graph with independent variable parameters after TBI.

Table II shows the Pearson correlation analysis. A strong correlation was observed between all parameters and VEGF (range r=0.910–0.957), with a significance value of (p<0.05). Figure 1 is a scatter plot graph demonstrating the homogeneity of the residual variant. The non-specific pattern prompts the need to perform multivariate analysis.

The correlation results are followed by multivariate linear regression analysis to determine the most influential parameters of angiogenesis. Statistical analysis showed a 95% contribution of AQP4 and MPO mRNA post-trauma in the brain after the administration of CAPE (Table III).

Table III: VEGF multivariate analysis with MPO, F2 isoprostane, and AQP4 parameters

Model		Unstandardized Coefficients		Standardized Coefficients	T	p-value
		B	Std. Error	Beta		
1	(Constant)	-504601.221	161188.755		-3.130	.011
	mRNA	99.960	33.668	.575	2.969	.014
	sAQP4	-.798	.603	-.252	-1.324	.215
	MPO	.041	.015	.395	2.770	.020
	F2iso	.952	.431	.298	2.211	.051
2	(Constant)	-361525.329	123653.703		-2.924	.014
	mRNA	69.528	25.436	.400	2.733	.019
	MPO	.042	.015	.405	2.755	.019
	F2iso	.684	.393	.214	1.741	.110
3	(Constant)	-422825.615	128174.539		-3.299	.006
	mRNA	86.192	25.483	.496	3.382	.005
	MPO	.053	.015	.504	3.441	.005

[a] VEGF dependent variable
[b] Predictor in the model: (Constant) F2isoprostane, mRNA AQP4 and MPO
[c] Predictor in the model: (Constant) mRNA AQP4 and MPO

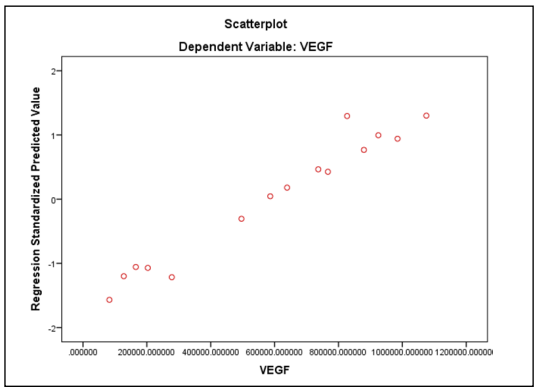

Figure 2. VEGF variable scatterplot graph with independent variable of MPO, AQP4 mRNA

The scatterplot graph in Figure 2 illustrates a correlation between VEGF as a dependent variable and the independent linear variable.

DISCUSSION

The effect of vascular endothelial growth factor (VEGF) against angiogenesis occurs normally or pathologically.[28] This molecule binds to endothelial cells through an interaction with high-affinity tyrosine kinase receptor flt-1 (VEGFR-1) and Flk-1/KDR (VEGFR2), produced predominantly in SDO endothelial cells.[29,30] In addition, VEGF has strong vascular permeability activity (several thousand times superior to histamine) and a direct effect on the tight junction endothelial SDO.[29–31] This molecule, alongside platelet-derived growth factor (PDGF), is a potent angiogenic factor with activity as a proinflammatory cytokine, estimated to improve endothelial cell permeability and upregulate molecular adhesion.[32] In addition, VEGF binds to specific transmembrane stimuli, thus signalling a pathway for the proliferation and migration of endothelial cells. This further ensures the maintenance of the immature types and increases vascular permeability.[32,33]

VEGF is mitogenic, angiogenic, and a potential mediator of vascular permeability. It also serves as a potent activator of angiogenesis and neurogenesis. Previous studies have demonstrated the role of CAPE in reducing vascular permeability in the blood of rats subjected to brain injury, while angiogenesis continues by evaluating the clinical condition of survivors up to the termination of the study.[34,35]

A strong correlation was identified between VEGF and Myeloperoxidase as well as AQP4 mRNA. This is associated with the presence of Myeloperoxidase (MPO) as an enzyme secreted by neutrophils and active macrophages or microglia. Hence, ROS formation is triggered, followed by the incidence of ischemia and the consequent disruption of the sodium pump in the astrocytes. This phenomenon further instigates swelling and cerebral edema.[3] Interleukin-1 induces endothelium in the brain vascular system, thus releasing the VEGF.[36] This product is known to induce astrocytes and release aquaporin (AQP) -4, which stimulate the vascular wall to facilitate water discharge into the interstitial brain tissue, resulting in cerebral edema.[37] These findings are congruent with the statistical tests, where AQP4 and MPO mRNA demonstrated a 95% contribution towards angiogenesis in the brain, following the incidence of an injury.

CONCLUSION

This study established a relationship between the angiogenesis process in the brain post-trauma, marked by the VEGF expression, and AQP4 mRNA as well as blood Myeloperoxidase (MPO) levels, following the administration of CAPE. These three factors were shown to have a strong correlation because statistical tests using multivariate linear regression analysis indicated a 95% contribution to the angiogenesis process of blood vessels in the brain.

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ORIGINAL ARTICLE

Perception of Combined Team-Based Learning and Project-Based Learning among Undergraduate Medical Students: An Integration of Active Learning Strategies in Medical Education

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ABSTRACT

INTRODUCTION: Team-based learning (TBL) is an active learning session in small groups equipped with an instructional strategy giving students the opportunity to apply knowledge through various phases of activities. The phases are: i) pre-class preparation, ii) individual readiness assurance testing (IRAT) and group readiness assurance testing (GRAT), iii) immediate feedback, and iv) knowledge application phase. However, a 2-hour TBL session could be exhaustive. To address this issue and improve students' enthusiasm towards self-learning process in TBL, project-based learning (PrBL) was incorporated in the final phase of TBL. This pilot study aimed to evaluate the perception of students on the implementation of combined TBL-PrBl in teaching and learning activity. TBL-PrBl also addresses the creativity element of the 21st century learning skills. **MATERIALS AND METHODS:** This cross-sectional pilot study was conducted among preclinical students enrolled in a Pathology course, involving 44 students. The research instrument was a validated questionnaire which assessed four key components in TBL namely; i) teamwork skills, ii) motivation, iii) subject-specific knowledge comprehension, and iv) overall satisfaction. **RESULTS:** Most students believed that TBL-PrBl improved teamwork, thinking skills, and enhanced understanding. 59.1% preferred TBL-PrBl over the didactic lecture, and 63.6% agreed that TBL-PrBl should be continued in the teaching and learning of Pathology. **CONCLUSION:** Based on the findings, TBL-PrBl has the potential to fulfil the 21st-century learning skills and fills in the gap of the limitation imposed by the traditional TBL.

Keywords
team-based learning, project-based learning, IRAT, GRAT

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INTRODUCTION

Team-based learning (TBL)

Team-based learning (TBL) was first initiated in medical school in the year 2001.[1] It is "an active learning and small instructional strategy that provides students with opportunities to apply conceptual knowledge through a sequence of activities that include individual work, teamwork, and immediate feedback".[2] The main objective of TBL is to go beyond the scope of the subject content by providing opportunities for students to apply knowledge and solve the given problems themselves.[2] Compared to the traditional, lecture-centred learning sessions, TBL encourages active student participation.[3,4] TBL is performed in several phases namely: i) pre-class preparatory phase where students are given learning material one week in advance, followed by ii) in-class readiness assurance test (RAT) phase, iii) timely feedback phase, and iv) the knowledge application phase.[5]

The idea is to engage students in individual learning processes while inculcating teamwork.[2] This helps to improve communication and social skills.[4] As more time is allocated for problem-solving and discussion among team members, TBL greatly improves students'

comprehension and retention of information.[6,7] Additionally, compared to the traditional lecture-centred learning method, TBL addresses the challenge of ineffective mass lectures, particularly when the availability of experts is limited.[7,8] As this learning method is a student -centred approach, TBL has been largely adopted in numerous medical schools aiming at producing graduates with critical thinking and capabilities to apply knowledge.[9,10]

Project-based learning (PrBL)

PrBL is a distinguishable form of teaching and learning activities (TLA) because of the "project" component that is not present in other forms of TLA.[11] The learning process of PrBL requires students to complete several steps in problem-solving that include i) defining problems, ii) discussing issues, iii) designing a model, iv) analysing data, and v) sharing findings with peers.[11] PrBL has been proven to improve students' attitudes towards self-learning, stimulate creativity and their higher-order cognitive skills.[12,13] PrBL has been widely utilized in many fields including science and mathematics.[14,15] However, only 20% of studies have been applying PrBL in a higher education setting.[16] A study in a clinical setting of medical school revealed that PrBL is an effective measure to inculcate empathy towards patients.[17] Thus, PrBL could also be applicable in theoretical learning of medical knowledge in preclinical subjects.

TBL vs. PrBL

The major phases of TBL include i) pre-class preparation, ii) readiness assurance test (individual and group), iii) feedback session and iv) theoretical application phase.[5] Meanwhile, in PrBL, the phases comprise of i) timely project planning based on a fundamental question, followed by ii) constructing a relevant model, and iii) presentation which test the model's applicability in a given real situation.[18] Both TBL and PrBL are student-centred learning methods accomplished in a group.

Combination of TBL-PrBL

In our faculty, TBL was introduced in 2022 intended to incorporate student-centred learning to enhance independent skill acquisition.[9] In the early phase of TBL implementation in our faculty, our preliminary study suggested that most students enjoyed learning via TBL method and most agreed that TBL should be incorporated in the curriculum. However, some preferred the traditional lecture-based methodology. Hence, we attempted to improve the current TBL method. Despite the advantages of TBL, some showed lack of participation from team members who were insecure of their knowledge, language, and communication skills.[9,10] Our observation also revealed that students were focusing more on the earlier phases such as IRAT, GRAT and feedback session. The lack of interest in the knowledge application phase may be due to exhaustion towards the end of a 2-hour period.

In our effort to overcome this issue and to enhance students' creativity and encourage everyone's contribution to the session, project-based learning (PrBL) was incorporated in the final phase of TBL. Current TLA in our faculty is outcome-based with a hybrid of traditional subject-based and system-synchronized. TBL was recently introduced to diversify and integrate student -centred learning methods. The 21st-century learning skills outlined the 4Cs elements which include Critical thinking, Creativity, Communication, and Collaboration which TBL addresses.[19] However, the creativity element could be limited in the medical theoretical learning phase, since it is traditionally bound to vast and detailed subjects that run within a packed duration of time.

The integration of different TLA methods in a single learning session such as the combination of TBL with case-based learning (CBL), and PBL with CBL have been performed and proven to effectively enhance academic and clinical performance.[20,21] This study is the first to explore on the combined TBL-PrBL method. As a preliminary stage, we incorporated PrBL as an element in TBL that could explore students' creativity in medical subjects.[2,19] In this pilot study, the objective is to evaluate students' perception on the implementation of TBL-PrBL in a single teaching-learning session of Pathology module. The finding of this study is hoped to serve as a basis for future research and improvement in medical curriculum setting.

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional pilot study was conducted among second-year pre-clinical students at the Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (UPNM) from April 2023 - June 2023. UPNM serves both civilian and cadet students, with the latter preparing for careers in the military upon graduation.

Sample Size and Sampling Techniques

Universal sampling method was employed involving all 44 Year 2 medical students enrolled at the Faculty of Medicine and Defence Health, UPNM. A minimum of 30 respondents is sufficient for determination of questionnaire reliability.[22]

Data Collection Tools

Data was collected using a validated questionnaire adapted from Khan et al. (2020), designed to evaluate four primary domains; i) teamwork, ii) students' motivation, iii) subject-specific knowledge understanding, and iv) satisfaction.[23] The questionnaire was administered online, with voluntary participation after providing informed consent. Responses were recorded on a 5-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). The total score was calculated by summing the scores of all items. The internal consistency of the 10 items was assessed using Cronbach's alpha, yielding a reliability coefficient of 0.986.

Intervention: Combined TBL-PrBL session

The topic focused in this study was chronic liver disease and portal hypertension, a critical topic within the pathology module, and applied a combined Team-Based Learning (TBL) and Project-Based Learning (PrBL) approach. Figure 1 illustrates the structure of the TBL-PrBL method.

Phase 1: Pre-class Preparation

Students received a lecture video and supplementary materials on liver disease two weeks prior to the TBL-PrBL. The objectives and study materials were communicated in advance, requiring students to prepare based on the provided content.

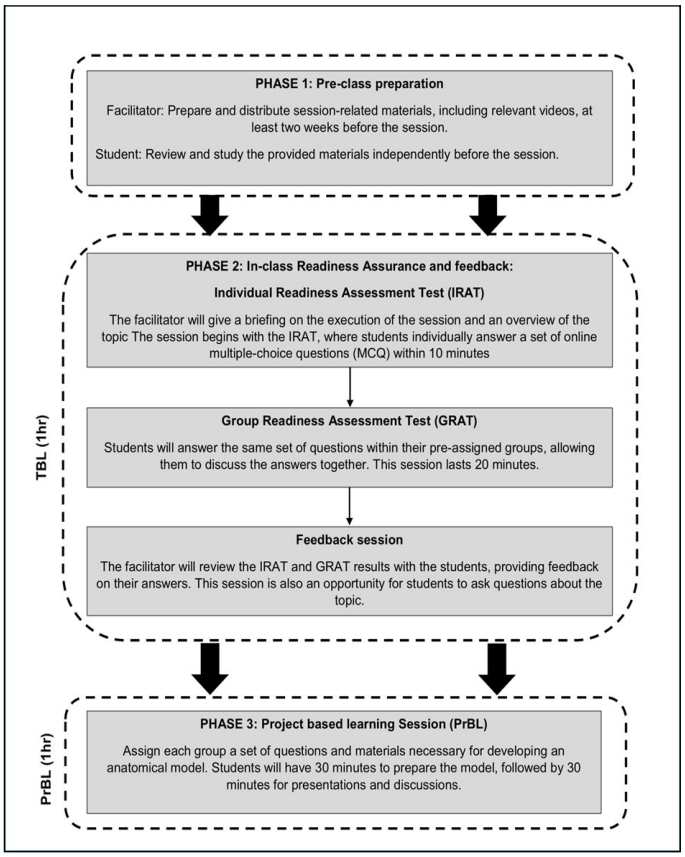

Figure 1: The phases of team-based learning (TBL) with incorporation of project-based learning (PrBL) in the final phase of teaching-learning activity.

Phase 2 TBL: In-class Readiness Assurance and feedback

The in-class session began with an Individual Readiness Assurance Test (IRAT) consisting of 10 multiple-choice questions (MCQs) delivered via the online platform (Kahoot). This was followed by the Group Readiness Assurance Test (GRAT), where students worked in predefined groups to discuss the MCQs. Groups were seated in a circle to facilitate effective discussion. The IRAT component aimed to evaluate understanding of the topic based on the preparatory materials, primarily testing the cognitive aspects of the session. The subsequent GRAT assessed both cognitive and affective domains, including teamwork, interpersonal skills, and communication abilities, as students collaborated to determine the correct answers.

Phase 2 TBL: Feedback session

A comprehensive discussion of each question, with detailed feedback was provided to each group. The instructor facilitated the session by reviewing each question and its corresponding answer, ensuring that students understood the rationale behind the correct responses. During the discussion, the instructor did not only clarify the correct answers but also addressed common misconceptions and errors that emerged during the IRAT and GRAT sessions. This allowed students to reflect on their thought processes. Additionally, the feedback session served as an opportunity for students to ask questions and engage in further discussion, promoting a deeper understanding of the subject.

Phase 3 PrBL: In-class application

Here, students transitioned from traditional clinical application to PrBL. Each team was tasked to create an anatomical model related to chronic liver disease and use it to answer clinical pathology-related questions. Teams were given 30 minutes to prepare their project, where all groups received the same prompt as shown in Figure 2.

1. Draw or construct a model of portal system and portosystemic anastomosis
2. Based on the model (in 1), describe the pathophysiology of portal hypertension and the given clinical manifestations:
    a. Oesophageal varices
    b. Haemorrhoids
    c. Caput Medusa
    d. Splenomegaly

Figure 2: Phase 3 Project-based learning instruction and questions given to students before project building.

While traditional PrBL involves several steps, including preparation, planning, and execution, this study employed a more streamlined approach with predetermined outcomes to facilitate student engagement.[23] Despite a more structured PrBL, students were encouraged to exercise creativity in developing their models. Raw craft materials such as paper, straws, glue, and plasticine were provided in advance to save time sourcing materials. Using the completed anatomical models (Figure 3), the groups were given 30 minutes for presentation and a question-and-answer session. All 3 phases were completed within a 2-hour period on the same day.

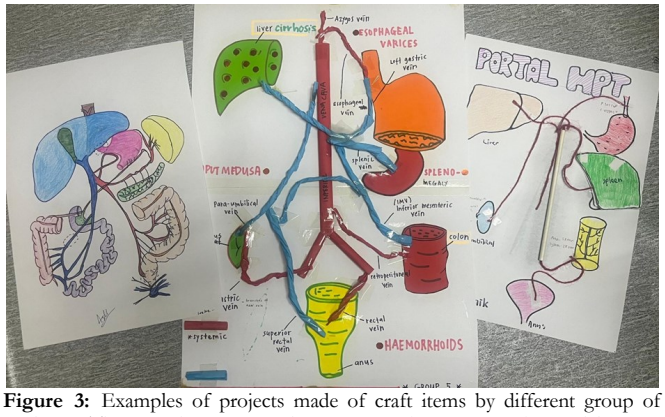

Figure 3: Examples of projects made of craft items by different group of students. The portal system and portosystemic anastomosis models were utilised by students for presentation on the given questions.

Statistical Analysis

Data was coded and entered into Microsoft Excel and analysed using IBM SPSS® Statistics v26 (IBM Corp., New York, USA) statistical software. The average score for each student was calculated on a 5-point Likert scale. The 5-point Likert scale responses were combined into 3 different categorical variables; i) 'agree' (strongly agree plus agree), ii) 'neutral', and iii) 'disagree' (strongly disagree plus disagree) for Chi-Square test. Chi-Square test was used to measure the associations between the different categorical variables (agree, neutral, and disagree) among the male or female students.

RESULT

All 44 students agreed to participate, 25 (56.8%) were female, and 33 (75.0%) were Bumiputra.

Table 1 depicts the student's perception on the combined TBL-PrBL session. Based on the responses, majority agreed that this method helps to improve teamwork skills (4.25±1.08), motivate to learn Pathology (4.16±1.12), expand reasoning skills (4.18±1.08), promote better understanding of the subject matter (4.27±1.11), stimulates thinking (4.20±1.07), reduces misconceptions about the topic (4.11±1.15), helps relate pathological principles to real life situation (4.20±1.07) and helps to gain an in-depth knowledge about the subject (4.09±1.18).

Despite majority agreeing that they preferred TBL-PrBL compared to didactic lecture and it should be included in

pathology module, these two items received the lowest mean scores, 3.90±1.20 and 3.98±1.21 respectively. For all the 10 items, there were no significant differences among male and female respondents. Additionally, when comparing bumiputra and non-bumiputra, there was no significant differences in their responses.

Likert scale was employed and students were required to give their opinion on each item in the questionnaire based on the 5 scales and scores (Strongly disagree (1 score), Disagree (2 scores), Neutral (3 scores), Agree (4 scores), Strongly agree (5 scores)). In the data tabulation, the two extreme scales (strongly disagree and strongly agree) were combined with the adjacent scales (disagree and agree respectively) for conciseness. Item 1: assessed students' team working skills, Items 2 and 3 assessed students' motivation, Items 4 to 8 assessed students' subject-specific understanding, Items 9 and 10 assessed students' satisfaction towards this method.

DISCUSSION

To the best of our knowledge, this is the first study that adapts the combination of team-based learning (TBL) and project based learning (PrBL) in a single teaching-learning session. Based on the results, the combination of TBL-PrBL helped students understand the subject matter and improved their teamwork skills and motivation.

Teamwork skills and motivation to learn

TBL-PrBL teaching-learning method integrates other learning domains to optimize student engagement.[24,25] Analysis of the data revealed strong agreement among students on the improvement of their teamwork skills (Item 1) and the motivation for them to learn pathology through this approach (Item 2). Through group discussions, the students learn cooperative problem-solving in the TBL and actively contribute and exchange ideas that were essential for the creation of models in the PrBL session. As a result, these interactive dynamics enhanced the learning process by fostering affective domain level 2 (responding) and psychomotor level 3 (guided response) competencies which further enriched their learning experience.[26]

Table 1: Students' perception on combined Team-Based Learning – Project-Based Learning for single Pathology module session (n=44).

Item	Questions	Score Mean ± SD	Categories	Participants n (%)	Male n (%)	Female n (%)	P-value*	Bumiputra n (%)	Non-Bumiputra n (%)	P-value*
1	It helps to improve team working skills	4.25 ±1.08	Disagree	3 (6.8)	1 (5.3)	2 (8.0)	0.874	3 (9.1)	0 (0.0)	0.720
			Neutral	9 (20.5)	3 (15.8)	6 (24.0)		6 (18.2)	3 (27.3)	
			Agree	32 (72.7)	15 (78.9)	17 (68.0)		24 (72.7)	8 (72.7)	
2	It motivates me to learn Pathology	4.16 ±1.12	Disagree	4 (9.1)	2 (10.5)	2 (8.0)	0.379	4 (12.1)	0 (0.0)	0.547
			Neutral	9 (20.5)	2 (10.5)	7 (28.0)		6 (18.2)	3 (27.3)	
			Agree	31 (70.5)	15 (78.9)	16 (64.0)		23 (69.7)	8 (72.7)	
3	TBL stimulates my thinking	4.20 ±1.07	Disagree	3 (6.8)	1 (5.3)	2 (8.0)	0.874	3 (9.1)	0 (0.0)	0.720
4	TBL improve my reasoning skills	4.18 ±1.08	Disagree	3(6.8)	1 (5.3)	2 (8.0)	0.679	3 (9.1)	0 (0.0)	0.861
			Neutral	10 (22.7)	3 (15.8)	7 (28.0)		7 (21.2)	3 (27.3)	
			Agree	31 (70.5)	15 (78.9)	16 (64.0)		23 (69.7)	8 (72.7)	
5	It promotes better understanding of the subject matter.	4.27 ±1.11	Disagree	3(6.8)	1 (5.3)	2 (8.0)	0.679	3 (9.1)	0 (0.0)	0.861
			Neutral	10 (22.7)	3 (15.8)	7 (28.0)		7 (21.2)	3 (27.3)	
			Agree	31 (70.5)	15 (78.9)	16 (64.0)		23 (69.7)	8 (72.7)	
6	TBL help to reduce my misconceptions about the topic.	4.11 ±1.15	Disagree	4 (9.1)	2 (10.5)	2 (8.0)	0.505	4 (12.1)	0 (0.0)	0.743
			Neutral	11 (25.0)	3 (15.8)	8 (32.0)		8 (24.2)	3 (27.3)	
			Agree	29 (65.9)	14 (73.7)	15 (60.0)		21 (63.3)	8 (72.7)	
7	This type of teaching helps me to relate pathological principles to real life situation.	4.20 ±1.07	Disagree	3 (6.8)	0 (0.0)	3 (6.8)	0.441	3 (9.1)	0 (0.0)	0.720
			Neutral	9 (20.5)	4 (21.1)	5 (20.0)		6 (18.2)	3 (27.3)	
			Agree	32 (72.7)	15 (78.9)	17 (68.0)		24 (72.7)	8 (72.7)	
8	It helps to gain an in-depth knowledge about the subject.	4.09 ±1.18	Disagree	6 (13.6)	3 (15.8)	3 (12.0)	0.799	6 (18.2)	0 (0.0)	0.198
			Neutral	7 (15.9)	2 (10.5)	5 (20.0)		4 (12.1)	3 (27.3)	
			Agree	31 (59.1)	14 (73.7)	17 (68.0)		23 (69.7)	8 (72.7)	
9	I prefer this type of teaching to didactic lectures.	3.90 ±1.20	Disagree	6 (13.6)	3 (15.8)	3 (12.0)	0.096	6 (18.2)	0 (0.0)	0.469
			Neutral	12 (27.3)	2 (10.5)	10 (40.0)		9 (27.3)	3 (27.3)	
			Agree	26 (59.1)	14 (73.7)	12 (48.0)		18 (54.5)	8 (72.7)	
10	I feel that this method should be included in pathology curriculum	3.98 ±1.21	Disagree	5 (11.4)	3 (15.8)	2 (8.0)	0.150	5 (15.2)	0 (0.0)	0.514
			Neutral	11 (25.0)	2 (10.5)	9 (36.0)		8 (24.2)	3 (27.3)	
			Agree	28 (63.6)	14 (73.7)	14 (56.0)		20 (60.6)	8 (72.7)	

Comprehension of the subject matter

It is evident that majority of students strongly agreed that the TBL-PrBL session promoted better comprehension and understanding of the subject matter. TBL served to facilitate students' comprehension of the subject matter through active engagement with questions, whereas the PrBL component further enhanced their understanding by producing an output reflective of their comprehension of the topic.[2,11] This multi-faceted pedagogical approach effectively catered to various cognitive levels outlined in Bloom's Taxonomy. The questions provided during the Individual Readiness Assurance Test (IRAT) and Group Readiness Assurance Test (GRAT) of TBL targeted the cognitive levels 1-2 of Bloom's Taxonomy, whereas the PrBL component primarily addresses levels 2-3, demanding students to comprehend the questions provided before applying their responses into mind maps or infographics as part of the project.[19] Higher-order thinking skills are essential for medical students to acquire as they equip them with the aptitude to make sound decisions, which is a critical skill in the medical field and domain.[24]

Students' satisfaction

Though the responses were generally positive, a small proportion (13.6%) of students did not prefer TBL-PrBL approach over didactic lectures and that the teaching-learning method should not be included in the pathology module (11.4%). This outcome could be attributed to the lack of familiarity with a newly introduced teaching-learning method especially when students have developed convenience towards lecture-based learning method.[27,28] These findings echoed Haidet et al. (2012) and Carrasco et al. (2019) as they reported a lack of preference and motivation of students towards TBL particularly in the early phase of transition from the traditional lecture-based method in the medical curriculum.[5,27] It is postulated that unfamiliarity with the teaching-learning methods coupled with uncertainties on how these sessions may influence their performance in final examinations, contributed to their preference for traditional didactic lectures over the newly introduced student-centred learning technique.[23] The incorporation of a blended approach combining TBL and PrBL aimed to address certain limitations imposed in the conventional TBL methodology. As students' collaboration and involvement in the second half of the TBL was not always consistent,[9,19] transitioning from a thematic question-answering approach in TBL to a more innovative model creation process can break the monotonous approach in TBL and maintain their interest and curiosity throughout the session.[19] However, it is ascertained that this pilot study on students' perception does not provide a solid assessment on the effectiveness of TBL and combined TBL-PrBL method with the didactic lecture-based approach.

Limitations

There are several limitations in this study that need to be addressed. This is a cross-sectional pilot study with small sample size, therefore the comparison between the traditional TBL with this combined TBL-PrBL method cannot be adequately assessed. This study evaluated students' perception based on a single TBL topic, therefore we cannot explore the potential of other confounding factors that could influence students' perceptions. This comprises the choice of topic, the difficulty level of the subject matter and the facilitator in charge. This combined method's limitation also include the challenge that the students face in adhering to the allocated timeframe for completing the model construction.

Future directions

As the combined TBL-PrBL approach is still new, we believe there are areas that can be further explored and improved in its implementation within the medical curriculum. Future studies could look into the perception of TBL in various topics, disciplines, different facilitators, larger sample size in a case-control study. To augment the practicality of this method, a short and simple project assigned earlier with instruction provided during preparative phase could be the way forward.

CONCLUSION

In conclusion, this study highlights the potential of TBL-PrBL approach to address the evolving demands of 21st-century learning skills. By bridging the gap of conventional TBL methods, this hybrid model offers a

potential role in enhancing student engagement and critical thinking. Looking ahead, we believe that further refinement and integration of TBL-PrBL methodologies into medical curriculum could lead to significant advancements in medical education and potentially extended to broader applications in higher education settings.

ETHICAL APPROVAL

Ethical approval for this study was granted by the UPNM Research Ethics Committee (Ethics No.: UPNM (FPKP) 14.01/02).

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ORIGINAL ARTICLE

The Development and Content Validation of a Needs Assessment Questionnaire for Visual Attributes Profiling in Students with Visual Impairment

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ABSTRACT

INTRODUCTION: Conducting a needs assessment is imperative to identify gaps in the current data management practices for visually impaired students. This study aims to evaluate the content validity of a needs assessment questionnaire, a critical precursor to developing a systematic visual attributes profile for this student population. By validating the questionnaire, the challenges and needs of visually impaired students can be accurately identified, enabling targeted interventions and informed policy decisions in special education. Ensuring the precision of the questionnaire establishes a foundation for understanding and addressing these students' needs, ultimately contributing to more effective educational environments. **MATERIALS AND METHODS:** The instrument underwent two phases, i.e. item development and a comprehensive assessment of item validity by six experts. The experts evaluated the instrument's relevance and comprehensibility using a four-point Likert scale. Microsoft Excel facilitated the analysis of the Content Validity Index (CVI), Content Validity Ratio (CVR), and modified kappa (K) statistics. **RESULTS:** The item content validity index (I-CVI) ranged from 0.83-1, with a Scale-level Content Validity Index (S-CVI/Ave) of 0.97, indicating acceptability. The Content Validity Ratios (CVR) for most items surpassed 0.7, indicating strong agreement among experts on their relevance with the interpretation of the K analysis of 70% excellent. However, three items in the second and third domains required revision and clarity enhancement. **CONCLUSION:** The content validity analysis showed that all items in the questionnaire were deemed appropriate. This suggests that the questionnaire is suitable for assessing the need to develop a systematic visual attribute profiling for students with visual impairment.

Keywords
Content Validity Index, Content Validity Ratio, Need Assessment, Visual Impairment, System Development Lifestyle

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INTRODUCTION

According to the latest report from the Special Education Division, Malaysia, 2616 students are classified as visually impaired, with 289 of them enrolled in special schools.[1] Visual impairment can profoundly impact cognitive and learning process abilities. Previous study has found that the involvement and academic performance of visually impaired students is generally lower compared to their sighted peers in mainstream classrooms.[2] Furthermore, research on teachers' perspectives regarding the academic involvement of visually impaired students is moderate.[3,4] Most teachers agreed that the academic and social challenges faced by these students are due to their visual impairment. Students with severe visual impairment and those enrolled in special education programmes often exhibit low self-assurance and academic achievement.

Visual anomalies can reduce the efficiency of the visual system and consequently reduce the capacity to perform optimally at school.[5] The key attributes related to the visual system that may be affected include visual acuity, visual field, and contrast sensitivity. These visual attributes are vital for diagnosing vision issues and deciding on the

best treatments. Despite the best treatment, eye anomalies can result in difficulty carrying out certain tasks, especially those involving vision. Therefore, it is important to understand the demand on the visual system and relate it to visual ability. Visual demand refers to the visual requirements specific to each task, which vary depending on the nature of the task.[6] Utilizing evidence-based information from medical records and data on the students' visual attributes should guide the teachers to meet students' visual demands in the classroom. Previous studies have primarily focused on management strategies for children with common refractive errors and non-strabismic conditions. However, there remains a limited focus on studying the visual attributes and demands of visually impaired students.[7,8] This gap is particularly significant given the diverse nature of visual impairment of children across different regions.[9] Recent global estimates indicate that approximately 2.2% of children and adolescents experience some form of visual impairment, with refractive errors being a leading cause.[10,11] Nonetheless, a profiling study in Malaysia concerning the causes of visual impairment and the utilization of low-vision aids has revealed congenital cataracts as the primary cause of visual impairment among students.[12] This underscores the importance of genetic consultation and the careful selection of visual aids, based on functionality and the student's visual needs to enhance visual performance. These findings highlight the critical role of detailed visual profiling in formulating tailored rehabilitation strategies.

In parallel with technological advancements, data profiling systems enable continual access to updated algorithms. In the education sector, data management systems are crucial for handling the increasing volume of data and restructuring administrative methods, thus impacting various aspects such as leadership, decision-making, human resources, communication, accountability, and strategic planning in schools.[13] These systems involve collecting, organizing, securing, and storing data for analysis and informed decision-making, replacing the traditional manual methods. In Malaysia, the Ministry of Education (MOE) employs The Educational Management Information System (EMIS) to systematically gather educational data from schools. Despite its intended utility, concerns regarding the quality and accuracy of the collected data have been voiced by high-ranking MOE officials.[14] Inclusive or special education faces additional challenges within this system, as essential details about students' conditions, impairments, and management are often overlooked. This omission poses difficulties for those tasked with tailoring the educational needs of these students, further highlighting the critical need for enhanced data collection practices specifically designed for special education populations.[15] Consequently, conducting a needs assessment is vital before developing tailored software systems to meet the visual needs of visually impaired students.

To date, questionnaires remain a prevalent and widely utilized method for needs assessment across various educational fields, including healthcare and software engineering.[16] Ensuring instrument reliability is crucial, especially in pilot studies, as validity evaluates how accurately an indicator measures the associated constructs.[17] This study aims to evaluate the content validation of a needs assessment questionnaire in the Malay Language, specifically designed for developing systematic visual profiling for visually impaired students. By rigorously assessing the questionnaire's content validity, this study ensures the reliability of tools used in educational planning and provides empirical evidence of its effectiveness in capturing relevant visual attributes and needs. The development of such tools has the potential to significantly enhance the educational experiences of visually impaired students by enabling educators to tailor interventions more effectively, fostering a more conducive learning environment.

MATERIALS & METHODS

Development of the Instrument/ Item generations

The development of the questionnaire items through literature review focused on the involvement of the students' management system. Two questionnaires identified from published articles were selected and modified to contribute to item generation.[18,19] The development process began with identifying the definition of the selected domain and drawing insights from relevant literature related to school database management

information systems and portals. A significant shift occurred as a web-based system replaced the conventional approach. The literature review results guided the formulation of the draft, encompassing four domains: i) current data management, ii) challenges in data management, iii) infrastructure system, and iv) top management support. This was followed by a refinement stage through discussion sessions, which included brainstorming to generate new ideas relevant to visually impaired students' needs and critical evaluation of each item for relevance and clarity. Subsequently, linguistic adaptation was carried out to ensure simplicity and comprehension in the Malay language. The final stage involved a preliminary review by a language expert to verify the clarity and cultural appropriateness of the items. This comprehensive process ensured that the questionnaire items were well-suited to the study's objectives and the target population.

Following the initial development, the lead investigator conducted a discussion session involving two panels; i) a senior lecturer, and ii) an undergraduate student specializing in Mobile Communications Systems, Networking, and Big Data. The aim was to gather information and ideas to refine the questionnaire. Qualitative analysis was applied to the data collected from these discussions, and new questionnaire items were incorporated based on the outcomes. A preliminary set of questionnaire was created to avoid duplication of items. These items were crafted using simple Malay language to ensure comprehension by the participants.

Content Validity Process

The judgment and quantification of the questionnaire were done according to the recommendation by the previous studies which involves forming expert panels, inviting experts for participation, analysing responses through item content validity index (I-CVI), content validity ratio (CVR), and modified kappa ($\varkappa$), and ultimately revising and finalizing measures.[20-23]

The expert selection process was rigorous to ensure a comprehensive evaluation of the questionnaire. The formation of the panel adhered to at least one criterion encompassing three essential conditions: i) active involvement in web-based software planning and development, along with possessing extensive knowledge and substantial experience, ii) expertise in managing and addressing issues associated with visually impaired students, and iii) demonstrated willingness to engage in the content validity process. Experts were identified based on their involvement in the low vision field, special education, and information technology within the past five years to promote diverse representation across disciplines. Table I lists the six expert panels recruited for the content validity examination.

Table I: List of expert panels

NO	POSITION	AFFILIATION
1	Assistant Director	Special Education Rehabilitation Unit, Ministry of Education
2	Associate Professor	Centre for Cyber Security, Faculty of Information Science and Technology, UKM
3	Senior Lecturer	Centre of Education and Community Wellbeing, Faculty of Education, UKM
4	Senior Lecturer	Centre for Information Systems Studies (Intelligent Systems), Universiti Teknologi MARA
5	Optometrist	Vision Care, Kajang Selangor
6	Principal	Sekolah Menengah Pendidikan Khas Setapak

The expert assessed the items of the instrument using item-rating scales recommended from the previous study.[24] These scales consisted of four points: 1=*'not relevant'*, 2=*'somewhat relevant'*, 3=*'quite relevant',* and 4=*'highly relevant'*. The experts were also requested to assess the understanding of the items and provide feedback, especially when they evaluated items 1=*'not relevant'*, and 2=*'somewhat relevant'*; or 1=*'not understood and confusing'*, and 2=*'understood but confusing'*.

The responses from the experts were analysed using I-CVI, CVR, and $\varkappa$. The I-CVI was calculated within a range of 0-1, indicating the proportion of experts awarding a score of 3 or 4 to an item. Items with I-CVI values of 0.79 or higher were deemed relevant, those between 0.70-0.79 required revision, and items with an I-CVI of 0.78 for more than five experts were considered for elimination. The Scale Content Validity Index (S-CVI) was determined using Average (Ave) and Universal Agreement (UA) methodologies, with acceptable values set at 0.8 or greater, emphasizing sensitivity to expert agreement.[19] The substitute for CVI is the $\varkappa$ which tackles the constraints of proportion agreement indices. In modified kappa, an *'excellent'* value is above 0.74, and a

'good' value falls between 0.60-0.74. Items in the questionnaire rated as excellent or good will be included in the research. Table II shows the range values for I-CVI and ϰ. The modified ϰ is determined by utilizing the probability of chance agreement (Pc) and I-CVI. The values and formula were based on previous literature.[24]

Table II: ICVI and ϰ range values

Item	Standard Range	Degree of Uniformity
Item Level-Content Validity Index (I-CVI)	<0.70	Eliminate
	0.70-0.79	Need for revision
	≥0.80	Appropriate
Modified Kappa (ϰ)	<0.40	Poor
	0.40-0.59	Fair
	0.60-0.74	Good
	>0.74	Excellent

Meanwhile, the CVR is conducted to evaluate item essentiality, ranging from -1 to +1. The proportion of awarding the score value by the experts was the same as I-CVI. The minimum permissible value of 0.78 for individual item acceptance, or 0.99 for a panel of six experts.

RESULTS

Items Development of Need Assessment Questionnaire

As previously outlined, the need assessment questionnaire preceding the development of the visual profiling system comprises four distinct domains; i) current data management, ii) challenges in data management, iii) data infrastructure, and iv) top management support to form 15 items. The first domain (current data management), encompassing Items 1-3, focused on the tools and systems currently utilized by teachers and administrative staff. Items 1 and 2 evaluated the usage of various tools such as physical paper or files, Microsoft Excel, Google Sheets, or dedicated School Data Management Systems. Meanwhile, Item 3 assessed the effectiveness of the current data handling processes.

The second domain explored the challenges encountered with the existing tools or systems. Items 4 and 5 addressed the specific obstacles, including limited accessibility, support provision difficulties, and communication barriers. The third domain (Items 6 and 7) emphasized the importance of incorporating visual characteristics, including issues related to visual impairment and the utilization of visual aids, within data infrastructures. In the same domain, (Items 8 to 11), were centred on knowledge related to web-based systems, assistive technologies, and software in managing visual profiling. The fourth domain*; top management support* (Items 12-15) highlights the support provided to teachers and staff in managing data information for students with visual impairment. It delved into the importance of collaboration, training, data security measures, and the necessity for specific features in data management systems.

Content Validation of Need Assessment Questionnaire

The content validation process employed statistical measures including Item-Content Validity Index (I-CVI), Content Validity Ratio (CVR), Universal Agreement (UA), and Modified Kappa (ϰ) to assess item relevance and validity across all domains. Table III summarizes these measures. Most of the items (80%) achieved excellent content validity with I-CVI values of 1.00, exceeding the acceptable threshold of 0.78. Items 4, 7, and 10 scored slightly lower with I-CVI values of 0.83. The CVR calculations demonstrated that the same three items scored 0.66, falling slightly below the significant threshold of 0.99 for six experts, suggesting that while these items are relevant, they may benefit from further refinement.

Kappa analysis revealed an *"excellent"* rating for all items in domain 1 (Items 1-3) and domain 4 (Items 12-15) and most in domain 3 (Items 6, 8, 9, and 11). These items were retained. Items 4, 7, and 10 received *"good"* ratings (ϰ=0.60), indicating strong but not unanimous agreement on their relevance and clarity, thus necessitated revisions. The overall Scale-Content Validity Index (S-CVI) for the 15-item questionnaire was calculated at 0.97, surpassing the 0.90 threshold for excellent content validity. Additionally, the S-CVI/UA of 0.85 was obtained, indicating a high universal agreement across all items.

These findings demonstrate the questionnaire's excellent overall content validity, effectively capturing intended constructs across all domains, with only minor revisions needed for three items.

Table III: Summary of Item-Content Validity

Domain	Panel in Agreement	I-CVI	CVR	UA	⍺	Interpretation	Decision
Data Management							
Item 1: *Data management using physical paper or files and sorting information via Excel or Google Sheets remains practical and relevant.*	6	1.00	1.00	1.00	1.00	Excellent	Retained
Item 2: *The School Data Management System is currently used to handle student profiles and information effectively.*	6	1.00	1.00	1.00	1.00	Excellent	Retained
Item 3: *The current process of managing student data and information in your school is efficient, easily managed, and readily referenced.*	6	1.00	1.00	1.00	1.00	Excellent	Retained
Challenges in Data Management							
Item 4: The following are primary challenges you encounter when managing data for visually impaired students, including a) limited information accessibility, and b) providing appropriate support.	5	0.83	0.66	0.00	0.60	Good	Revise
Item 5: *Communicating with visually impaired students, parents, and clinicians presents difficulties in the context of managing students' data*	6	1.00	1.00	1.00	1.00	Excellent	Retained
Data Infrastructure							
Item 6: *Managing the visual needs of the students should be tailored to their visual characteristics and level of visual impairment.*	6	1.00	1.00	1.00	1.00	Excellent	Retained
Item 7: The existing student management data in your school contain information regarding the visual characteristics of students, issues, visual impairment levels, and visual aids.	5	0.83	0.66	0.00	0.60	Good	Revise
Item 8: *Web-based data and information handling systems offer numerous advantages, including easy access and updates and reduced reliance on physical storage.*	6	1.00	1.00	1.00	1.00	Excellent	Retained
Item 9: *Assistive technology or software is crucial in effectively managing student profiles and information.*	6	1.00	1.00	1.00	1.00	Excellent	Retained
Item 10: *The following are the assistive technology and software used to manage student profiles and information; School Information Management Systems, E-Portfolios, and Cloud Storage and Collaboration Tools.*	5	0.83	0.66	0.00	0.60	Good	Revise
Item 11: *Parent-teacher communication Apps and Mobile Apps for Classroom Management can facilitate electronic communication between parents, teachers, and students.*	6	1.00	1.00	1.00	1.00	Excellent	Retained
Top Management Support							
Item 12: *Improved accessibility to information and support for alternative materials are essential aspects of a profiling system for visually impaired students*	6	1.00	1.00	1.00	1.00	Excellent	Retained
Item 13: *Electronic records should enable communication with clinicians and parents to enhance the efficient management of visually impaired students' data.*	6	1.00	1.00	1.00	1.00	Excellent	Retained
Item 14: *Collaboration with support staff or other professionals is vital in effectively managing profiling data for visually impaired students*	6	1.00	1.00	1.00	1.00	Excellent	Retained
Item 15: *Training or professional development is necessary to effectively utilize assistive technology or software in managing student profiles and information.*	6	1.00	1.00	1.00	1.00	Excellent	Retained
S-CVI/Ave					**0.97**		
S-CVI/UA					**0.85**		

DISCUSSION AND CONCLUSION

The developed items for the need assessment questionnaire will determine the importance and effectiveness of the forthcoming visual profiling system. The proposed system anticipates comprehensive profiling by integrating socio-demographic, medical history, and visual characteristics information. This transition aims to enhance data management strategies, cultivate an improved learning environment, and optimize the use of visual aids by precisely characterizing students with visual impairment, moving away from outdated paper-based records.

In this study, the validation analysis of the need assessment instrument has utilized techniques that are frequently employed in health care and nursing research, as indicated by previous studies.[17,25] This is to ensure that the problematic areas can be identified as well as, minimize language errors, assess appropriateness, and

ensure respondents interpret questions accurately.[26] This approach enhances the reliability and applicability of the questionnaire in educational settings.

To the best of our knowledge, this is the first study to develop a need assessment questionnaire for visually impaired students' data systems. In this study, the authors meticulously designed comprehensive domains to address various aspects and explore topics such as current tools and systems, challenges encountered, knowledge of web-based systems, visual profiling in managing students with visual impairment, and support structures available for teachers and staff in data management. The extensive coverage of these domains offers the groundwork for a detailed study of the visual profiling system's evolution and possible impact on meeting the different needs of the educational context. This holistic approach provides a solid foundation for future research and development in this field.

Furthermore, a team of six panel experts were enlisted to oversee the process of validating, modifying, and enhancing the instrument. The number of experts falls within the range suggested previously.[17,18]

The high content validity scores (I-CVI ranging from 0.83-1.00, S-CVI/Ave of 0.97) indicated that the questionnaire effectively captured the intended constructs. These results suggest that the instrument could be a valuable tool for educators and policymakers in assessing and improving data management practices for visually impaired students. Previous studies recommended a minimum CVI score of 0.83 for six to eight experts.[23] Regarding the overall content validity, the S-CVI/Ave value was 0.97, and the overall agreement S-CVI/UA was 0.85, indicating robust content validity for all items. Literature suggested an acceptable validity with S-CVI values of at least 0.8.[23,25,27] Moreover, the S-CVI for this instrument aligned with congruity levels, as values above 0.74, between 0.6-0.74, and between 0.4-0.59 were considered 'excellent', 'good', and 'fair', respectively. In this context, all items in the instrument were classified as 'excellent'. However, findings from the CVR calculations had identified three items with a score of 0.60, leading to revisions based on expert recommendations and consensus as high CVR scores indicated consensus on the importance of specific items in the instrument.[28]

Feedback and comments from the expert panels might serve as an additional means of assessment to enhance the content validity indices. In response to feedback and expert input, specific revisions were made to enhance the questionnaire's clarity based on $\varkappa$ values. Notably, in domain 2 (Challenges in data management), Item 4 underwent a revision to improve clarity, addressing concerns raised by experts regarding the comprehension of bullet-pointed questions. It has been revised from "*The following are primary challenges you encounter when managing data for visually impaired students, including a) limited information accessibility, and b) providing appropriate support?*" to *"Limited information on accessibility and appropriate support are the main challenges in managing data for visually impaired students"*

Additionally, Items 7 and 10 in the data structure domain were rephrased to enhance readability and to better align with the expert expectations. Notably, Item 7 were revised from "*The existing student's management data in your school contain information regarding visual characteristics of students, issues, visual impairment levels, and visual aid*s to *"The existing student's data contains information regarding visual characteristics, level of visual impairment, and recommended visual aids"*

The results of this study demonstrate satisfactory content with construct validities of the questionnaire supporting its suitability for assessing the necessity of developing visual attribute profiling for students with visual impairment.[25] The outcomes of the profiling development represent a strategic initiative in addressing evidence-based visual characteristics and demands. These insights offer valuable guidance for educators, optometrists, and clinical instructors in customizing management strategies for students with visual impairment.

However, the absence of a face validity analysis in this study limits the ability to completely evaluate the questionnaire's initial impression and user-friendliness. Although face validity is not a comprehensive measure of an instrument's effectiveness, it is an important

preliminary assessment to determine the questionnaire's apparent relevance and acceptability for potential users.[26] Incorporating face validity into future studies would improve the evaluation's completeness and provide a more nuanced view of the questionnaire's first impression. Further studies in the future can corroborate the assessment of the instrument's reliability, enhancing the applicability of the assessment tool.

In conclusion, this study contributes significantly to the field by providing a validated instrument for assessing the need for visual attribute profiling in visually impaired students' education. The assessment of content validity through CVI (I-CVI & S-CVI), Modified Kappa, and CVR demonstrated excellent content validity for the items in the instrument, highlighting its suitability and potential as a valuable tool for improving data management practices. This thorough approach to content validity is crucial for Information System (IS) organizations and researchers engaged in developing accurate instruments for both preliminary and major research. This paper describes the specific approach used to create and evaluate instruments, ensuring that the content measurements are carefully examined before implementing the system. The examination of content validity in this study highlights the suitability of the instrument, confirming its capacity to attain a notable degree of validity. This study contributes significantly to establishing confidence in the process of preparing reliable instruments for empirical studies by recognizing content validity as a crucial factor.

As educational systems increasingly rely on data-driven decision-making, this validated questionnaire will be essential in ensuring that the unique needs of visually impaired students are effectively met, ultimately enhancing their educational outcomes.

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ETHICAL APPROVAL

The ethical consideration of this study has been approved by Universiti Kebangsaan Malaysia (JEPUKM_JEP-2023-470). The study adhered to the tenet of the Helsinki Declaration.

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ORIGINAL ARTICLE

Prevalence and Perinatal Outcomes of Group B Streptococcus Positive Mothers in a University Hospital in Pahang, Malaysia

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ABSTRACT

INTRODUCTION: Group B *streptococcus* (GBS) is a leading cause of early neonatal infection and is related to various maternal infections. This study aims to determine the prevalence of GBS-positive mothers and their pregnancy outcomes in a University Hospital in Pahang, Malaysia. **MATERIALS AND METHODS:** A comparative cross-sectional study was conducted from October 2021-May 2022, involving 230 pregnant women between 35-38 weeks follow-up at this hospital. Rectovaginal swab (RVS), high vaginal swab (HVS), and midstream urine (MSU) cultures were sent for GBS screening in asymptomatic mother, and positive mothers received intrapartum antibiotic prophylaxis (IAP) as per protocol. Maternal outcome analysed were preterm pre-labour rupture of membrane (PPROM), preterm labour, maternal pyrexia, and puerperal infection. Whereas, neonatal outcomes include prematurity, low Apgar score, requirements of NICU/SCN admission and antibiotic; and diagnosis of neonatal early-onset GBS (EOGBS) disease. **RESULTS:** 58.6% of participants were tested GBS-positive based on either RVS, HVS, or MSU culture. There was no significant association between maternal GBS status, sociodemographic, and clinical background except for being overweight (mean BMI 26.3 kg/m^2, p= 0.047). Maternal and neonatal outcomes were not significantly different between GBS-positive and GBS-negative mothers. **CONCLUSION:** The prevalence of GBS colonisation (58.6%) was higher compared to reports worldwide. However, the implementation of GBS screening and IAP had successfully prevented the development of EOGBS disease and complication for both mothers and neonates. Therefore, screening for asymptomatic mother is important and effective for GBS infection.

Keywords
Group B Streptococcus, Prevalence, Screening, Intrapartum antibiotic prophylaxis, Perinatal outcomes

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INTRODUCTION

Streptococcus agalactiae, commonly known as Group B Streptococcus (GBS), is a facultative gram-positive microorganism. In several women, GBS is part of the natural gastrointestinal and vaginal microbiomes.[1] Gastrointestinal tract is a reservoir for GBS and source of genitourinary colonisation.[1] Despite being among natural microbiome, maternal colonisation with GBS in the genitourinary or gastrointestinal tracts is the primary risk factor for early-onset neonatal GBS (EOGBS) disease. EOGBS has been recognised as one of the leading causes of neonatal sepsis, pneumonia, and meningitis.[2]

Historically, since the 1970s, GBS has been identified as one of the major infectious cause of early neonatal morbidity and mortality in industrialised countries, leading to case-fatality rates of approximately 50%.[3] However, following the implementation of preventative measures, including the GBS screening policy and intrapartum antibiotic prophylaxis (IAP) approach, a marked decline in GBS diseases has been seen to date.[4]

It has been globally reported that the rates of maternal GBS colonisation range from 0-35%, which may differ between geographic locations.[5] When left untreated, about

50% of neonates of GBS-positive mothers will be colonised, and 1-2% will progress to EOGBS.[6]

A study by Muller et al concluded that maternal GBS colonisation during pregnancy and delivery constitutes not only a threat to neonates, but also to the mother as well. The possible complications that may affect the mother comprise peripartum infections, such as bacteraemia, sepsis, meningitis, endometritis, and caesarean or perineal wound infections.[7]

Despite these alarming outcomes brought by maternal GBS colonisation to both neonates and mothers; the information available on the colonisation rate and perinatal outcomes are still limited in most Asian nations, including Malaysia. In addition, the evaluation of current preventive measures taken for GBS prevention are also not properly reported.

To date, only a single local study has been published in Malaysia. The prospective pilot study (n=56) was conducted almost two decades ago.[8] The researchers reported that the prevalence of GBS-positive mothers was 32.0%. However, perinatal outcomes of both mothers and neonates were not clearly reported.

Thus, the present study employed a comparative cross-sectional research design to elucidate the present prevalence of GBS colonisation among pregnant women and to evaluate maternal and neonatal outcomes by adopting universal GBS screening protocol. The findings will highlight the importance of GBS colonisation and its screening during pregnancy among pregnant women and medical practitioners. The results will also fill the current research gap and contribute to the local database. This will aid in clinical decision-making strategy, specifically on the construction and implementation of GBS screening programme protocol.

MATERIALS AND METHODS

This study was conducted at the Antenatal Clinic, Sultan Ahmad Shah Medical Centre (SASMEC)@IIUM, Kuantan, Pahang from October 2021 - May 2022. This study involved all pregnant women who were seen for follow-up at 35-38 weeks of gestation. Pregnant women with a previous baby affected by EOGBS, a known case of GBS bacteriuria in the current pregnancy, unable to understand Malay or English, and who has not consented to GBS screening tests were excluded.

The study sample size and power were calculated using OpenEpi, Version 3.01, an open-source calculator. The final estimated sample size for this study was based on the calculation of GBS colonisation rate. Using the single proportion formula and considering a maternal GBS colonisation rate of approximately 10-30%,[9] a precision level of 5-95% Confidence Interval, the calculated sample size was 197 participants. Upon considering a non -response rate of 20%, the estimated sample size was increased to 230 participants.

Data Collection

A convenient sampling method was employed in recruiting participants in this study. All pregnant women who fulfilled the inclusion and exclusion criteria were approached to participate in the study. Data was collected in three phases which were i) during clinic visits between 35-38 weeks of gestation, ii) immediately after delivery, and iii) at six weeks post-delivery.

Data on sociodemographic characteristics was collected using participant personal background form. Three samples were sent for GBS screening tests, including rectovaginal swab (RVS), high vaginal swab (HVS), and midstream urine (MSU). The samples were tested for GBS culture and sensitivity. For this study, the microbiology lab used Christie-Atkinson-Munch-Peterson (CAMP) test protocols to identify *Streptococcus agalactiae*, which is a Group B *Streptococcus* that produces a positive CAMP factor reaction. This method is gold standard test for antenatal *Streptococcus agalactiae* screening despite latest development in molecular testing for GBS, as sensitivity was improved with broth enrichment, and it allows for antibiotic susceptibility testing to be done.[10]

GBS screening results were reviewed through the hospital health electronic information system and documented in participants' electronic case notes. They were managed

accordingly based on their GBS status. GBS positive status is defined by the presence of at least one positive GBS culture in either RVS, HVS, or MSU culture. GBS is considered negative if all the tests were negative. Participants with positive cultures of GBS were covered with intrapartum antibiotic prophylaxis (IAP) as per Malaysian National Antimicrobial Guideline 2019.[10] Intravenous ampicillin 2g stat and 1g 4 hourly at the onset of labour or leaking was employed as the antibiotic of choice. In the case of participants allergic to penicillin, intravenous cefazolin, cefuroxime, vancomycin, or clindamycin was given as an alternative. In addition, participant with a high colony count positive GBS urine culture, taken as the value of ≥100 000 CFU/mL, was considered as GBS bacteriuria and recommended for appropriate antibiotics therapy at the time of diagnosis.[11] Participants with mixed colony were not considered and not treated for GBS bacteriuria. GBS bacteriuria was treated with oral amoxicillin 500 mg three times a day (TDS) for a week upon diagnosis. Repeated MSU culture and sensitivity was performed after one week post-antibiotics completion to ensure the clearance of infection.

After delivery, data related to perinatal outcomes was collected. PPROM is defined as ruptured membranes before 37+0 weeks of pregnancy but is not in established labour. Diagnosis was made by maternal history, followed by a sterile speculum examination demonstrating liquor. If, on speculum examination, no amniotic fluid is observed, tests such as Amniocator test of vaginal fluid or alkaline pH test strips were used for the amniotic fluid detection. Preterm labour is defined as, pregnancy presented with symptoms of labour before 37+0 weeks of gestation regardless of cervical changes. Whereas maternal pyrexia is defined as the presence of temperature of ≥38°C which developed after labour onset or within 24 hours post-delivery. Puerperal infection is defined as any new prescription of antibiotics for presumed or confirmed perineal wound-related infection, endometritis, uterine infection, urinary tract infection or other systemic infections.

Non-reassuring Apgar Score is defined as a score of 0-6. NICU or SCN admission means requirements for admission regardless of indication within Day 0-6 of life. Antibiotic administration to neonates is the requirement for antibiotics administration regardless of indication within Day 0-6 of life. For neonatal EOGBS, it is GBS disease confirmed by microbiological culture of blood, cerebrospinal fluid (CSF), or other sterile fluids taken on Day 0-6 of life.

All the data were extracted from the hospital electronic health information system. For participants that delivered in other hospitals, data were collected from the birth record in participants' antenatal and neonatal record books. Furthermore, after six weeks post-delivery, participants were contacted to inquire about any requirements of antibiotics treatment during the confinement period that signify puerperal infection.

Data Analysis

Data was analysed according to respective groups; either GBS-positive or GBS-negative, regardless of intrapartum antibiotic prophylaxis status. Participants' sociodemographic and clinical characteristics were analysed individually. All the data analyses were performed descriptively using SPSS Statistics 25 for Window. A chi-squared test was used for all categorical variables to assess if GBS colonisation differed by maternal and neonatal outcomes. Null hypotheses of no significant difference were rejected if $P<0.05$, signifying statistical significance.

Workflow Chart

Figure 1 illustrates the study workflow, showing a total of 230 pregnant women who agreed to participate in this study. However, only 215 were included for analysis after 15 were excluded due to various reasons as stated in the figure.

RESULT

Findings from this study showed that the prevalence of GBS-positive mothers was 58.6% (n = 126) based on either positive rectovaginal swab (RVS), high vaginal swab (HVS), or midstream urine (MSU). From the 126 positive cases, 79.4% were positive for RVS culture, while 60.3% and 38.9% were positive for HVS and MSU, respectively.

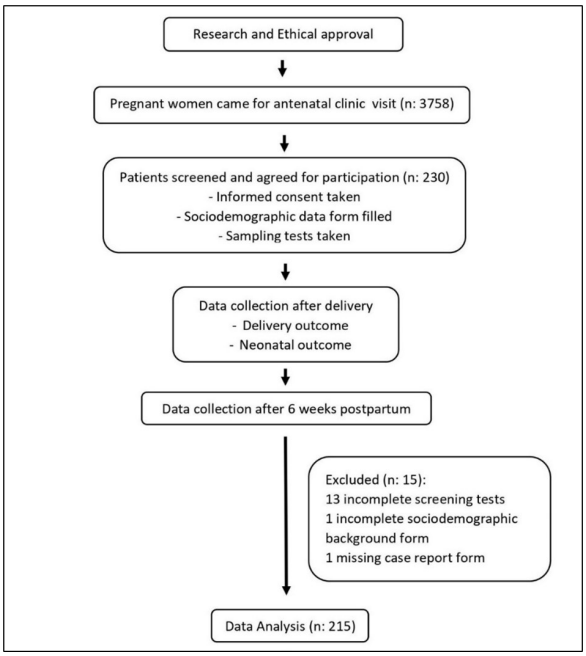

Figure 1: Workflow Chart

The sociodemographic characteristics of the participants is shown in Table 1. There was homogenous sociodemographic characteristics among the GBS-positive and GBS-negative mothers in the study population.

Table 1: Sociodemographic characteristics of the participants

	Overall, N (%)	GBS Status		P value
		GBS-positive, N (%)	GBS-negative, N (%)	
Age (years)	31.0 (4.4)*	30.6 (4.3)*	31.7 (4.6)*	0.071
Ethnic origin				0.000
Malay	183 (85.1)	118 (93.7)	65 (73.0)	
Chinese	26 (12.1)	8 (6.3)	18 (20.2)	
Indian	2 (0.9)	0 (0.0)	2 (2.2)	
Others	4 (1.9)	0 (0.0)	4 (4.5)	
Religion				0.002
Muslim	186 (86.5)	118 (93.7)	68 (76.4)	
Buddhist	26 (12.1)	8 (6.3)	18 (20.2)	
Christian	1 (0.5)	0 (0.0)	1 (1.1)	
Hindu	2 (0.9)	0 (0.0)	2 (2.2)	
Education level				0.088
Primary	1 (0.5)	1 (0.8)	0 (0.0)	
Secondary	50 (23.3)	23 (18.3)	27 (30.3)	
Tertiary	164 (76.3)	102 (81.0)	62 (69.7)	
Occupational status				0.772
Working	164 (76.3)	97 (77.0)	67 (75.3)	
Non-working	51 (23.7)	29 (23.0)	22 (24.7)	
Monthly household income				0.672
Low	122 (56.7)	74 (58.7)	48 (53.9)	
Middle	87 (40.5)	48 (38.1)	39 (43.8)	
High	6 (2.8)	4 (3.2)	2 (2.2)	

* mean (SD)

Table 2, shows the clinical characteristics of study participants. There was no significant association between GBS status and underlying clinical backgrounds, except for BMI (p=0.047). Using WHO BMI classification, mean BMI for GBS-positive mothers was 26.3 kg/m2 (overweight), while GBS-negative mothers was 24.8 kg/m2 (normal). Other medical illnesses included uncomplicated conditions such as asthma, COVID-19 positive, thyroid disease, and other haematological disorders, which were recorded in 10.2% of the participants.

Table 2: Clinical characteristics of participants

	Overall n (%)	GBS Status		P value
		GBS-positive n (%)	GBS-negative n (%)	
Parity				0.431
Primigravida	84 (39.1)	52 (41.3)	32 (36.0)	
Multipara	131 (60.9)	74 (58.7)	57 (64.0)	
Gestational Diabetes Mellitus				0.800
Yes	80 (37.2)	46 (36.5)	34 (38.2)	
No	135 (62.8)	80 (63.5)	55 (61.8)	
Hypertension				0.139
Yes	7 (3.3)	6 (4.8)	1 (1.1)	
No	208 (96.7)	120 (95.2)	88 (98.9)	
BMI* (kg/m2),	25.7 (5.5)^	26.3 (5.9)^	24.8 (4.8)^	0.047
Obesity				0.157
Yes	49 (22.8)	33 (26.2)	16 (18.0)	
No	166 (77.2)	93 (73.8)	73 (82.0)	
Anaemia				0.836
Yes	54 (25.1)	31 (24.6)	23 (25.8)	
No	161 (74.9)	95 (75.4)	66 (74.2)	
Other medical problems				0.387
Yes	22 (10.2)	11 (8.7)	11 (12.4)	
No	193 (89.8)	115 (91.3)	78 (87.6)	
Mode of Delivery				0.623
SVD**	153 (71.2)	89 (70.6)	64 (71.9)	
Vacuum	11 (5.1)	8 (6.3)	3 (3.4)	
Forceps	1 (0.5)	1 (0.8)	0 (0)	
LSCS***	50 (23.3)	28 (22.2)	22 (24.7)	

*BMI – body mass index, **SVD – spontaneous vertex delivery, ***LSCS – lower segment caesarean section. ^ mean (SD)

Maternal outcomes are described in Table 3. Though no maternal pyrexia was reported, 7.4% of mothers experienced puerperal infection over the course of first six weeks of postpartum, with no significant difference between the GBS status groups.

Table 3: Maternal outcomes

	Overall n (%)	GBS Status		P value
		GBS-positive n (%)	GBS-negative n (%)	
PPROM*				0.072
Yes	14 (6.5)	5 (4.0)	9 (10.1)	
No	201 (93.5)	121 (96.0)	80 (89.9)	
Preterm labour				0.392
Yes	16 (7.4)	11 (8.7)	5 (5.6)	
No	199 (92.6)	115 (91.3)	84 (94.4)	
Maternal pyrexia				N/A
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
No	215 (100.0)	126 (100.0)	89 (100.0)	
Puerperal infection				0.392
Yes	16 (7.4)	11 (8.7)	5 (5.6)	
No	199 (92.6)	115 (91.3)	84 (94.4)	

**PPROM: Preterm pre-labour rupture of membrane*

Neonatal outcomes are described in Table 4. For neonatal outcomes, a similar pattern to maternal outcomes was observed. None of the neonatal outcomes depicted any significant difference in reference to maternal GBS colonisation. Two neonates were delivered with non-reassuring Apgar scores (0-6) and both were from the GBS-positive mothers. The neonates were delivered vaginally after a diagnosis of intrauterine death (IUD). Both cases presented with complaints of reduced foetal movement at term. Both mothers had no underlying complicated antenatal issues. Post-delivery assessment revealed no obvious congenital anomaly or syndrome. All cultures sent for IUD workup were negative for GBS.

Table 4: Neonatal outcomes

	Overall n (%)	Maternal GBS Status		P value
		GBS Positive n (%)	GBS Negative n (%)	
Gestational age				0.572
Preterm	10 (4.7)	5 (4.0)	5 (5.6)	
Term	205 (95.3)	121 (96.0)	84 (94.4)	
Apgar score				0.232
Non-reassuring	2 (0.9)	2 (1.6)	0 (0.0)	
Reassuring	213 (99.1)	124 (98.4)	89 (100.0)	
NICU/SCN* admission* **				0.064
Yes	79 (36.7)	53 (42.1)	26 (29.2)	
No	134 62.3)	71 (56.3)	63 (70.8)	
Antibiotic administration*				0.156
Yes	57 (26.5)	38 (30.2)	19 (21.3)	
No	156 (72.6)	86 (68.3)	70 (78.7)	
EOGBS**				N/A
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
No	215 (100.0)	124 (100.0)	91 (100.0)	

*NICU/SCN – Neonatal Intensive Care Unit/Special Care Nursery
**EOGBS – Early neonatal GBS infection
***Two intrauterine death (0.9%) excluded for NICU/SCN admission and antibiotic administration analysis

DISCUSSION

Group B Streptococcus (GBS) Prevalence

In this study, 58.6% of pregnant mothers were tested positive for GBS colonisation, which is higher than the average worldwide estimation as stated in the initial hypothesis. CDC reported that worldwide colonisation rates vary, with estimated prevalence ranging from 10-30%.[2] The country with the highest GBS colonisation rate was Zimbabwe with 60.3% being infected at some point during pregnancy. Nevertheless, the colonisation rate decreased as the pregnancy progressed, falling to 21% at delivery, from 47% at 20 weeks to 24.2% at 26 weeks.[5] A study conducted in a university hospital in Kuala Lumpur reported 32% GBS-positive prevalence among patients visiting the antenatal clinic.[8]

The high prevalence of GBS-positive reported in this study, could be attributed to universal screening approach, which entailed three types of cultures for screening: HVS, RVS and MSU. In contrast, if only RVS culture was conducted, about 20% of mothers with GBS colonisation would not have received intrapartum antibiotics prophylaxis. This finding is consistent with a study conducted by Quinlan et al.[12] RVS culture was able to yield the highest GBS-positive results (80%) compared to HVS (60%) and MSU (39%).

Sociodemographic and Clinical Characteristics

The participants between both study groups were homogenous except for BMI, whereby GBS-positive mothers were likely to be overweight. A study in Spain concluded that maternal obesity poses a considerable and distinct risk for the occurrence of GBS colonisation at term.[13] Clinically, the present study population was mainly pregnant women at a lower risk with a low number of complicated medical comorbidities. However, the number of those with diabetes was higher compared to hypertension (37.2% vs 3.3%), which might be due to the higher prevalence of obesity (22.8%) and overweight (mean BMI) among the participants. The 25% anaemia rate among participants is slightly lower than previously reported rate among the general female population in Malaysian at 30%.[14]

Perinatal Outcomes

There was no significant difference in the perinatal outcomes between GBS-positive and GBS-negative mothers. There incidence of PPROM, preterm labour and puerperal infection reported in this study were within the global prevalence rate of 3-7%,[15] 5-10%,[16] and p 5-7%[17] respectively.

The pregnancy outcomes of GBS-positive mothers in this study, were associated with minimal complications, comparable to the general population following the implementation of GBS screening and intrapartum antibiotic prophylaxis. Moreover, this reflects the effectiveness of GBS screening and IAP practice as part of the preventive strategies against EOGBS.

Through no EOGBS was reported, 2 cases of IUD were documented in this study born to GBS-positive mothers, which should be considered as a significant burden. A study reported that 1% of stillbirths in developed nations and 4% in sub-Saharan Africa are caused by GBS cases.[18] Additionally, the study emphasised that GBS probably causes more deaths during antenatal period than after birth. However, till date, prelabour antibiotics therapy is not recommended in vaginal GBS colonization unless mother develop infection in the case of GBS bacteriuria.[19]

Study Strength, Limitations and Recommendations

This study is a comprehensive, comparative cross-sectional study where participants were followed up from pregnancy until delivery, while reporting the neonatal and puerperal outcomes. However, since this is not a multi-centre study, data obtained cannot be inferred to the Malaysian population. GBS prevalence and perinatal outcomes were not investigated or compared before employing the universal screening approach in the studied population; and, no adverse events that could be causally related to the IAP administration following GBS screening were studied.

For future studies, a larger sample size from multi-centres and multi-regional involvement should be conducted for optimal estimation of GBS colonisation rate and burden among pregnant mothers in Malaysia. Since GBS screening approach could be universal and risk-based, it is worth comparing how different approaches result in diverse outcomes among the Malaysian population. Thus, a randomised controlled trial could be considered in future studies. Further investigations are required to evaluate patients' response rate to GBS screening programme and their acceptance. A study on knowledge, attitude, and practice (KAP) can be conducted among patients, and practicing medical personnel. The findings obtained could be used to further guide the present health education strategies among Malaysian population and healthcare providers.

CONCLUSION

This study revealed a high prevalence of GBS (58.6%). However, the perinatal outcomes for GBS-positive mothers were favourable with widespread GBS screening and IAP administration, or at least comparable to those of GBS-negative mothers. Thus, GBS screening and IAP practice are effective to prevent maternal and neonatal complications related to GBS exposure. Based on these findings, the adoption of universal GBS screening approach is recommended as an effective method of GBS screening in the Malaysian population. The present data highlights the unmet need for routine GBS testing throughout pregnancy. This study also provides support for more research in this area, including studies on GBS screening strategy, KAP, cost analysis, and antibiotics resistance or adverse outcomes.

CONFLICT OF INTEREST

None

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

The ethical approval was obtained from the IIUM Research Ethics Committee (IREC) on 20th September 2021 (Approval number: IREC 2021-251).

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ORIGINAL ARTICLE

New Insights on Dietary Assessment Recommender System for Pre-University Adolescents

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ABSTRACT

INTRODUCTION: An individual's health status will be influenced by their nutritional status, which is mainly based on their eating habits. Adolescence is an essential phase for growth and development that will be influenced by healthy eating habits. In view of this, a dietary recommender system to understand and improve dietary habits is crucial. In this study, the dietary recommender system, consisting of meal routines, food preferences, and dietary practices of pre-university adolescents, will be presented. **MATERIALS AND METHODS:** This study was conducted at a pre-university centre, involving a sample of 125 students. A self-administered structured questionnaire was used to collect demographic data, daily meal routines, food intake frequency, and dietary behaviour patterns. Two weeks before completing the questionnaire, the students were instructed to monitor their dietary practices. **RESULTS:** The food intake frequency survey was divided into two categories: food intake less than three times a week (< three times/week) and three times a week or more (≥ three times/week). The results showed that cereal consumption was most frequent at 87.2% for food intake < three times/ week, while meat consumption was highest for food intake ≥ three times/week (84.8%). Almost 81% of students reported snacking between meals, with the majority snacking less than twice daily (60.8%). Females showed a higher tendency to snack. In terms of dietary behaviour patterns, there were significant differences between genders in terms of overeating and unbalanced food intake. The four primary dietary behaviour patterns were found to be positively correlated with each other. The correlation study results indicated positive relationships between dietary behaviour patterns and body mass index (BMI), except for a negative relationship between high fat/high calorie diet and BMI. **CONCLUSION:** Multiple regression analysis suggested that overeating, having a high fat/ high calorie diet, unbalanced food intake, and dietary impulses collectively explains variations in BMI.

Keywords
Dietary practices; Food intake; Malaysia; Meal routines; Pre-university adolescents

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INTRODUCTION

With recent improvements in economic and sociocultural situations, modern diets have changed. It is well-known that changes in eating patterns frequently result in nutritional imbalances, sharply raising the incidence of chronic diseases.[1] According to the National Health & Morbidity Survey[2], 30.4% of adults were overweight, and 19.7% were obese, accounting for 50.1% of overweight or obese individuals in Malaysia. When compared to data from 2011 and 2015, the trends for overweight and obesity are still on the rise.[3]

Daily dietary practices have a significant impact on human health. Poor choices in food consumption can increase the likelihood of developing certain illnesses and disorders, such as diabetes, high blood pressure, and obesity[4]. As dietary habits and chronic diseases are strongly correlated, nutritional assessment is becoming increasingly crucial for disease prevention and management. This underscores the importance of examining the dietary habits of an individual.

The period of life known as adolescence falls between childhood and adulthood. It is a transitional period in which individuals experience rapid physical and psychological growth and development. This is also recognized as the transition from childhood to adulthood. Moreover, pre-university students experience living away from home for the first time and have less parental or guardian supervision over their dietary behaviours. Pre-university adolescents are thus a vulnerable group that should be the focus of this study.

Adolescence is also a period susceptible to obesity. Obesity is primarily attributed to a lack of physical activity, outdoor activities, and the consumption of fat-rich junk foods.[5] Individuals who regularly consume a diet high in sugar, saturated fat, and salt are more prone to developing obesity.[6] Some standard dietary practices among adolescents include snacking on high-energy foods, irregular meal patterns typically involving fast food, skipping meals especially breakfast, and inadequate intake of fruits and vegetables.

Previous research on measuring the overall quality of dietary habits has been limited as it does not thoroughly evaluate individual dietary behaviours, particularly among pre-university adolescents.[7-9] In light of this, this paper aims to address this gap. The study's purpose is to monitor dietary behaviours by examining each individual's dietary habits, with the goal of assessing meal routines, food preferences, and dietary practices of pre-university adolescents, which are referred to as the dietary assessment recommender system.

The paper is organized as follows: Section 2 describes the methodology, Section 3 presents the findings, Section 4 discusses the collected results and section 5 concludes the paper.

MATERIALS AND METHODS

The present study utilized a quantitative approach using a structured questionnaire. The questionnaire consisted of three sections, with Section 1 focusing on demographics. Section 2 included information about daily meal routines and food intake frequency. Section 3 employed a dietary pattern evaluation tool to investigate dietary behaviour patterns. This evaluation tool was adapted from Do Lee, Kim, Choi, Kim, Cho and Sohn.[10] The 34-item questionnaire was designed to assess dietary habits and was categorized into unbalanced food intake pattern (5 items), dietary impulse pattern (8 items), overeating pattern (9 items), and high fat and calorie pattern (12 items). A 1–5 scale was used to rate dietary habits and behaviours, with 1 being "not at all", 2 being "no", 3 being "average", 4 being "yes", and 5 being "very much so". This tool can help identify dietary behavioural issues. The study was conducted among pre-university adolescents in a pre-university centre. A survey was administered using a self-administered structured questionnaire to 125 students. Two weeks before data collection, respondents were asked to monitor their dietary practices to ensure data reliability[11]. The questionnaire was tested for internal reliability during a pilot test with a sample of 35 students chosen by simple random sampling. Students were briefed about the study objectives, and written informed consent was obtained accordingly. Participation was voluntary and anonymous[12].

IBM SPSS Statistics Version 25 was used to input and analyse the collected quantitative data. A hypothesis t-test was used to investigate gender differences in the four major dietary behaviour patterns. The relationship between dietary behaviour pattern scores and body mass index (BMI) was examined via Pearson's correlation. A p-value less than 0.05 ($p\text{-value}<0.05$) was considered significant. Multiple regression analysis was utilized to estimate the amount of BMI variance attributed to overeating, high fat/high calorie diet, unbalanced food intake, and dietary impulse.

RESULTS

This study included 69 female participants with an average age of 18.87 years and a body mass index (BMI) of 21.50 kg/m² and 56 male participants with an average age of 18.89 years and a BMI of 21.58 kg/m². Table 1 presents the findings from the examination of the meal routine. 79.2% of the participants had lunch every day, while the dinner routine was followed by 71.2% daily.

Regarding the breakfast routine, 64.0% occasionally consume breakfast. The snacking routine between meals among participants, as shown in Table 1, indicates that 60.8% of the participants snack less than twice daily, with females comprising 35.2%. Moreover, females showed a higher tendency towards snacking, regardless of the daily snacking frequency.

The types of food intake frequency are displayed in Table 1. There are 12 types of food with a frequency of less than three times a week (<3 times/week) or three times or more a week (≥3 times/week). Cereal intake was the most frequent < 3 times/week (87.2%), followed by roots and tubers (78.4%) and soft drinks (71.2%). Meat intake showed the highest frequency for ≥3 times/week, at 84.8%. Oils, fats, and eggs were the second and third most frequent foods at 83.2% and 78.4%, respectively.

Table 2 displays the results of the dietary behaviour pattern scores by gender. The dietary behaviour pattern is divided into four major categories: overeating pattern, high fat/high calorie pattern, unbalanced food intake pattern, and dietary impulse pattern, rated on a five-point Likert scale, where 1 represents "not at all" and 5 represents "very much so". A higher score denotes undesirable dietary habits. The scores for each dietary behaviour pattern: overeating, high fat/high calorie, unbalanced food intake, and dietary impulse ranged from 9 to 45, 12 to 60, 5 to 25, and 8 to 40, respectively. Females scored 28.68 points for the overeating pattern, higher than males at 26.39 points (p-value<0.05). Males scored 16.73 points for unbalanced food intake pattern compared to female's 15.55 points (p-value<0.05).

The relationship between dietary behaviour pattern scores and body mass index (BMI) was examined using Pearson's correlation. Figure 1 displays the correlation analysis findings. There was a positive correlation across all four dietary behaviour patterns. Dietary impulse was positively correlated with the high fat/high calorie pattern (r=0.458, p<0.01). A notable positive correlation was observed between high fat/high calorie and dietary impulse with overeating. A positive correlation (r=0.191, p<0.05) was found between dietary impulse and

Table 1: Meal Routines and Food Intake Frequency among the Participants

	Male n (%)	Female n (%)	Total n (%)
Breakfast			
Everyday	21 (16.8%)	16 (12.8%)	37 (29.6%)
Sometimes	32 (25.6%)	48 (38.4%)	80 (64.0%)
None	3 (2.4%)	5 (4.0%)	8 (6.4%)
Lunch			
Everyday	46 (36.8%)	53 (42.4%)	99 (79.2%)
Sometimes	10 (8.0%)	15 (12.0%)	25 (20.0%)
None	0	1 (0.8%)	1 (0.8%)
Dinner			
Everyday	46 (36.8%)	43 (34.4%)	89 (71.2%)
Sometimes	10 (8.0%)	24 (19.2%)	34 (27.2%)
None	0	2 (1.6%)	2 (1.6%)
Snacking			
Yes, < 2 times daily	32 (25.6%)	44 (35.2%)	76 (60.8%)
Yes, ≥ 2 times daily	11 (8.8%)	14 (11.2%)	25 (20.0%)
No	13 (10.4%)	11 (8.8%)	24 (19.2%)
Food intake frequency			
Cereals			
< 3 times/week	45 (36.0%)	64 (51.2%)	109 (87.2%)
≥ 3 times/week	11 (8.8%)	5 (4.0%)	16 (12.8%)
Roots and tubers			
< 3 times/week	41 (32.8%)	57 (45.6%)	98 (78.4%)
≥ 3 times/week	15 (12.0%)	12 (9.6%)	27 (21.6%)
Vegetables			
< 3 times/week	14 (11.2%)	17 (13.6%)	31 (24.8%)
≥ 3 times/week	42 (33.6%)	52 (41.6%)	94 (75.2%)
Fruits			
< 3 times/week	20 (16.0%)	26 (20.8%)	46 (36.8%)
≥ 3 times/week	36 (28.8%)	43 (34.4%)	79 (63.2%)
Meat			
< 3 times/week	8 (6.4%)	11 (8.8%)	19 (15.2%)
≥ 3 times/week	48 (38.4%)	58 (46.4%)	106 (84.8%)
Egg			
< 3 times/week	12 (9.6%)	15 (12.0%)	27 (21.6%)
≥ 3 times/week	44 (35.2%)	54 (43.2%)	98 (78.4%)
Seafood	32 (25.6%)	46 (36.8%)	78 (62.4%)
< 3 times/week	24 (19.2%)	23 (18.4%)	47 (37.6%)
≥ 3 times/week			
Legumes, nuts and seed			
< 3 times/week	37 (29.6%)	51 (40.8%)	88 (70.4%)
≥ 3 times/week	19 (15.2%)	18 (14.4%)	37 (29.6%)
Milk and milk products			
< 3 times/week	22 (17.6%)	31 (24.8%)	53 (42.4%)
≥ 3 times/week	34 (27.2%)	38 (30.4%)	72 (57.6%)
Oils and fats			
< 3 times/week	8 (6.4%)	13 (10.4%)	21 (16.8%)
≥ 3 times/week	48 (38.4%)	56 (44.8%)	104 (83.2%)
Condiments			
< 3 times/week	26 (20.8%)	30 (24.0%)	56 (44.8%)
≥ 3 times/week	30 (24.0%)	39 (31.2%)	69 (55.2%)
Soft drinks			
< 3 times/week	38 (30.4%)	51 (40.8%)	89 (71.2%)
≥ 3 times/week	18 (14.4%)	18 (14.4%)	36 (28.8%)

Table 2: Dietary Behaviour Patterns Scores by Gender and Results for every Predictor in a Regression Model that Predicts BMI

Dietary behaviour pattern type	Male (n = 56)	Female (n = 69)	Total (n = 125)	p-value
Overeating	26.39 ± 5.82	28.68 ± 6.38	27. 66 ± 6.22	< 0.05
High fat/high calorie	37.57 ± 7.65	37.81 ± 7.32	37.70 ± 7.44	0.858
Unbalanced food intake	16.73 ± 3.09	15.55 ± 3.38	16.08 ± 3.29	< 0.05
Dietary impulse	25.14 ± 7.02	26.54 ± 7.21	25.91 ± 7.13	0.279
Regression model	B [95% CI]	β	sr^2	p-value
Overeating	0.280 [0.137, 0.422]	0.368	0.1102	0.000
High fat/high calorie	-0.104 [-0.228, 0.020]	-0.164	0.0201	0.099
Unbalanced food intake	0.002 [-0.246, 0.249]	0.001	0.0000	0.988
Dietary impulse	0.016 [-0.116, 0.148]	0.024	0.0004	0.809

unbalanced food intake. Additionally, overeating, high fat/ high calorie, and unbalanced food intake were positively correlated. Nevertheless, there is insufficient evidence to suggest a positive correlation between overeating and high fat/high calorie with unbalanced food intake within the population. Figure 1 indicates that overeating, dietary impulse, and unbalanced food intake have a positive correlation with BMI, while a weak negative correlation exists between high fat/high calorie and BMI.

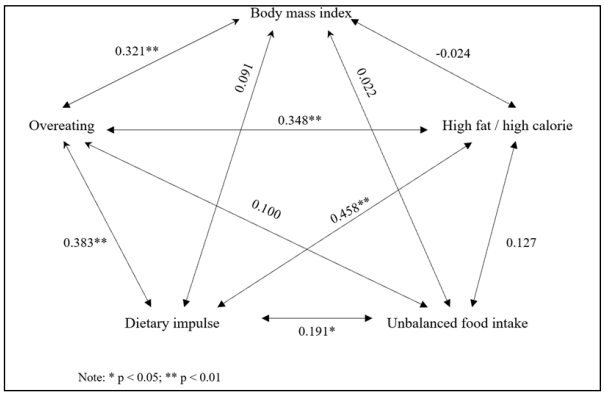

Figure 1: Pearson's Correlation Coefficient Model between Body Mass Index, Overeating, High Fat/High Calorie, Unbalanced Food Intake and Dietary Impulse

Overeating, high fat/high calorie, unbalanced food intake and dietary impulse were examined using a standard multiple regression analysis (MRA) to determine their influence on variation in BMI. The analysis revealed that 12.4% of BMI variability was attributable to a combination of overeating, high fat/high calorie, unbalanced food intake, and dietary impulse (R^2=0.124, adjusted R^2=0.095, F (4 , 120)=4.257, p-value<0.01). The results in Table 2 display the squared semi-partial correlations (sr^2), as well as the unstandardized (B) and standardized (β) regression coefficients for each predictor in the model.

DISCUSSION

With the rise in diseases associated with poor dietary habits, it is more crucial than ever to provide healthcare through nutritional counselling based on an assessment of eating habits. The quality of one's diet has a significant impact on health through food consumption, but study on pre-university adolescents is limited.[13] Therefore, it is necessary to investigate the dietary behaviour patterns among pre-university adolescents. Our goal in this study was to establish new insights on dietary patterns and conduct a survey on 125 pre-university students. Considering the survey's findings, the main meals routine in a day, food intake frequency, snacking routine between meals, and dietary behaviour pattern scores were obtained and assessed, applying to the evaluation of dietary quality in the field of nutrition education.

Most participants consumed two or three main meals daily, which is essential for overall health. This result aligns with a study conducted among medical school students in Bede, Cumber, Nkfusai, Venyuy, Ijang, Wepngong and Kien.[14] However, many of them either snack between meals or skip breakfast. A minority of the respondents occasionally skip lunch or dinner, but most of them sometimes skip breakfast. Meal skipping is a relatively widespread habit among pre-university students. Despite the fact that breakfast is crucial for the body's health and well-being, students may find it challenging to eat because they are rushing to go for their classes.[15] Some may purposely skip breakfast because they are self-conscious about their appearance and body weight. This is more typical in females who are mindful of what they eat.[16] The majority of the respondents have snacks in-between meals, possibly to help them meet their body's energy requirements while they engage in their academic activities. This is similar to findings observed among undergraduate students in a private university located in Nigeria[17].

The majority of respondents' meal patterns indicate that they frequently consumed meat, oils, fats, and eggs for ≥ three times a week. Meanwhile, for < three times a week, the top three food consumed were cereals, roots, tubers, and soft drinks. This could have an impact on the respondents' access to nutrients, i.e., minerals present in these dietary groups. This dietary diversity indicates an indication of a greater understanding of the fundamental nutritional values of various food groups. This ensures optimal nutrition that will benefit the individual's nutritional and health status[18].

A survey on dietary habits and behaviour was conducted, consisting of 34 items in total. The questions were classified into overeating, high fat/high calorie, unbalanced food intake, and dietary impulse. From the findings, the overeating and unbalanced food intake scores showed significant difference between female and male students. Female students obtained higher overeating scores compared to male students. On the contrary, male students scored higher than female students on unbalanced food intake pattern. There is a positive correlation between the four main dietary behaviour patterns. For example, when the overeating score increases, the high fat/high calorie, unbalanced food intake, and dietary impulse scores also increase. This indicates that an unhealthy dietary pattern will lead to another problem in the dietary pattern[19]. There is a positive correlation between overeating, unbalanced food intake, and dietary impulse with body mass index (BMI). This highlights that when overeating, unbalanced food intake, and dietary impulse scores increase, the BMI will also increase. A higher BMI indicates an unhealthy body status. However, there is a weak negative relationship between high fat/high calorie and BMI. This reflects that there are good unsaturated fats (i.e., monounsaturated), which can lower the risk of getting disease.[20]

From the multiple regression analysis, 12.4% of the variation in BMI can be explained by overeating, high fat/ high calorie, unbalanced food intake, and dietary impulse. If this study were to be repeated numerous times with samples taken from the same group, overeating, high fat/ high calorie, unbalanced food intake, and dietary impulse would, on average, explain around 9.5% of the variance in BMI. Additionally, the analysis of variance (ANOVA) is significant (p-value<0.05), showing that R^2 deviates far from zero. In other words, the combination of overeating, high fat/high calorie, unbalanced food intake, and dietary impulse can account for a greater variation in BMI than would be predicted by chance.

From Table 2, the unstandardized regression coefficient, B, for overeating is 0.280. This suggests that a 1-unit increase in overeating will result in a predicted 0.280-unit increase in BMI, after controlling high fat/high calorie, unbalanced food intake, and dietary impulse. Meanwhile, overeating has a standardized regression coefficient, or β, of 0.368. In other words, a 1 SD increase in overeating will result in a 0.368 SD increase in BMI, after controlling high fat/high calorie, unbalanced food intake, and dietary impulse.[21]

From the analysis, overeating can account for variance in BMI. It is a significant predictor, t(120)=3.891, p-value <0.01. There is a 95% confidence level that the true population B is contained in the interval between the lower and upper bounds. For example, B=-0.104 for high fat/high calorie is within the lower bound of -0.228 and upper bound 0.020. The corresponding predictor is not significant when a confidence interval comprises zero. This is true for high fat/high calorie, unbalanced food intake, and dietary impulse. For the zero-order correlations, the Pearson's correlation for overeating and BMI is r=0.321. This is similar to the Figure 1 correlation analysis. Here, the semi-partial correlation (sr) for overeating is 0.332, suggesting that overeating is the sole cause of about 11.02% of the variation in BMI.

CONCLUSION

Adolescence is a stage of rapid growth, impacting nutritional requirements and dietary preferences. Many pre-university adolescents experience living independently for the first time, thus becoming the primary decision-makers regarding their dietary behaviour. They may avoid certain foods due to personal preference, peer pressure or other factors. This study has shown positive correlations between overeating, unbalanced food intake, dietary impulse patterns and

Body Mass Index (BMI) thus highlighting the need for regular nutrition education programs focusing on appropriate dietary practices.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Prevalence of Chronic Kidney Disease and Its Associated Factors among Type-2 Diabetes Mellitus Patients at Kuantan Primary Health Clinics

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ABSTRACT

INTRODUCTION: Chronic kidney disease (CKD) in type-2 diabetes mellitus (T2DM) patients leads to end-stage renal failure and cardiovascular complications. This study aims to determine the prevalence of CKD and its associated factors at primary health clinics in Kuantan. **MATERIALS AND METHODS:** 304 T2DM patients' records aged 18 years and above were retrospectively selected by systematic random sampling in four health clinics, analyzed using descriptive statistics and multiple logistic regression. CKD is defined as positive proteinuria, or microalbuminuria in at least two of three consecutive urine specimens or calculated eGFR <60ml/min/1.73 m2 for more than three months. **RESULTS:** The mean age was 59.1 +8.89 years, 69.1% (n=210) Malay and 57.6% (n=175) females. The prevalence of CKD among T2DM was 55.3% (n=168) (95% CI=54.8 to 55.9%). Out of 168 T2DM with CKD, 87.5% (n=147) had diabetes for ≥ five years, 90.5% (n=152) had at least two comorbidities, and 54.2% (n=91) were on insulin. Glycaemic(HbA1c<7%) and blood pressure(<130/80) among T2DM with CKD achieved targets were 28% (n=64) and 38.1% (n=47) respectively. Multivariable analysis showed higher odds of having CKD among T2DM with poor blood pressure (AOR=2.634, p-value=0.001) and glycaemic control (AOR=4.178, p-value=<0.001) compared to those with good control and among those with retinopathy (mild NPDR AOR=7.472, p-value=<0.001; moderate NPDR AOR=13.594, p-value=<0.001) compared to no retinopathy. **CONCLUSION:** CKD present in half of T2DM. It's associated with poor blood pressure, glycaemic control and retinopathy. Early detection of retinopathy and CKD, and aggressive diabetic intervention are vital to curbing CKD progression.

Keywords
Chronic Kidney Disease, Type-2 Diabetes Mellitus, Primary Health Clinics.

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INTRODUCTION

Malaysia exhibits the highest prevalence of type-2 diabetes mellitus (T2DM) within the Western Pacific area and ranks among the highest globally.[1] It is projected that the prevalence of T2DM among Malaysian people aged 18 and above will reach 7 million individuals by the year 2025.[2] The prevalence of chronic kidney disease (CKD) is also anticipated to be higher, as T2DM is a significant contributing factor to the development of CKD. The prevalence of CKD has been reported to range from 16.8% to 83.7%, showing variability across different stages of CKD.[3–6] Diabetes continues to be the primary risk factor associated with the onset and progression of CKD. T2DM with kidney disease observed an increased mortality risk. Among T2DM without kidney disease, standardized mortality was found to be 11.5% (95% CI, 7.9%–15.2%) and may be increased to 31.1% (95% CI, 24.7%–37.5%) among those with kidney disease.[7] In 2019, there were around 2.5 million reported cases of CKD that

were associated with T2DM on a global scale. This high prevalence of CKD contributed to more than 400,000 mortality and 10 million disability-adjusted life years (DALYs). Unfortunately, the Asia Continent exhibits the highest prevalence of CKD associated with diabetes, especially in South and East Asia. While in Europe, the prevalence of chronic kidney disease (CKD) in T2DM is almost half of the prevalence in Asia.[8]

Patients with CKD have a significantly high risk of developing renal failure, cardiovascular disease, and premature mortality. The transition of CKD to end-stage renal disease (ESRD) is a significant clinical event that carries considerable morbidity, especially among older individuals. It has been estimated that approximately 9% of cardiovascular mortality per year is due to CKD.[9] Given the numerous complications and the high-risk nature associated with CKD, it becomes one of the major concerns that must be emphasized in the management of T2DM at the primary care level. It is imperative to appraise sociodemographic and clinical background such as diabetes treatments, duration of diabetes, as well as glycaemic and blood pressure control among primary care T2DM patients. The primary objective of this study was to assess the prevalence of T2DM patients with CKD in primary health clinics and its associated factors in Kuantan, Malaysia. Thus, an appropriate measure of intervention may be considered to delay the progression of CKD among T2DM patients.

MATERIALS AND METHODS

This cross-sectional retrospective study was conducted on a study population of 13826 registered active diabetic patients getting treatment from 12 government health clinics in Kuantan, Malaysia. Secondary data was collected from October 2021 to March 2022 from clinical diabetic records available in the four largest government health clinics using a purposive sampling method after ethical approval. These data were collected manually from the patient's diabetic records system, done by using systematic random sampling of the population of primary care T2DM patients where every sixth person on the alphabetically arranged list name was chosen and identified according to inclusion and exclusion criteria. The inclusion criteria were adult T2DM patients (aged 18 years old and above) with a follow-up of at least two visits per year and availability of blood and urine parameters (HbA1c, renal profile and urine protein) within the last six months. Patients who had lost follow-up for the past 12 months or incomplete clinical data were excluded from selection.

The sample size was calculated using a single proportion formula using OpenEpi version 3. Based on the latest report in Northern Thailand[6], the expected prevalence of CKD is 24%, with an absolute precision of 5% and a non-response rate of 10%. Therefore, the minimum sample required was 304. The sample size of each clinic was based on the proportion of diabetic patients, for a total of 304. A data collection form developed explicitly for this study was used to obtain the information needed. The retrieved information comprised the sociodemographic and clinical data, including age, gender, race, anthropometric measurements, body mass index (BMI), duration of diabetes in years, smoking status, blood pressure (BP), laboratory results (HbA1c, low-density lipoprotein cholesterol-LDL), comorbidities (hypertension, hyperlipidaemia, and obesity) and the grades of diabetic retinopathy. Data on treatment, oral glucose-lowering drugs (OGLDs) only, insulin, or both were also gathered. The diagnosis of CKD was made either by looking at the patient's urine albumin excretion (UACR) and/or calculating the glomerular filtration rate (eGFR). All information available in the hard copy of patients' records was collected manually.

Chronic kidney disease (CKD) was defined as positive proteinuria or microalbuminuria on two out of three consecutive urine specimens, repeated after three to six months, or a calculated eGFR of less than 60ml/ min/1.73m2 that has been present for more than three months in the absence of other causes of kidney disease, such as glomerulonephritis, IgA nephropathy (IgAN) and autoimmune conditions.[10] Good glycaemic control was defined as the latest HbA1c of less than 7% (cut-off level for CKD patients) during data collection time within a six-month period, while good blood pressure control was defined as the latest recorded BP of less than 130/80 mmHg for patients with CKD or less than 140/80 mmHg

for patients without CKD. Good LDL control was defined as less than 2.6 mmol/L. All defined parameters were based on the Malaysian Clinical Practice Guidelines (CPG) on the management of T2DM (6th edition).[11]

The results were analysed using the IBM® SPSS® Statistics software version 20.0 for descriptive statistics. All categorical variables were summarised using frequencies and percentages (%), whereas the normally distributed continuous variables were described using mean and standard deviation (SD). Otherwise, median and interquartile ranges were used to describe the non-normally distributed continuous variables. Simple and multiple logistic regression analyses were performed using StataIC 15 software to assess the socio-demographic factors and clinical characteristics associated with CKD in T2DM patients in this study. The results were presented as odds ratio (OR) for simple logistic regression or adjusted OR for multiple logistic regression with a confidence interval (CI) of 95%. All the available variables were tested in the simple logistic regression so that significant variables were captured and included in the multiple logistic regression model. The final model with only significant variables from the multiple logistic regression was then checked for multicollinearity using the variation inflation factor (VIF) test and further checked for the model fitness using the classification table, area under the receiver operating characteristic (ROC) curve, also Pearson and Hosmer-Lemeshow chi-square tests, which all showed good model fitness.

RESULTS

304 records of T2DM patients from the four largest government health clinics in Kuantan were studied. Majority were Malays (n=210, 69.1%) and females (n=175, 57.6%). Overall, 44.1% (n=134) of the patients were older than 60. The prevalence of CKD among T2DM patients at the time of the study was 55.3% (n=168, 95% CI=49.7, 60.9). Table I describes the T2DM patients' sociodemographic and clinical characteristics as a whole and according to the presence of CKD or not. The majority of the patients had had T2DM for more than five years with at least two comorbidities, and they were mostly overweight or obese. Almost half of the patients (with or without CKD) had not achieved the LDL target (<2.6 mmol/L). More than half of the patients had uncontrolled blood pressure and glycaemic control, especially those with T2DM with CKD. Insulin was initiated mainly due to poor glycaemic control despite optimally tolerated OGLDs.

Simple logistic regression analysis revealed that CKD among T2DM patients was significantly associated with longer duration of diabetes, higher BMI in kg/m², poor blood pressure and glycaemic control, the grades of retinopathy, and treatment received, as shown in Table II. Multiple logistic regression analysis (Table II) showed that only blood pressure, HbA1c and grade of retinopathy were significantly associated with CKD among these T2DM patients. Respectively, T2DM patients with poor blood pressure control (≥130/80 for CKD patients or ≥140/80 for non-CKD patients) were 2.634 (95% CI=1.482, 4.684) times at higher odds (at risk) with the *p*-value of 0.001, while those with poor glycaemic control (HbA1c ≥7%) were 4.178 (95% CI=2.363, 7.387) times at higher odds of having CKD compared to those with good blood pressure or glycaemic control. Those with mild Nonproliferative Diabetic Retinopathy (NPDR), moderate NPDR, and those with unknown status of retinopathy were 7.472 (95% CI=3.817, 14.627), 13.594 (95% CI=3.609, 51.206), and 4.787 (95% CI=2.239, 10.235) at higher odds of having CKD compared to those with no retinopathy.

DISCUSSION

Most patients in this study were Malay and females, which is similar to another study.[12] Such an ethnic distribution may be attributable to the population of the Kuantan area, which is predominantly Malay (78.5%). A similar distribution was observed in the latest Malaysia National Diabetes Registry 2020, which the highest prevalence of T2DM was recorded in the population of this age group.[3] Centres for Disease Control and Prevention (CDC) has highlighted CKD is common in diabetes mellitus(DM) patients, with approximately one in three adults with DM having CKD. CKD prevalence in DM varies widely between countries ranging from 27.1% in Shanghai, China, to 83.6% in Tanzania.[4] In this study, the prevalence of CKD among T2DM patients attending primary health

Table I: Socio-demographic and clinical profile among Type 2 diabetic patients in Kuantan.

Characteristics	Overall (n=304)	Chronic Kidney Disease (CKD)	
		Yes (n=168) (55.3%)	No (n=136) (44.7%)
	Freq.[a] (%)	Freq.[a] (%)	Freq.[a] (%)
Age (years):	59.1 (8.89)[b]	59.4 (9.05)[b]	58.7 (8.70)[b]
< 60	170 (55.9)	88 (52.4)	82 (60.3)
> 60	134 (44.1)	80 (47.6)	54 (39.7)
Gender:			
Male	129 (42.4)	73 (43.5)	56 (41.2)
Female	175 (57.6)	95 (56.5)	80 (58.8)
Race:			
Malay	210 (69.1)	121 (72.0)	89 (65.4)
Chinese	67 (22.0)	31 (18.5)	36 (26.5)
Indian	27 (8.9)	16 (9.5)	11 (8.1)
Duration of diabetes (years):			
< 5	53 (17.4)	21 (12.5)	32 (23.5)
5 - 10	134 (44.1)	77 (45.8)	57 (41.9)
> 10	117 (38.5)	70 (41.7)	47 (34.6)
Smoking status:			
No	227 (74.7)	121 (72.0)	106 (77.9)
Yes	77 (25.3)	47 (28.0)	30 (22.1)
Comorbidities:			
Nil	2 (0.7)	1 (0.6)	1 (0.7)
1	27 (8.9)	15 (8.9)	12 (8.8)
2	140 (46.1)	68 (40.5)	72 (52.9)
> 3	135 (44.4)	84 (50.0)	51 (37.5)
Body Mass Index (kg/m²):	28.9 (5.77)[b]	29.7 (6.01)[b]	27.8 (5.30)[b]
< 18.5 (underweight)	4 (1.3)	1 (0.6)	3 (2.2)
18.5 - 24.9 (normal)	69 (22.7)	34 (20.2)	35 (25.7)
25.0 - 29.9 (overweight)	115 (37.8)	63 (37.5)	52 (38.2)
> 30 (obese)	116 (38.2)	70 (41.7)	46 (33.8)
Blood pressure (mmHg):			
Good control[c]	151 (49.7)	64 (38.1)	87 (64.0)
Poor control[d]	153 (50.3)	104 (61.9)	49 (36.0)
HbA1c (%):	7.35 (2.7)*	8.40 (3.3)*	6.55 (1.5)*
Good control (< 7)	138 (45.4)	47 (28.0)	91 (66.9)
Poor control (> 7)	166 (54.6)	121 (72.0)	45 (33.1)
LDL[e] (mmol/L):	2.7 (0.98)[b]	2.8 (1.05)[b]	2.7 (0.88)[b]
< 1.8	37 (12.2)	19 (11.3)	18 (13.2)
1.8 - 2.6	127 (41.8)	71 (42.3)	56 (41.2)
> 2.6	140 (46.1)	78 (46.4)	62 (45.6)
Grades of retinopathy:			
No retinopathy	126 (41.4)	33 (19.6)	93 (68.4)
Mild NPDR[f]	93 (30.6)	72 (42.9)	21 (15.4)
Moderate NPDR[f]	26 (8.6)	23 (13.7)	3 (2.2)
PDR[g] / ADED[h]	5 (1.6)	3 (1.8)	2 (1.5)
Unknown	54 (17.8)	37 (22.0)	17 (12.5)
Diabetic treatment:			
OGLDs[i] only	173 (56.9)	77 (45.8)	96 (70.6)
Insulin only	12 (3.9)	12 (7.2)	0 (0.0)
Insulin + OGLDs[i]	119 (39.1)	79 (47.0)	40 (29.4)
Indication of insulin initiation:			
Advanced diabetic complications	3 (1.0)	3 (1.8)	0 (0.0)
Symptomatic hyperglycaemia regardless of HbA1c	1 (0.3)	1 (0.6)	0 (0.0)
HbA1c > 10% or FBS[j] > 13 mmol/L on diagnosis	15 (4.9)	13 (7.7)	2 (1.5)
Poor glycaemic control despite optimal OGLDs[i]	114 (37.5)	74 (44.0)	40 (29.4)
Not on insulin	173 (56.9)	77 (45.8)	94 (70.6)

[a]frequency
[b]Mean (standard deviation)
[c]<130/80 for CKD, <140/80 for non-CKD
[d]≥130/80 for CKD, ≥140/80 for non-CKD
[e]low-density lipoprotein cholesterol
[f]Non-Proliferative Diabetic Retinopathy
[g]Proliferative Diabetic Retinopathy
[h]Advanced Diabetic Eye Disease
[i]oral glucose-lowering drugs
[j]fasting blood sugar
*Median (interquartile range) #with 2 missing values

Table II: Factors associated with chronic kidney disease among Type 2 diabetic patients in Kuantan using Simple Logistic Regression for univariate analysis and Multiple Logistic Regression for multivariable analysis (n=304).

Characteristics	Univariate analysis		Multivariable analysis[a]	
	Odds ratio (OR) (95% CI[b])	p-value	Adjusted OR (95% CI[a])	p-value
Age (years):				
< 60	Reference	-	-	-
> 60	1.380 (0.873, 2.182)	0.168	-	-
Gender:				
Male	Reference	-	-	-
Female	0.911 (0.576, 1.440)	0.690	-	-
Race:				
Malay	Reference	-	-	-
Chinese	0.633 (0.364, 1.101)	0.105	-	-
Indian	1.070 (0.474, 2.417)	0.871	-	-
Duration of diabetes (years):				
< 5	Reference	-	-	-
5 - 10	2.058 (1.076, 3.936)	0.029	-	-
> 10	2.270 (1.169, 4.404)	0.015	-	-
Smoking status:				
No	Reference	-	-	-
Yes	1.372 (0.810, 2.325)	0.239	-	-
Body Mass Index (kg/m²):			-	
< 18.4 (underweight)	Reference	-	-	-
18.5 - 24.9 (normal)	2.914 (0.289, 29.414)	0.365	-	-
25.0 - 29.9 (overweight)	3.635 (0.367, 35.991)	0.270	-	-
> 30 (obese)	4.565 (0.461, 45.241)	0.194	-	-
Blood pressure (mmHg):				
Controlled[c]	Reference	-	Reference	
Uncontrolled[d]	2.885 (1.806, 4.609)	<0.001	2.634 (1.482, 4.684)	0.001
HbA1c (%):			-	-
Good control	Reference	-	Reference	
Poor control	5.206 (3.186, 8.506)	<0.001	4.178 (2.363, 7.387)	<0.001
Comorbidities:				
Nil	Reference	-	-	-
1	1.250 (0.071, 22.132)	0.879	-	-
2	0.944 (0.058, 15.400)	0.968	-	-
> 3	1.647 (0.101, 26.911)	0.726	-	-
Grades of retinopathy:				
No retinopathy	Reference	-	Reference	
Mild NPDR	9.662 (5.158, 18.100)	<0.001	7.472 (3.817, 14.627)	<0.001
Moderate NPDR	21.606 (6.086, 76.703)	<0.001	13.594 (3.609, 51.206)	<0.001
PDR / ADED	4.227 (0.676, 26.425)	0.123	2.793 (0.376, 20.753)	0.316
Unknown	6.134 (3.051, 12.330)	<0.001	4.787 (2.239, 10.235)	<0.001
LDL[e] (mmol/L):			-	-
< 1.8	Reference	-	-	-
1.8 - 2.6	1.201 (0.577, 2.502)	0.624	-	-
> 2.6	1.192 (0.577, 2.463)	0.636	-	-
*Diabetic treatment:				
OGLDs[f] only	Reference	-	-	-
Insulin (with or without OGLDs[f])	2.836 (1.759, 4.573)	<0.001	-	-

[a]Included all the significant variables from simple logistic regression in the analysis but only the significant variables are reported
[b]confidence interval
[c]<130/80 for CKD, <140/80 for non-CKD
[d]≥130/80 for CKD, ≥140/80 for non-CKD
[e]low-density lipoprotein cholesterol
[f]oral glucose lowering drugs
Significant at α=0.05

clinics in Kuantan was 55.3% (95% CI=54.8-55.9%). This finding was a bit higher than most similar studies conducted in other nations, where the percentage of CKD was reported to be around 30% to 40%. Nevertheless, a study conducted in a primary care polyclinic in the northern region of Singapore found that 53% of T2DM patients had CKD, similar to this study.[13] Additionally, CKD was found to affect about 50% of patients with T2DM globally.[14] CKD was more common in certain patient populations, including the elderly, those with youth -onset DM, obese, and specific ethnic groups.[15] This study was done in a suburban region, with a multi-ethnicity population which may contribute to the higher range of CKD prevalence, due to the clinical, metabolic, socioeconomic, and behavioural factors.[16,17] It is also expected that the prevalence might be lower compared to a tertiary setting.[18]

Among T2DM patients with CKD, 87.5% had diabetes for five years or more, 90.5% had at least two comorbidities, including hypertension or dyslipidaemia, which reflects a high prevalence of multimorbidity, defined as the co-occurrence of at least two chronic noncommunicable diseases in the same individual. The prevalence of overweight and obesity in T2DM with CKD was 37.5% and 41.7%, respectively. The mean body mass index was 29.7 kg/m^2. The prevalence of overweight and obesity was higher compared to the national prevalence which was 30.4% and 19.7%, respectively.[2] The metabolic effect of T2DM may have contributed to the greater prevalence of obesity and overweight in this study, which shows that obesity has a recognized association with T2DM with or without CKD. In fact, Malaysia has the highest prevalence of adult obesity in Southeast Asia, which is a risk factor for a number of non-communicable diseases.[19]

In this study, slightly more than half of the patients failed to achieve the targeted blood pressure control as outlined by the Malaysian Clinical Practise Guideline (CPG) for the Management of DM.[11] Most of the patients with uncontrolled blood pressure were among those with CKD, with similar findings for glycaemic control. The measurement of HbA1c serves as the indicator for assessing diabetes management. In Malaysia, the National Diabetes Registries (NDR) has implemented an annually audited programme, which aims to achieve a target of over 30% of randomly selected patients with an HbA1c level below 6.5% for all T2DM patients.[3] In this study, good glycaemic control of T2DM with CKD was taken as less than 7% as recommended by the CPG[11]. 28% of the T2DM patients with CKD in this study achieved good glycaemic control, almost achieving the NDR target. The majority of T2DM patients with CKD (88.7%) have LDL levels greater than 1.8 mmol/L, which is considered an unmet goal for high-risk individuals.[11] The high prevalence of CKD among T2DM patients in this study could be attributed to high blood pressure and poor glycaemic control. It was proven that hypertension and poor glycaemic control, as well as dyslipidaemia, are associated with the occurrence and progression of CKD.[20]

Pharmacological treatment analysis showed that 54.2% of T2DM with CKD were on insulin. Biguanides and sulphonylureas were the two groups of OGLDs most commonly used due to their availability in primary care, cost-effectiveness, good reputation, and acceptance.[21] For many years, CPG has consistently advocated the utilisation of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) in the management of CKD in T2DM patients.[11] In addition, sodium-glucose cotransporter 2 inhibitor (SGLT2i) medications are highly recommended for patients with T2DM and CKD.[10] In the foreseeable future, it is anticipated that a variety of potentially efficacious and recommended treatments for CKD may become readily accessible within primary care settings, such as glucagon-like peptide-1 receptor agonists (GLP-1RAs) and the nonsteroidal mineralocorticoid receptor antagonist (MRA) known as finerenone.

Multivariable analysis showed that poor glycaemic control, uncontrolled blood pressure, mild NPDR and moderate NPDR were significantly associated with T2DM with CKD. Hyperglycemia triggers a series of pathological processes, resulting in a progressive decline in the glomerular filtration rate. T2DM with poor glycaemic control had a four times higher risk of developing CKD compared to those with good glycaemic control. This finding corroborates the reports in other studies whereby an increased risk of developing CKD was observed among patients with poor glycaemic control.[22] The beneficial

effect of early intensive glycaemic control in reducing the risk of CKD was conclusively demonstrated in landmark trials, the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS).[23] Additionally, this study identified uncontrolled blood pressure as one independent risk factor for CKD. Another study has also highlighted a similar result of a strong association between uncontrolled blood pressure and CKD in T2DM patients.[24] In general population, hypertension is a significant risk factor for CKD, and equally, CKD is the most prevalent cause of secondary hypertension. A local study among hypertensive population revealed that T2DM increased the risk of developing CKD by 2.621% compared to non-diabetic individuals.[25]

Diabetic retinopathy and diabetic-related CKD are both caused by microvascular damage in these organs. The eye and the kidney have significant similarities in their developmental, anatomical, and pathological pathways. Thus, CKD frequently correlates with the presence of diabetic retinopathy. A multivariable analysis revealed that both mild NPDR and moderate NPDR were identified as risk factors for CKD in T2DM patients. This finding was supported by several studies which demonstrated similar findings and a significant association between diabetic retinopathy and CKD progression.[26,27] In Malaysia, a consistent pattern of retinopathy and CKD prevalence among T2DM patients was observed in each annual report, suggesting a strong correlation between these two conditions.[3] Consequently, retinal vascular assessments, such as office fundoscopy or camera fundoscopy, which are readily accessible in primary care clinics, may have the potential to aid in the prediction of CKD outcomes among T2DM with retinopathy. PDR is a highly specific indicator for the diagnosis of diabetic-related CKD.[28] Although Proliferative Diabetic Retinopathy (PDR) or Advanced Diabetic Eye Disease (ADED) was found to have higher odds of having CKD than those with no retinopathy, it was not significant statistically, which could be due to the small number of T2DM patients with PDR or ADED in this study.

Given the high cost of care in managing CKD complications, preventive strategies are shifting towards primary prevention. Early screening for T2DM in the population is crucial for early diagnosis and treatment to detect asymptomatic T2DM, whereby early interventions have the potential to yield positive outcomes and prevent the progression of diabetic complications, including CKD. Identifying evidence of kidney injury using UACR or eGFR is secondary prevention, which is widely available in primary care clinics.[29,30] Early diagnosis of CKD in T2DM may prevent progression to ESKD, lower the risk of cardiorenal metabolic complications and death, improve quality of life and reduce healthcare costs.

There are several strengths of this study. Despite the high prevalence of T2DM and CKD, very little is known about CKD among T2DM and its associated risk factors in Malaysia, particularly in Pahang. Significant factors associated with CKD in T2DM patients were identified in this study, including poorly controlled glycaemic, uncontrolled blood pressure, and retinopathy status. Additionally, this study unveiled the socio-demographic and clinical profile among T2DM patients at primary health clinics with and without CKD. It could serve as a guide for the implementation of more effective surveillance for T2DM patients and aggressive intervention can be steered to curb the disease complications.

Despite these strengths, the cross-sectional design of this study comes with its limitations. Using the secondary data, this study was able to identify the factors associated with CKD but could not confirm the cause-and-effect relationship between the variables. Moreover, this study was only able to report the prevalence of CKD among T2DM patients, which might also be comprised of CKD with hypertension or other renal diseases due to the difficulties in confirming the presence of diabetic kidney disease per se from the clinical records. For adults, the WHO definition of overweight and obesity was used for the analysis, which might result in a slight discrepancy in the BMI descriptive analysis. Purposive sampling was used to select the largest primary health clinics in Kuantan, which is a limitation as the data might not represent the entire Malaysian T2DM population. Thus, the generalizability of this study's findings to other T2DM populations in Malaysia might warrant further study.

CONCLUSION

Around half of T2DM patients in this study had evidence of CKD. Those with poor glycaemic control and high blood pressure had a higher risk of having CKD compared to the groups with good control. Hence, aggressive intervention should be well-thought-out for all primary care T2DM patients to achieve good glycaemic and blood pressure control to curb the progression of CKD. It is imperative to do a timely retinal examination for early identification of retinopathy status as it is associated with CKD progression. The challenge is to develop the most effective approach to perpetually improve diabetes management, and effectively prevent CKD progression at the primary care.

AUTHOR CONTRIBUTION

Fa'iza Abdullah was involved in the conceptualisation of the study, data collection and reviewing as well as editing the writing of the paper. Qamarul Azwan and Muhammad Arif Mustaqim were involved in the data collection, initial data analysis and drafting of the manuscript. Nor Azlina was responsible for checking and finalising the data analysis and editing of the paper, while Mohd Aznan was involved in the manuscript revision for important intellectual content. All authors have agreed and are accountable for the final manuscript.

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CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

INSTITUTIONAL REVIEW (ETHIC COMMITTEE)

Ethical approval for this research was obtained from IIUM Kulliyyah Research Committee (IIUM/305/20/4/1/7) (Research ID: 693) and The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) (NMRR-21-1834-60299).

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per guidelines)

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ORIGINAL ARTICLE

Validating Fibula Length as a Reliable Estimator for Femoral Nail Length: A Comparative Analysis with the Standard AO Method

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ABSTRACT

INTRODUCTION: An appropriate femoral nail length is required to be measured preoperatively to ensure optimal surgical outcomes. Conventionally, measurements are obtained clinically or radiographically on the contralateral femur or by using forearm referencing. This study is aimed to determine whether fibula length can be used as an additional clinical method for estimating maximum femoral nail length. **MATERIALS AND METHOD:** This study involves measuring the femurs and fibulas of 140 patients using a standard tape measure. Femur length is measured adhering to the standard Arbeitsgemeinschaft für Osteosynthesefragen (AO) method, while fibula length was measured from the tip of the fibula head to the tip of the lateral malleolus. Pearson correlation coefficient (r) determines any correlation between the two measurements. **RESULTS:** The overall mean femoral length was 37.98cm (SD=2.72), with a range of 32.0 to 46.5 cm, and the mean fibula length was 37.72cm (SD=2.61), with a range of 32.4 to 47.0 cm. A robust and positive correlation (r=0.940, p<0.001) was observed between fibula length and femoral length. Age, body mass index, and gender did not affect this correlation. Both inter-observer and intra-observer reliabilities were high. A formula for estimating maximum femoral nail length was derived from the correlation graph: femoral nail length = 1 + (0.98 x fibula length). **CONCLUSION:** Fibula length demonstrates a strong correlation with femoral length, offering a reliable alternative clinical method for estimating femoral nail length. This method proves particularly useful in cases of bilateral femoral fractures with concurrent forearm fractures where forearm referencing method is impractical.

Keywords
Femoral length, fibula length, femoral shaft fracture, intramedullary nail

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INTRODUCTION

Femoral shaft fractures frequently present in emergency departments, often stemming from high-energy trauma such as road traffic accidents. The global incidence of these fractures range from 1.0 to 2.9 million annualy,[1-3] necessitating hospital admissions and operative intervention. Currently, the preferred surgical approach for femoral shaft fractures is intramedullary nailing, acknowledged as the gold standard.[4-6] Consequently, operation theatres are required to maintain a diverse inventory of nail sizes. However, the practicality of assuming the availability of all nail sizes during surgery is limited. Hence, it is essential for orthopaedic surgeons to preoperatively assess and determine the appropriate size and length of nails.

Polytrauma involving bilateral femoral fractures and bilateral upper limb fractures present significant challenges. Such injuries necessitate careful planning and precise management, highlighting the importance of accurately estimating femoral nail length. Studies indicate that polytrauma cases, while relatively uncommon, demand significant resources and advanced surgical techniques due to their complexity.[7-9] These findings reinforce the critical need for reliable methods to estimate femoral nail length. The conventional method for estimating femoral nail length involves

radiographic measurements of the intact contralateral femur.[10] Nevertheless, there are alternative clinical methods, recommended by Arbeitsgemeinschaft für Osteosynthesefragen (AO), for estimating femoral length that obviate the necessity for x-ray radiation. The AO Foundation, or the Association for the Study of Internal Fixation, is a medically guided, not-for-profit organization led by an international group of surgeons who specialize in the treatment of trauma and disorders of the musculoskeletal system. It is a globally recognized organization that focuses on improving patient outcomes in trauma and musculoskeletal disorders through research, education, and innovation.[10,11]

Additionally, recently studies propose an alternative method, measuring forearm length from the tip of the olecranon to the tip of the little finger, offering utility in bilateral femoral fractures or instances where patient characteristics impede palpation of the greater trochanter (GT).[10,12-15] Despite their efficacy, these clinical methods may prove insufficient in cases involving bilateral femoral fractures coinciding with bilateral upper limb fractures or in patients with known upper limb bone or joint deformities.

Considering these challenges, our study seeks to investigate the viability of fibula length as an alternative clinical method for estimating femoral nail length. This investigation is particularly relevant in scenarios where measuring the contralateral femur or utilizing the forearm referencing method is impractical.

MATERIALS AND METHODS

We conducted a cross-sectional study involving 140 participants recruited from the orthopaedic clinic and ward of a single tertiary trauma centre. Employing a systematic random sampling method, every third patient seen in the clinic or admitted to the ward was selected. Inclusion criteria encompassed individuals of both genders aged 18 to 60 years. Exclusion criteria comprised participants with lower limb deformities, limb length discrepancies, bone or joint pathologies, a history of lower limb fractures, and known skeletal diseases. The study received approval from the Human Research Ethics Committee of Hospital Universiti Sains Malaysia (USM/JEPeM/20120704).

The lower limbs of the participants were exposed, and the femoral and fibula lengths of each participant were measured by two independent observers (Observer A and Observer B) on separate occasions. Each measurement was taken three times by each observer using a standard, flexible 150-centimeter (cm) measuring tape (Seca) and recorded to the nearest 0.1 cm. The participants and observers were blinded to the measurements to ensure unbiased results. To minimize measurement bias, the observers initially measured using the inch side of the tape and then flipped it to record the measurement in cm. Participants were not informed of the specific measurements being taken.

Observers were unaware of each other's measurements and their own previous measurements for the same participant, ensuring objective and unbiased data collection. The femoral length was measured from the greater trochanter (GT) to the superior pole of the patella, following the standard AO method (Fig. 1A). The GT was identified as the most prominent bony landmark at the proximal lateral thigh, while the superior pole of the patella was identified as the most proximal tip of the patella in full knee extension. The fibula length was measured from the tip of the head of the fibula to the tip of the lateral malleolus (Fig. 1B). The tip of the fibula head was identified as the first prominent bony landmark below the knee joint line on the lateral aspect of the proximal leg, and the tip of the lateral malleolus was identified as the most distal tip on the lateral aspect of the leg.[16]

Figure 1: Measurement of the (A) femoral length from the GT to the superior pole of the patella, and (B) fibula length from the tip of the fibula head to the tip of the lateral malleolus.

Upon completion of data collection, all information was entered and analysed using SPSS version 26. Descriptive statistics summarized socio-demographic characteristics, presenting numerical data as mean (SD) or median (IQR) based on normality distribution and categorical data as frequency (percentage).

RESULTS

The demographic profile of the 140 participants is summarized in Table I. There were 107 males and 33 females. The mean age was 28.78 years (SD=8.61). Participants ranged from 18 to 57 years old, and the mean body mass index (BMI) was 23.68 (SD=4.49), with 54 participants having a BMI exceeding 25. Table II provides a summary of measurements conducted by Observers A and B, including the average measurements. The overall mean femoral length was 37.98cm (SD=2.72), with a range of 32.0 to 46.5 cm, and the mean fibula length was 37.72cm (SD=2.61), with a range of 32.4 to 47.0 cm. Correlation analyses are also presented in Table II, revealing a robust and positive correlation between the overall average measurements of the femur and fibula (r= 0.940, p< 0.001). Specifically, both Observer A (r=0.916, *p* <0.001) as well as Observer B (r=0.921, p<0.001) demonstrated a strong positive correlation between femur and fibula measurements. The linear correlation is visually depicted in Figure 2 and a formula for estimating maximum femoral nail length is derived from the correlation graph:

$$\mathbf{y} = 0.98 \times \mathbf{x},$$

where **y** is the femoral length or the maximum femoral nail length, and **x** is fibula length.

Table I: Demographic data of the participants (n = 140)

Variable		Mean (SD)	n (%)
Age (year)		28.79 (8.61)	
Gender	Female		33 (23.6)
	Male		107 (76.4)
Race	Malay		120 (85.7)
	Chinese		10 (7.1)
	Indian		10 (7.1)
Weight (kg)		66.24 (17.55)	
Height (cm)		165.98 (8.59)	
BMI		23.68 (4.49)	
	< 25		86 (61.4)
	25 and above		54 (38.6)

SD: standard deviation, BMI: body mass index

Table II: The mean of femur and fibula length taken by Observers A and B, the overall mean of both measurements, and the, correlations between the femur and fibula measurements

Variable (cm)	Mean (SD)	Correlation	p-value
Femur A	37.77 (2.79)	0.916	<0.001
Fibula A	37.79 (2.67)		
Femur B	38.19 (2.80)	0.921	<0.001
Fibula B	37.66 (2.62)		
Overall Femur	37.98 (2.72)	0.941	<0.001
Overall Fibula	37.72 (2.61)		

SD: standard deviation

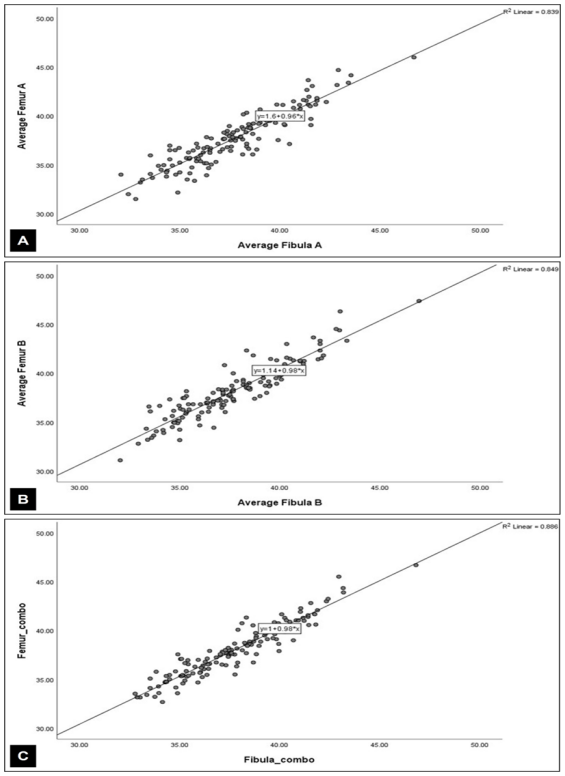

Figure 2: Linear correlations between femoral and fibula length measured by (A) Observer A, (B) Observer B, and (C) the overall average of both measurements.

Controlling for age, BMI, and gender, Table III illustrates a consistently strong and positive correlation between femur and fibula lengths measured by both observers (Observer A: r^A = 0.916-0.883, p<0.001; Observer B: r^B = 0.923-0.907, p<0.001). Notably zero-order correlations indicate that age, BMI, and gender exerted no influence on the relationship between femoral and fibula lengths.

Table III: The correlation of femur and fibula lengths with respect to the age, BMI, and gender.

		Age	BMI	Gender	
Variable	Correlation	Correlation	Correlation	Correlation	p-value
Femur A	0.916	0.916	0.914	0.883	<0.001
Fibula A					
Femur B	0.921	0.923	0.921	0.907	<0.001
Fibula B					

BMI: body mass index

Interclass correlation (ICC) analyses in Table IV affirm a high degree of reliability and consistency between Observers A and B for femoral and fibula lengths. The ICC values indicate good reproducibility and consistency between readings taken by the observers, both individually and collectively. Overall, this underscores the robustness and reliability of the femur and fibula measurements, confirming their consistency and strong correlation between observers.

Table IV: Interclass correlation coefficient (ICC) for inter-observer and intra-observer consistencies of the femoral and fibula lengths.

Variable	Interclass Correlation	95% (CI)		F-Stat	df1	df2	P-value
		Lower Bound	Upper Bound				
ICC for inter-observer consistency.							
Femur	0.938	0.906	0.958	17.505	139	139	<0.001
Fibula	0.972	0.961	0.980	36.287	139	139	<0.001
ICC for intra-observer consistency of the measurements recorded by Observer A and Observer B on the femur and fibula.							
Femur A	0.981	0.975	0.986	55.94	139	278	<0.001
Fibula A	0.996	0.994	0.997	224.12	139	278	<0.001
Femur B	0.987	0.983	0.990	76.36	139	278	<0.001
Fibula B	0.992	0.989	0.994	129.39	139	278	<0.001
ICC for intra-observer consistency between the femur and the fibula measurements of each observer.							
Femur and Fibula A	0.956	0.938	0.968	22.617	139	139	<0.001
Femur and Fibula B	0.958	0.941	0.970	23.768	139	139	<0.001

CI: confidence intervals, df: degrees of freedom

DISCUSSION

In the historical evolution of intramedullary fixation, Bircher introduced the initial form in 1886 with ivory pegs, a technique later refined by Gerhard Kuntscher during World War II, subsequently establishing itself as the gold standard for femoral shaft fracture fixation.[17-19] Intramedullary nailing aims to restore femoral length and provide an appropriately sized nail for stable fixation, avoiding complications such as knee joint perforation or peri-implant fractures resulting from excessively long or short nails.[9,12]

Traditionally, radiographic measurements of the intact femur from the greater trochanter (GT) to just above the distal femur's epiphyseal scar determine the ideal femoral nail length.[10,19,20] This represents the adequate longest femoral nail length that is required. However, this radiographic method necessitates x-ray radiation and accurate magnification, posing limitations.[12,14] Alternatively, AO has proposed clinical measurement methods, including measuring from the GT to the superior pole of the patella, or the lateral knee joint line minus 2 cm.[10,15,20] Despite these practices, clinical and radiographic methods prove ineffective in cases of bilateral comminuted femoral bone fractures.[12,20,21] Another clinical alternative involves measuring the forearm's length until the tip of the ipsilateral little finger, which has demonstrated a strong correlation with femoral length, serving as a viable alternative for estimating femoral nail length.[12-15] However, it is noteworthy that these methods necessitate intact, disease-free bilaterally forearms, hands, and fingers, devoid of joint pathologies, deformities, or malalignments, as the measurements span multiple joints and bones.

Karakas and Harma[21] previously attempted to estimate femoral medullary length, measured from the piriformis fossa to the intercondylar notch by integrating fibula length and femoral head diameter obtained through computed tomography (CT) scanning. However, due to the necessary distance requirement between the nail tip and the intercondylar notch, an adjustment involving subtracting the distance from the distal nail tip to the intercondylar notch was needed. This method, despite its potential, introduces a resource-intensive aspect by mandating the use of CT scanning for femoral nail length estimation.

To our knowledge, the utilization of clinical measurements of the fibula for estimating femoral nail length has not been investigated. Our rationale for choosing to correlate fibula length stems from its anatomical characteristics. Positioned as a long bone in the lateral aspect of the leg, just posterolateral to the tibia and below the knee joint, the fibula is distinguishable by a superficial styloid process at its proximal end, easily palpable from the lateral aspect of the fibula head. Distally, it terminates as the lateral malleolus.[16] This distinctive anatomy allows for a straightforward measurement of the fibula length, given its singular, palpable bone structure that does not transverse any joints. This approach contrasts with the method involving the measurement of the forearm plus the little finger, which entail multiple bones and joints. Similarly, the AO method, which relies on the palpation of the GT, poses challenges in obese patients.[13,15,22] Our decision to

focus on the fibula as a surrogate for femoral nail length estimation is grounded in its practical accessibility and simplicity, offering a viable alternative to existing methodologies.

In the present study involving 140 participants, we successfully established a robust and positive correlation between femoral length and the fibula length, unaffected by the participants' age, BMI, or gender. Moreover, our study demonstrated commendable inter-observer consistency in fibula measurements, highlighting the reliability of measuring fibula length. Additionally, a high level of agreement between observers on the femur and fibula length measurements further validated the method. The results of the study unveil a practical solution to the challenge of clinically estimating femoral nail length when traditional methods like contralateral femur and forearm referencing are impractical. Our findings indicate that measuring fibula length offers a reliable and straightforward method for estimating femoral nail length. This method reduces the reliance on radiographic measurements, lowers costs, and is particularly valuable in resource-limited settings or complex clinical scenarios, such as bilateral comminuted femoral fractures with concurrent bilateral forearm fractures. The proposed formula for estimating femoral nail length offers a straightforward and effective alternative.

Beyond addressing this clinical conundrum, the findings also suggest potential implications for incorporating fibula measurements in anthropometry studies focusing on human anatomy within the local population.

This study marks the inaugural comparison of fibula length to femoral length for estimating the optimal femoral nail length. Nonetheless, it is crucial to acknowledge certain limitations within this study, including its relatively modest sample size comprising 140 patients, primarily of a singular ethnicity and male gender. Despite these constraints, the findings presented herein serve as a robust foundation, laying the groundwork for subsequent investigations in diverse populations. Further studies exploring this methodology in varied demographic groups are warranted to enhance the generalizability and broaden the understanding of its applicability.

CONCLUSION

Measuring fibula length proves to be a reliable and straightforward method, demonstrating a strong correlation with femoral length, unaffected by variables such as age, BMI, or gender. The derived formula provides a simple an accurate means of estimating the maximum femoral nail length without resorting to unnecessary x-ray radiation. This method is particularly advantageous in situations where palpating the greater trochanter poses challenges or in cases involving bilateral comminuted femoral fractures with concurrent bilateral forearm fractures. The study establishes the effectiveness and practicality of using fibula length as a dependable alternative in various clinical scenarios.

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ORIGINAL ARTICLE

The Level of Self-Efficacy in Obesity Counselling and its Associated factors Among Primary Care Doctors in East Coast Malaysia

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ABSTRACT

INTRODUCTION: Obesity counselling is imperative in the management of obesity. Hence the self-efficacy of the primary care doctors (PCDs) in obesity counselling influences the outcome. This study investigated the level of self-efficacy in obesity counselling among PCDs and its associated factors. **MATERIALS AND METHODS:** This was a web-based cross-sectional survey involving 156 PCDs working in government health clinics. Participants were selected by simple random sampling and were invited through a letter. Participants then visited the survey website and filled up an online questionnaire. The level of self-efficacy was assessed using the Obesity, Nutrition, and Physical Activity Counselling by Residents (ONPAR) questionnaire. The data was analysed using SPSS software version 22 and presented as mean (SD) or frequency (%). Simple and multiple linear regression analysis were performed. Significant p-value was set at 0.05 with a 95% confidence interval. **RESULTS:** The response rate was 79.5%. The mean score for self-efficacy in obesity counselling was 66.9% (10.67) with the lowest mean score was for the "*confidence in prescribing a plan for physical activity for someone with arthritic knees*". The mean knowledge score was 55.4% (23.9). The level of self-efficacy was associated with knowledge on obesity management guidelines recommendations (p=0.02, 95% CI 0.02, 0.17). **CONCLUSIONS:** The level of self-efficacy in obesity counselling among government PCDs in East Malaysia was modest. The best predictor of higher self-efficacy in obesity counselling is knowledge of the obesity management guidelines recommendations. A structured training program is needed to improve self-efficacy among primary care doctors.

Keywords
Knowledge, obesity, primary health care, self -efficacy.

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INTRODUCTION

Obesity is a major health concern globally.[1,2] Its prevalence in Malaysia is increasing,[2] and is the highest among the Southeast Asia nations.[1] Malaysia National Health Morbidity Survey 2019 (NHMS19) showed one in two adults in Malaysia were overweight or obese. The steady rising trend in obesity prevalence among the adults from 17.7% in 2015 to nearly 20% in 2019 is concerning as obesity is linked to various health implications[3-5] including cardiovascular disease,[6] which is a leading cause of death worldwide.[7] Furthermore, obesity has also shown a strong relationship with the development of cancers such as endometrial, breast and colorectal cancers[5] which makes it even more important to curb its growth.

Obesity counselling plays a crucial role in the management of obesity.[8,9] Primary care doctors (PCDs), being the first contact, may initiate crucial discussions about weight control, offer guidance on healthy lifestyle decisions, and create customised treatment strategies for their patients.[10] Previous research indicated that patients who received weight counselling from PCDs were more likely to modify their diet, enhance physical activity habits, and achieved weight loss,[11,12] highlighting the importance of obesity-related discussions with these patients.

Studies also showed the effectiveness of obesity counselling is determined by various factors, including the

self-efficacy of PCDs in the task.[13] Self-efficacy is conceptualised as an individual's belief in their ability to successfully perform a specific task, which influences their approach to challenges and their perseverance in overcoming barriers.[14] Research suggests that PCDs with higher levels of self-efficacy in obesity counselling are more likely to engage in obesity management.[15] Conversely, PCDs with low self-efficacy may struggle to engage patients in meaningful discussions about weight management and may not feel confident in their ability to provide effective obesity management.[16]

Despite the high prevalence of obesity, literature shows that the level of self-efficacy in obesity counselling among doctors is low to average.[17-19] The low-to-average level is contributed by various factors including inadequate knowledge in obesity management, lack of structured programmes and monitoring, environmental barriers to weight loss, and previous experiences of unsuccessful obesity management.[20] Most of these earlier studies were among health professionals in the developed countries with advanced healthcare system.[19,20] Yet, studies examining the self-efficacy in obesity counselling among doctors in the developing countries are scant.

A Malaysian study among community pharmacists found that the participants were willing to help patient who want to lose weight, but their services were limited to blood pressure and blood sugar measurement, giving dietary and exercise advice, and selling weight loss products.[21] Another study found that health practitioners in Malaysia had the motivation and capacity to engage in obesity management.[22] Yet, they did not assess the level of self-efficacy of the practitioner and found that despite being motivated, the study participants did not discuss the weight problems with their patients.

The limited consultation time, having more important health issues to manage and perceived poor motivation by patients were the given reasons for not discussing weight by this cohort.[22] Noting the importance of self-efficacy and the lack of studies in the area, this study aimed to investigate the level of self-efficacy in obesity counselling among PCDs and its associated factors. Findings from this study may aid the stakeholders to design appropriate interventions to enhance self-efficacy among PCDs in managing obesity in community settings.

MATERIALS AND METHODS

Study Design and Population

This was a web-based cross-sectional study conducted from October 2016 to January 2017. The study involved PCDs at government health clinics in three states in east-cost of Malaysia. The inclusion criteria included having the Malaysian Medical Council full registration number and working experience in government health clinics for at least three months. Family Medicine Specialists (FMS) were excluded as they had advanced training in primary care counselling.

The sample size was calculated for each objective, and the highest number was taken as the study sample size. The largest sample size was from the objective meant to determine the factors associated with self-efficacy in obesity counselling, calculated using the general formula; $n=50 + 8m$ (where m is the number of the independent variables) for testing the multiple correlations.[23] Given that ten independent variables were included in the multivariate regression model, the minimum sample required for the regression analysis was 130. After adding a 20% non-response rate, the estimated sample size was 156.

Data Collection Procedure

The list of eligible PCDs (n=589) were obtained from the three respective state health departments. Study samples were selected from the list using a simple random table. An invitation letter containing the study explanatory statement and the approval letter from the Ministry of Health was sent to the selected participants. Data collection was conducted via Surveymonkey®. Participants were asked to visit the survey website and answer the questionnaire within four weeks. Each participant was assigned an identification code as a username and a common password to access the questionnaire. An implied informed consent statement was shown on the introductory page of the survey website, where participants gave consent by clicking *'Yes'* and *'Agree to proceed'*. A reminder text message was sent to participants who had not responded after four weeks. Another four weeks were

provided to complete the questionnaire before we concluded the data collection. The responses were stored in the Surveymonkey® database, which was only accessible to the principal investigator.

Measures

The level of self-efficacy in obesity counselling was measured using a questionnaire from a previous study, the Obesity, Nutrition, and Physical Activity Counselling by Residents (ONPAR) survey with permission. The questionnaire consisted of nine items with a 5-point Likert scale response (1 for "Strongly Disagree", 2 for "Disagree", 3 for "Neither agree nor disagree", 4 for "Agree", and 5 for "Strongly Agree"). The total score was converted to percentage, and the level of self-efficacy was reported as a mean percentage score. A higher mean score represented a higher self-efficacy level. The questionnaire has a person reliability score of 0.85 and an item reliability score of 0.98. It was originally used among senior postgraduate trainees in family medicine, internal medicine, and obstetrics and gynaecology. This questionnaire was appropriate for our study as it has been tested in the healthcare population. The language was kept in its original English language, which is the common language used in medical practice in Malaysia.

The factors associated with self-efficacy in obesity counselling were divided into doctor's demographics, clinical characteristics, and knowledge of clinical practice guidelines for obesity management. The doctor's characteristics included age, ethnicity, and gender. Clinical characteristics variables were working duration in primary care, involvement in the non-communicable disease team, having a family medicine specialist at the clinic, and having formal training in counselling skills, physical activity recommendations and dietary advice.

Knowledge of clinical practice guidelines for obesity was assessed using seven multiple choice questions regarding the definitions of obesity and overweight in adults and adolescents, weight reduction target, physical activity recommendation for long-term weight loss, and limit of sugar-sweetened beverages. The questions were adapted from Physician Survey of Practice in Diet, Physical Activity, and Weight Control: Questionnaire on Adult Care[24] and developed based on the Malaysian clinical practice guidelines for obesity.[25] Participants chose one correct answer for each question, and the knowledge of clinical practice guideline was measured as the percentage of the number of correct answers out of seven items and was presented as mean (SD) of the percentage score.

Analysis

Data were analysed using SPSS software version 22.[26] Descriptive statistics were used to summarise the socio-demographic characteristics. Data were presented as mean (SD) or frequency (%), as appropriate. A significant p-value was set at 0.05, with a 95% confidence interval. The level of self-efficacy was reported as the mean (SD) percentage score. Multiple linear regression analysis was performed to determine the factors associated with self-efficacy in obesity counselling. The independent variables were age, ethnicity, gender, working duration in primary care, involvement in the non-communicable disease team, having a family medicine specialist at the clinic, having formal training in counselling skills, having formal training in physical activity recommendations, having formal training in dietary advice, and knowledge on clinical practice guidelines for obesity.

A two-step regression analysis was applied, starting with a univariate analysis of each independent variable. Variables with moderate association ($p<0.20$) with self-efficacy were included in multivariate analysis, applying the simultaneous multiple regression approach. Significant interactions ($p<0.05$) were retained in the final model. Preliminary screening of the residual plots was conducted to ensure no violation of multiple regression assumptions (normality, linearity and homoscedasticity, and outliers). Multicollinearity was checked through correlations between independent variables, tolerance, and variance inflation factor.

RESULTS

Out of the 156 doctors invited, 124 completed the survey, giving the response rate of 79.5%. There was no missing data for all items. The mean (SD) age of the participants

Table 1: Participants' demographic and clinical set-up and training (n=124)

Participant's characteristics	n (%)	Mean (SD)
Age		30.7 (4.21)
Sex		
Male	37 (29.8)	
Female	87 (70.2)	
Ethnic		
Malay	112 (90.3)	
Others	12 (9.7)	
Working duration in primary care (years)		2.2 (2.4)*
Presence of a family medicine specialist		
Yes	60 (48.4)	
No	64 (51.6)	
Involvement in NCD^ team		
Yes	98 (79)	
No	26 (21)	
Formal training in counselling		
Yes	43 (34.7)	
No	81 (65.3)	
Formal training in physical activity		
Yes	37 (29.8)	
No	87 (70.2)	
Formal training in dietary and nutrition advice	33 (26.6)	
Yes	91 (73.4)	
No		

**=Median (IQR), ^non-communicable disease*

was 30.7 (4.21) years old. The median (IQR) for working duration in primary care was 2.2 (2.4) years. Table 1 shows the demographic profile of the participants.

The mean (SD) self-efficacy in obesity counselling score among primary care doctors was 66.9% (10.67). The respondents gave the highest mean score for *"the confidence in discussing weight loss in a way that would maintain a positive relationship with the patient"*. Meanwhile, the lowest mean score was for the *"confidence in prescribing a plan for physical activity for someone with arthritic knees"*. Table 2 shows the mean score for each self-efficacy item.

Table 2: Mean score for self-efficacy items

Self-efficacy items	Mean (1 to 5)	(SD)
I feel confident in my ability to improve overweight patients' dietary habits.	3.46	(0.76)
I am confident in my ability to assist patients in developing a plan for physical activity.	3.41	(0.78)
I feel well-prepared to follow evidence-based guidelines in counselling my overweight patients on diet.	3.26	(0.84)
I'm confident that I could discuss weight loss in a way that would maintain a positive relationship with the patient.	3.71	(0.59)
I am able to determine if a patient meets appropriate guidelines for physical activity.	3.38	(0.73)
I am able to identify specific community resources to support a patient's effort to lose weight.	3.10	(0.87)
I feel confident prescribing a plan for physical activity for someone with arthritic knees.	2.93	(0.89)
I am able to motivate and guide patient for behaviour change during interview.	3.51	(0.74)
I am effective in assisting patients who express an interest in making a change with weight (setting goals, next steps, follow-up).	3.39	(0.89)

The mean (SD) correct answers given by the participants was 3.88 (1.7) out of seven items. Most participants answered correctly on the question regarding the target for weight reduction among obese and overweight patients to prevent diabetes mellitus but did poorly on the question on the physical activity recommendation for overweight and obese individuals to achieve long term weight lost. The percentage of correct answers for each item is presented in Table 3. The mean percentage for correct answer for knowledge was 55.4% (23.9).

Table 3: Percentage of correct answers for knowledge questions

	Items*	Percentage of participants answer correctly
1	What is the cut-off point for overweight in adults?	68.5%
2	What is the cut-off point for obesity in adults?	62.1%
3	What is the cut-off point for overweight in children and adolescents?	54.0%
4	What is the cut-off point for obesity in children and adolescents?	67.7%
5	What is the target of weight reduction among obese and overweight patients to prevent type II DM?	77.4%
6	What is the physical activity recommendation for overweight and obese individuals to achieve long term major weight loss?	16.1%
7	What is the limit of sugar-sweetened beverages should a person have in a day to prevent type II DM?	41.9%

Six factors showed moderate correlations with self-efficacy in the univariate analysis and were retained in the multivariate analysis. Simultaneous multiple regression was used to predict whether sex, involvement in NCD team, training in counselling skills, training in physical activity recommendation, training in dietary advice and level of knowledge of obesity management guidelines predict the level of self-efficacy in obesity counselling. We found that the level of knowledge of obesity management guideline was significantly associated with the level of self-efficacy in obesity counselling (p=0.02, 95% CI 0.02, 0.17) (Table 4). An increase in one standard deviation unit of the level of knowledge score would likely result in an increase in the level of self-efficacy in obesity counselling by 0.21 standard deviation unit. This model explained 16.2% of the variance in self-efficacy in obesity counselling (R^2=0.162, F (6, 117) =3.76, p<0.05).

Table 4: Multivariate linear regression analysis of factors associated with self-efficacy in obesity counselling.

Variables	B (standardised coefficient) [a]	Standard error	p-value	95% confidence interval
Sex	0.07	2.02	0.42	-2.35, 5.65
Involvement in NCD team	0.16	2.30	0.08	-0.50, 8.62
Training in counselling skills	0.09	2.11	0.37	-2.29, 6.08
Training in physical activity recommendation	0.13	2.34	0.19	-1.55, 7.69
Training in dietary advice	0.09	2.51	0.35	-2.61, 7.33
Knowledge on CPG recommendation	0.21	0.04	0.02	0.02, 0.17

[a] *Simultaneous multiple regression model was applied.*

DISCUSSION

Primary care doctors in our study showed moderate self-efficacy in obesity counselling, with a mean self-efficacy score of 66.9%. This indicates that the primary care doctors in this survey were ambivalent about their capacity to deliver obesity counselling to their patients. This finding is consistent with earlier literature that showed despite the high prevalence of obesity in the community, medical practitioners lack sufficient self-efficacy to deliver obesity counselling to patients in need.[19,20] While our study focused on doctors in primary care or family medicine, other studies among internal medicine and obstetrics and gynaecology residents also revealed the same low level of self-efficacy in obesity counselling,[19] suggesting a general low in self-efficacy across various medical domains.

A recent study in Malaysia reported that health providers were motivated to manage obesity.[22] However, their efforts were limited by short consultation time, having more pressing health issues to handle and perceived patients' low motivation to manage their weight. Interestingly, these providers who mentioned high motivation to manage obesity also expressed a need for more training in this area,[22] which suggests that although they want to counsel their patients, their current capabilities in obesity management may not be as good. Our data supports this observation, where health providers showed the least self-efficacy in situations that required in-depth knowledge, such as physical activity counselling for patients with knee arthritis (Table 2) while having the highest efficacy in their counselling skills.

Good knowledge of the local obesity management guidelines has been found to be a predictor of self-efficacy in our participants. This is expected since knowledge of the guidelines will aid the practice of primary care doctors and make them more assertive in their management approach. Our finding also concurred with previous findings in literature that health providers with good knowledge will have more self-efficacy and confidence in obesity management.[20,27] Training in counselling skills, physical activity recommendations and dietary advice showed significant associations in our univariate analysis, but it was not sustained in the multivariate model. This finding may suggest that while attending a training or workshop to increase knowledge is important, the amount of acquired knowledge is more significant in improving the self-efficacy level in our study cohort. It aligns with social cognitive theory, indicating that individuals who achieved performance mastery through an intervention experienced an improvement in their confidence and self-efficacy.[14]

Knowing the current level of self-efficacy among our primary care doctors is an essential initial step towards future interventions to improve their capability to manage obesity effectively. As the prevalence of obesity in Malaysia is already high and continues to increase,[2] primary care providers should be well-equipped and well-trained to manage patients with obesity effectively. The four ingredients of effective intervention in empowering health practitioners suggested by Katz et al still stands.[28] These include i) deliberate dissemination of information to the practitioners to improve their knowledge, ii) development of skills to motivate patients to act, iii) development of robust sense of self-efficacy to face difficulties, and iv) creating and arranging social support to achieve and maintain changes.[28] Clinical management leaders and policymakers should plan measures to improve the knowledge among doctors in primary care, especially on the local obesity management guidelines as suggested by Katz et al. The training content should not be limited to basic dietary and physical activity advice but

should be expanded to include modifications to suit personalised patient needs. The content and methods of obesity training or guidelines should ensure a good grasp of knowledge by PCDs. In addition, PCDs should also be exposed on various counselling technique and clinical mentoring or credentialing approaches may be needed in addition to the traditional workshop or talk to enhance performance mastery.

At the time this study was done, the clinical practice guideline (CPG) on obesity was still in its outdated version. The new obesity CPG was released last year and emphasizes more on the need for individualization of obesity treatment and discuss more options for weight reduction approaches.[29] Diet modifications and physical activities prescription need to be tailored according to the patient's profile, readiness and preference instead of general advice.[29] The current CPG is more comprehensive and include sections on psychological and behavioural therapy which is an integral element in changing one's behaviour. Nonetheless, the training on the new guidelines need to include the practical approach through workshops and case studies to help the PCDs in their counselling of more difficult patients especially those with multiple comorbidities or physical limitations. As shown by our results, many PCDs knows the general management of obesity but when it comes to difficult cases such as specific physical activity recommendation, many scored poorly. In addition, the training must include workshops in motivational interview since behavioural changes requires patient's participation to ensure its success.

The strength of this study lies in the probability sampling method applied in this survey. The findings may be generalised among the government PCDs within east coast Malaysia healthcare providers. However, the findings are limited only to the region, and we need to be cautious if we want to extrapolate it to all PCDs in Malaysia due to the possibility of different exposures and practice. Larger nationwide study involving the private and public PCDs need to be carried out to get the true picture of the self-efficacy level of all PCDs in Malaysia. Moreover, this study was carried out before the new CPG was released and the obesity issue was not so popular in the mainstream media. Since the released of the new CPG in 2023, several training workshops has been carried out by the Ministry of Health Malaysia. It would be interesting to repeat a similar study in the next few years to see if the outcome would be different. Additionally, the cross-sectional study design limits the study's exploration of the causal relationship between exposures and outcomes. Lastly, only less than 20 per cent of the factors associated with self-efficacy in obesity counselling were explained by our regression model and thus further exploration is warranted to identify more factors influencing the self-efficacy level among the PCDs.

CONCLUSION

Obesity has a far-reaching effect to the individual and the society, and puts a strain on health care resources. Hence, obesity needs to be tackled promptly. PCDs play a huge role to prevent, reduce, and manage obesity complications since they are operating in the community. Nonetheless, the current level of self-efficacy in obesity counselling among the PCDs in our study is only moderate at best. The best predictor of high level of self-efficacy in obesity counselling is knowledge of the local guidelines, and thus immediate action is needed to enhance the knowledge on obesity management among all PCDs as well as polishing their counselling skills so that they may be more equip to handle obesity patient.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

NAY contributed to the conception and design of the study, data analysis and write the initial draft. MAFAZ contributed to the conception and design of the study, conducted the research, collected, analyse, and interpreted the data. SSY provided advice on study design and methodology and edited the manuscript's final draft. RAR contributed to the conception and design of the study, data analysis and substantially edited the manuscript before final submission. All the authors have critically

reviewed and approved the final draft of this manuscript and are responsible for the content and similarity index of the manuscript.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest in the conduct and publication of this study.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

The study protocol was reviewed and approved by the Universiti Sains Malaysia Human Research Ethics Committee (USM/JEPeM/16040167) and the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-16-724-30306(IIR)). The study adhered to the Declaration of Helsinki, 2013, and all participants provided consent before inclusion where in this web-based survey, a consent statement was shown on the introductory page of the survey website and participants needed to give consent by clicking 'Yes' and 'Agree to proceed' before they can answer the questionnaire.

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CASE REPORT

Silent Storm: Ventricular Standstill Masquerading as Seizure in Adams-Stokes Syndrome

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ABSTRACT

Paroxysmal ventricular standstill is one of the rarest but life-threatening cause of Adams-Stokes (A-S) syndrome. We present the case of an elderly female who experienced recurrent episodes of convulsions, described as tonic movements of all limbs followed by brief loss of consciousness, due to paroxysmal ventricular standstill. The diagnosis was confirmed when an episode of convulsions coincided with an ECG strip showing ventricular standstill, and the convulsions stopped once the arrhythmia resolved, as observed on the cardiac monitor. The diagnosis was further supported by the absence of additional convulsive episodes after the insertion of a temporary transvenous pacemaker, which corrected the arrhythmia. Adams -Stokes syndrome refers to a lack of brain perfusion caused by inadequate or inefficient cardiac contractility due to a cardiac arrhythmia. This can result in abnormal brain activity, leading to convulsions or syncope.

INTRODUCTION

Paroxysmal ventricular standstill (PVS) occurs when there is no electrical or mechanical activity of the ventricles despite a normal functioning atria. This translates to presence of p waves followed absence of qrs complex in an electrocardiography strip. In turn, this leads to decreased cardiac output and significant decreased cerebral perfusion even when the episode lasts only for few seconds which manifest as Adams-Stokes (A-S) attack with seizures and loss of consciousness.

The common ethologies for ventricular standstill includes ischemic heart disease, electrolyte imbalances, drug toxicity and structural heart diseases. In rare occurrences ventricular standstill has also been seen in patient with acute gastroenteritis due to exaggerated vagal tone.[4] The prevalence of ventricular standstill worldwide and in Malaysia in unclear as this is a rare cardiac arrhythmia occurring sporadically around the world. We present a rare case of seizures caused by Adams-Stokes syndrome secondary to paroxysmal ventricular standstill. Other causes of Adams-Stokes syndrome are cases of both tachyarrhythmias, such as ventricular fibrillation, and bradyarrhythmias, such as heart blocks. Ventricular standstill is comparable to ventricular fibrillation in terms of severity of the arrhythmia as it is associated with high mortality therefore it is essential to recognize this disease. The prognosis is poorer with patients with longer duration of PVS. Hence, patients with recurrent and frequent episodes of PVS require immediate attention to improve morbidity and mortality associated with the arrhythmia.

CASE REPORT

An 88 years old lady with no known medical illness presented with multiple convulsive episodes described as tonic movement of bilateral upper limb and lower limb associated with loss of consciousness which lasted for ten to fifteen second each episode which self aborted with no drowsiness or confusion following the convulsive episode. Further history from the patient revealed that she did not have a prior history of ischemic heart disease or hospital admissions for any reason. She had no significant drug history and was not on any medications, including beta blockers. She also strongly denied experiencing chest pain

or any symptoms suggestive of acute coronary syndrome during this presentation. Upon arrival to the Emergency Department (ED) of Hospital Tawau her vital signs were stable. The patient had a similar episode of tonic movement of bilateral upper limb and lower limb which resolved spontaneously at the ED. Initial impression by the emergency team was seizure for investigation, and immediate CT brain done together with routine blood investigations and ECG. The CT brain was normal. Thyroid function test showed T4 level of 15.60 pmol/L and TSH level of 1.54 mIU/L.

Analysis of electrolyte showed potassium level of 4.4 mmol/L, sodium level of 141 mmol/L, serum calcium level of 2.23 mmol/L, magnesium level of 1.04 mmol/L and phosphate level of 1.22 mmol/L. Other blood investigations were unremarkable as well. ECG showed prolonged PR interval (Figure 1). The initial impression was breakthrough seizure to rule out epilepsy with a differential diagnosis of cardiac syncope. Patient given intravenous phenytoin and planned for admission to cardiac coronary unit with continuous cardiac monitoring. In the ward the patient developed further frequent similar episodes of convulsion and repeated ECG noted to have complete heart block (Figure 2). Transcutaneous pacemaker was inserted. Despite being on a transcutaneous pacemaker with maximum output of 200 milliamps, the patient continued to have convulsive episodes lasting few seconds, cardiac monitor showed there were no electrical capture from transcutaneous pacemaker and cardiac monitor strip revealed ventricular standstill (Figure 3). Temporary Transvenous Pacemaker (TPM) was inserted uneventfully after urgent consultation with cardiology team and manage to obtain electrical and mechanical capture (Figure 4). The patient had no more episodes of tonic movements following TPM insertion. Phenytoin which was started in emergency department was off. Patient was transferred to Hospital Queen Elizabeth, Sabah, Malaysia, tertiary center for permanent pacemaker insertion.

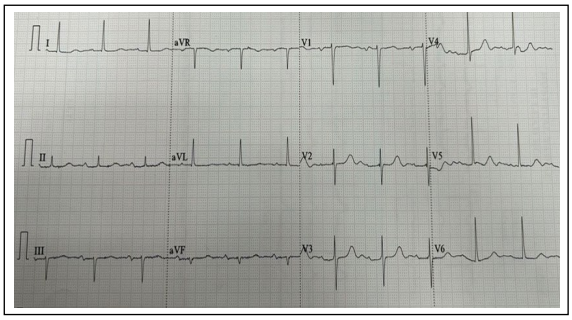

Figure 1 : ECG at Emergency Department showing prolonged PR interval, first degree AV block

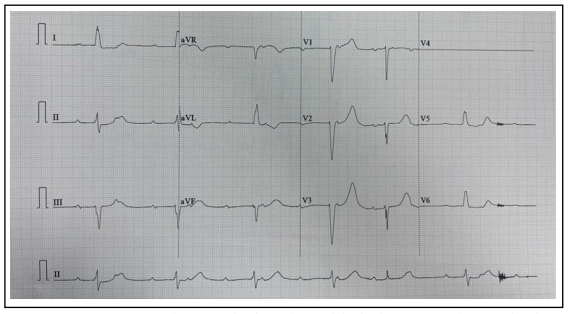

Figure 2 : ECG in ward showing third degree atrioventicular (AV) block

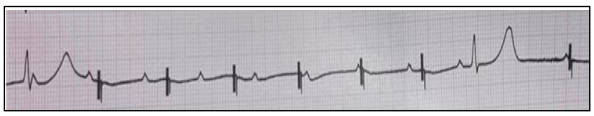

Figure 3 : Cardiac strip showing ventricular standstil and failure of transcutaneous pacemaker to have electrical capture

Figure 4 :ECG strip showing paced rhythm after transvenous pacing

DISCUSSION

Ventricular standstill is the absence of ventricular contraction due to the absence of impulse formation in ventricles or propagation of supraventricular impulse.[5] This translates to absence of ventricular rhythm with a normal atrial activity in an electrocardiography.[5] The exact pathogenesis of PVS is unclear. It is associated with conduction defects between the atria and ventricles. The etiology of ventricular standstill can be divided into primary causes which are due to structural, degenerative or idiopathic, while secondary causes include hypoxia, acidosis, electrolyte imbalance, hypothermia and drug induced causes.[1] Presentation of PVS can vary, ranging from being asymptomatic and incidentally detected during Holter monitoring, to presenting as seizures or syncope as part of Adams-Stokes syndrome, as in the case presented, and in rare instances, presenting as cardiac arrest requiring cardiopulmonary resuscitation. It is difficult to distinguish

seizures or syncope secondary to neurological conditions from those caused by Adams-Stokes syndrome, which has led to the over diagnosis of epilepsy. Approximately 20% of misdiagnosed epilepsy cases are due to cardiovascular causes.[9] In this case the patient's presentation of convulsive episodes presumed to be due to a neurological problem, and emphasis placed on a neurological workup, including a CT brain scan. A detailed history can help in making the diagnosis of Adams-Stoke syndrome which characterized by abrupt transient loss of consciousness (TLOC) from cardiac pathology. An immediate return of consciousness following a convulsive episode is due to cardiac syncope and not epilepsy.

Seizure secondary to epilepsy had significantly more myoclonic jerks (100% vs 51%) and had longer episodes (median in seconds 29.0 vs 3.6).[9] Other differentiating factor are myoclonic jerks were lesser (<10) in Adams Stokes syndrome compared to epileptic seizures (<20).[9] Our patient's convulsive episode lasted only for 10 to 15 seconds and only had tonic movement with no myoclonic jerks. "Slow-flat-slow" or "slow" pattens are seen in EEG findings during Adams-Stokes attack.[8] TLOC has four special characteristic pattern of history which are short duration, abnormal motor control, loss of responsiveness and amnesia for the period of LOC.[9] Investigation that should ideally be performed for diagnosis of syncope include carotid sinus massage, orthostatic challenges, electrocardiography, electrophysiological study, cardiac bio markers, echocardiography, exercise stress test and coronary angiography.[9]

Many of these tests were not done for this patient as we were in a resource limited centre and diagnosis made at the early stage with demonstration of symptoms correlating with observed ventricular standstill in cardiac monitor. Following identification of cause of the Adams Stokes attack, it is essential to treat the primary cause of this attack which in this case was paroxysmal ventricular standstill. Based on the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay the management of a patient with PVS, which is a form of atrioventricular (AV) block, is to rule out structural heart disease, either through transthoracic echocardiography or other advanced imaging modalities, depending on the clinical suspicion of structural heart disease. In cases of complete heart block or advanced AV block such as in this case, the patient would require permanent pacemaker insertion.[10] Subsequently, decision on the use of a single or dual-chamber pacemaker and the placement of the pacing lead made based on factors such as heart function, frequency of pacing, and the presence of atrial fibrillation.[10] In this case, a temporary pacemaker inserted to urgently abort the PVS episodes and patient transferred to a tertiary cardiac centre for further management.

CONCLUSION

This case is a reminder to physicians that ventricular standstill may present as convulsive episode mimicking possible neurological disorder or epilepsy. Early recognition and prompt steps such as regular ECG and continuous cardiac monitoring would allow early diagnosis and initiation of appropriate treatment. Although ventricular standstill is a dangerous arrhythmia associated with high mortality, this case showed that prompt treatment with cardiac pacing reduces chances of mortality and resolves the symptoms.

CONSENT

Written and verbal consent were obtained from the patient for publication of this case report

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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CASE REPORT

"Glossofibrolipoma" : An Unusual Presentation of Multiple Fibrolipomas on the Tongue

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ABSTRACT

Lipomas are slow-developing benign tumours composed of adipose cells depicted as "yellow epulis" by Roux in 1848. Lipoma occurrence is uncommon in oral cavity but even more rare in the tongue region. They present as yellowish, painless mass that may occasionally lead to functional and aesthetic complications. This paper describes a 55-year-old female having multiple tongue lumps that causes mastication difficulties. The lumps were excised in total from its base. The postoperative recovery was uneventful, and no complications were noted. The lumps were histopathologically identified as fibrolipoma which is a variant of lipoma. Histologically fibrolipoma shows infiltrative feature onto adjacent tissue, creating confusion in differential diagnosis. Thus, it is imperative that a careful histological assessment coupled with regular follow-ups are done especially considering the unusual development of fibrolipoma on the tongue.

INTRODUCTION

Lipomas are benign mesenchymal tumors consisting of adipose tissue commonly encountered at various parts of human body, though it is rare in oral cavity. Lipomas are named as "yellow epulis" by Roux in 1848 and are usually asymptomatic unless they reach a considerable size during which time they exert "mass-effect" upon nearby structures, causing complications. Lipomas usually present as painless, well-circumscribed, slow-growing lesions. Although they are encountered throughout the body, their prevalence in the oral region is rare. Previously cited studies have reported oral lipomas incidence rate ranging from 1% to 4.4%.[1, 2]

Specifically, prevalence of lipoma on the tongue region is even rarer. Lipomas have several variants described by its histological features, encapsulation as well as local tissue invasion. The variable histological patterns of intraoral lipomas are categorized as simple lipoma, fibrolipoma, spindle cell lipoma, osteolipoma, sialolipoma, chondrolipoma, angiolipoma and intraosseous lipoma.[3] Compared to conventional lipoma, the other variants are rare particularly fibrolipoma that has dubious histological characteristics leading to possible diagnostic doubts. This paper endeavours to report a rare case of multiple fibrolipomas on the tongue.

CASE REPORT

A 55-year-old Malay lady was referred to the Dental and Maxillofacial Clinic, Sultan Ahmad Shah Medical Centre to consult regarding a gradually enlarging non-tender mass on her tongue for the past 2 years. One month prior to consultation, she had noticed another similar mass adjacent to the existing one. She denied any history of trauma, discharge or pain at the site but noted discomfort during mastication. She also denied similar swellings elsewhere on her body. There was no hoarseness of voice, no difficulty in swallowing nor constitutional symptoms. The patient is diagnosed with hypertension, diabetes mellitus type II, dyslipidaemia and gout for which she received treatment as well as regular follow-ups at primary healthcare clinic. The patient's family history and social history were unremarkable.

Figure 1: Two yellowish ovoid submucosal masses on the right lateral border of the tongue.

Intraorally, we noted a yellowish, smooth, sessile mass on the right lateral border of the tongue measuring about 2cm x 1.5cm x 1.5cm in size (Figure 1). Upon palpation, the mass was non-tender, non-pulsatile and was slip sign positive. Another similar featured lesion measuring 0.5cm at its longest dimension was identified posterior to the original mass. There was no generalized ulceration, bleeding, restriction in tongue movement, neurosensorial disturbances, facial swelling or regional lymphadenopathy. She was partially edentulous, retaining only two lower posterior teeth and does not use dentures. Our initial clinical impression was lipoma and an intraoral biopsy under local anaesthesia was planned. The procedure was performed by administering 2.2 ml Mepivacaine 2% with epinephrine 1:100,000 as local field block followed by a longitudinal incision at the lateral tongue edge (Figure 2).

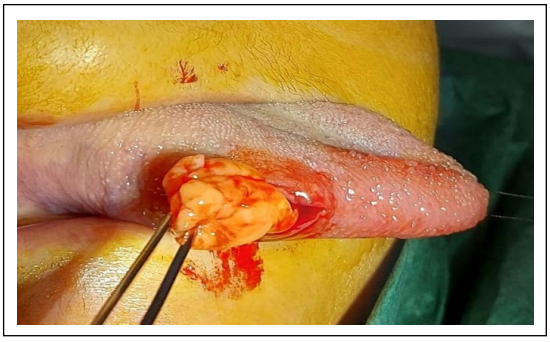

Figure 2: Total excision of lipoma under local anaesthesia.

Macroscopic examination indicated three independent well -encapsulated, smooth, yellowish lesions that were non-adherent to surrounding structures. The largest lesion measured 2cm x 1.5cm x 1.2cm as seen in Figure 3 while others measured 1 to 1.4 cm in its largest dimension. The lesions were excised completely, and specimens were sent for histopathological examination. The mucosa were reapproximated and closed using resorbable sutures. The postoperative recovery was rapid and uneventful. Histological examination of the specimen sections showed numerous well-circumscribed, mature adipose lobules intermixed with a prominent amount of fibrous connective tissues and scattered blood vessels (Figure 4) that was confirmed to be fibrolipoma. Regular post-operative review showed no signs of potential recurrence in the past 2 years.

Figure 3: Gross specimen appears smooth surfaced, yellowish and well-encapsulated mass.

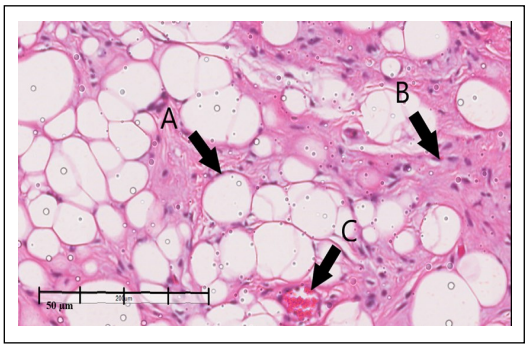

Figure 4: Histology of specimen depicting well-circumscribed, mature adipose lobules (A) intermixed with a prominent amount of fibrous connective tissues (B) and scattered blood vessels (C).

DISCUSSION

Fibrolipoma is a rare histological variant of lipoma described as mature adipocytes interlaced by stands of fibrous tissue and the fibrous component is markedly apparent even in the macroscopic analysis.[4] The abundant fibrous connective tissue coupled with potential ulceration and atrophic changes, implies that fibrolipoma may mimic infiltrative malignant lesion such as liposarcoma leading to possible doubts regarding diagnosis.[4] Recent systematic review stated that only 12% of intraoral fibrolipoma arises from tongue, the remainder originates from lip, buccal mucosa, buccal sulcus, floor of mouth , palate, and retromolar region.[5] Generally, lipomas are present in tissues with high adipose concentration; which does not

coincide with tongue tissue. Furthermore, occurrence of multiple fibrolipomas in the tongue is also very low making it even rare.

The exact etiopathogenesis of intraoral fibrolipomas remains elusive, but hypothesis includes sequalae of endocrinal imbalance, degeneration of fibromatous tumour or maturation of lipoblastomatosis.[6] Recent study suggests possible factors such as trauma, chromosomal abnormalities, chronic irritation, hormonal imbalance and metabolic conditions as well.[5] Additionally, peak incidence of oral lipomas ranges between 40 to 60 years which is consistent with our case presentation.[5] The same study stated that oral lipoma has no significant gender predilection which has generally been the consensus amongst most studies.

Clinically, tongue fibrolipomas are typically asymptomatic unless they enlarge to become space occupying lesion that leads to complications involving swallowing, speech and others.[4] The mainstay treatment for fibrolipoma usually entails surgical excision and the recurrence of such lesions afterwards are very low.[7] From the histopathological view point; due to greater composition of collagenous fibrous bands, fibrolipoma may exhibit pseudo-infiltration characteristics onto adjacent tissue resembling a malignant infiltrating lesion.[4] It is therefore essential to perform a proper histological evaluation to differentiate malignant form of lipoma from fibrolipoma. Additionally, the need for accurate histological diagnosis is relevant since fibrolipoma have greater proliferation rate compared to other simple lipoma variants.[4,6] It is the gist of this case report, to present the awareness to all regarding this variant of lipoma which can histologically mimic malignant features.

CONCLUSION

Lipoma of the tongue is quite a rare pathological occurrence; and it is further exceptionally uncommon if its variant is a fibrolipoma. It is necessary that the histological features of these lesions should be well scrutinized to prevent a misdiagnosis of malignancy. Surgical excision is still the treatment of choice and coupled with thorough examination, differential diagnosis, accurate histopathologic analysis and careful follow-up, such lesions can be managed well.

CONFLICT OF INTEREST

nil.

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