REVIEW ARTICLE

An Updated Review of Type 1 Diabetes in Malaysia

Nurhanani MN[a], Hasni M[b], Ahmad Mahfuz G[c*], Masita A[d]

[a]Autoimmune Unit, Allergy and Immunology Research Centre, Institute for Medical Research, National Institutes of Health, Ministry of Health, Malaysia
[b]Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia
[c]Faculty of Industrial Sciences and Technology, Universiti Malaysia Pahang, Kuantan, Pahang, Malaysia
[d]Allergy and Immunology Research Centre, Institute for Medical Research, National Institutes of Health, Ministry of Health, Malaysia

Keywords
Type 1 diabetes mellitus, pathology, autoimmunity, Malaysia

Corresponding Author
Dr. Ahmad Mahfuz Gazali
Faculty of Industrial Sciences and Technology,
Universiti Malaysia Pahang,
Lebuhraya Tun Razak, 26300 Kuantan, Pahang.
Email: mahfuz@ump.edu.my

Received: 3rd November 2021; Accepted: 4th Jan 2022

Doi: https://doi.org/10.31436/imjm.v21i3

ABSTRACT

The emerging phenomenon of early-onset type 2 diabetes mellitus (T2D) among Malaysians and misclassification of the types of diabetes may impact the estimation of prevalence and incidence of type 1 diabetes mellitus (T1D). Studies have shown that prevalence of T1D among three major ethnic groups in Malaysia was highest among Chinese, followed by Malays and Indians. More than half of T1D patients had diabetes ketoacidosis (DKA) which corresponded with the overall poor glycaemic control. However, the incidence of chronic complications, such as nephropathy was lower. The prevalence of autoantibodies was reported to be highest for anti-islet cell antibody (ICA). Majorty of Malaysian children had one or two daily insulin injections as part of the treatment. Generally, older patients responded better to insulin therapy and yielded better glycaemic control than younger patients. While significant advances have been made in understanding T1D in the Malaysian population, more research is warranted to improve the clinical assessment and outcome of the disease. The present narrative review aims to summarise the overall status of T1D in Malaysia, which includes epidemiology, clinical presentation, diagnosis, complications, and management.

INTRODUCTION

Type 1 diabetes mellitus (T1D) is a chronic autoimmune disorder characterised by an elevated blood glucose concentration caused by lack of insulin in the circulation. The lack of insulin, an important hormone secreted by beta (ß)-cells of the pancreas in promoting the uptake of glucose into other organs, is caused by infiltration and attack of immune cells, which subsequently result in the death of the ß-cells. Uncontrolled blood glucose will lead to complications such as micro- and macrovascular diseases, neuropathy, microalbuminuria and others.[1]

However, since the discovery of insulin in 1921, the disease could be controlled by insulin administration. Insulin administration to patients only meant to alleviate the main symptoms of T1D by reducing the blood glucose concentration. Despite advances made in T1D treatment, it is estimated that over one million children and adolescents are affected by T1D worldwide.[2] The incidence of T1D is increasing worldwide, but there is considerable variation by country, with some regions of the world having a much higher incidence than others. Finland, Sweden and Norway are among the top five countries worldwide, having a high incidence rate of T1D patients in the below 15-year age group.[3]

This situation prompted us to review literature related to T1D in Malaysia. Malaysia is a country located in the South-East Asia, with a multi-ethnic population consisting of Malay (55%), Chinese (23%), Indian (6.9%) and others.[4] The World Bank categorises Malaysia as an upper-middle-income country, in which rapid development is occurring since its independence in 1957. Interestingly, the reasons for the increasing prevalence of T1D worldwide are unclear, but it could be related to environmental and lifestyle-related changes associated with rapid development.

Environmental and lifestyle-related changes associated with the rapid development are strong reasons to perform research and investigation on T1D in this rapidly

developing country. To our knowledge, no such review has been written to summarise the state of T1D in Malaysia. This review aims to share the important information on T1D among patients in Malaysia from published literature.

EPIDEMIOLOGY

Based on the results from the International Diabetes Federation (Diabetes Atlas 9th Edition, 2019), over a quarter of the prevalent cases in the 0-14-year and 0-19-year age groups are in the European region. In the Western Pacific region, incidence rates were only available for 11 out of 36 countries. Therefore, estimated cases for Malaysia were extrapolated from another country, which does not accurately represent the local landscape of T1D.[3] Nevertheless, there were several studies of T1D in the Malaysian population. Lim published one of the earliest reports about T1D in Malaysia in 1991, where twenty patients under the age of 40 years old were diagnosed with T1D.[5] However, the report only included patients attending Diabetes Clinics in two district hospitals in the state of Pahang which is located in the East Coast of Peninsular Malaysia. It was further reported that T1D prevalence was 0.07 per 1000 inhabitants and the mean age at diagnosis was 22 years. Twenty-three percent of T1D patients reported a family history of diabetes in their first-degree relatives.

There have been other studies on T1D patients under the age of 40 years. Ismail *et al.* reported that 329 from 926 patients recruited throughout seven hospitals in Peninsular Malaysia were classified as T1D patients (35.5%).[6] These T1D patients were diagnosed with the disease at the mean age of 30.6 years. The report further stated that 36.2% of T1D were Malays, while 27.9% were Chinese. In line with Ismail *et al.*, another study reported the mean age of diagnosis was at 30.2 years for T1D patients aged more than 18 years. In this study, with a sample size of 114 T1D patients, 42.1% were males, while the remaining 57.9% were females.[7] The most recent study about T1D patients under the age of 40 reported that the mean age of diagnosis was 19.14 years.[8] In this study, they investigated the frequency of diabetes-associated autoantibodies (DAA) in a cohort of 194 T1D patients. The cohort consisted of 42.8% male and 57.2% female T1D patients. The study reported that 66.5% of the patients were Malays, 13.4% were Chinese, 14.9% were Indians, and 5.2% were of other ethnicities.

Another study reported a cohort of T1D patients from the age of 18 years onwards. Bujang *et al.* investigated the cause of death among 665 T1D patients. About 36.2% of T1D patients were males, while the remaining 63.8% were females. In this cohort, 87% of the patients were Malays, 6.2% were Chinese, 5.7% were Indian, and 1.1% were others.[9] They reported that adult-onset T1D in Malaysia was diagnosed between the ages of 20 and 30. T1D affects more females than males, while the majority of T1D patients were Malays. Apart form this, no official information was reported about the incidence rate of T1D among adults.

One study on young Malaysians with T1D by Tan *et al.* reported a total of 52 diabetic patients aged between 12 to 20 years old. From this cohort, 51.9% were females, and 48.1% were males. Chinese patients made up 42.3% of total patients with T1D followed by Malays and Indians with equal frequencies (28.8%).[10] In contrast to adult-onset T1D, juvenile-onset T1D was carefully investigated in the Diabetes in Children and Adolescents Registry (DiCARE).[11] This registry was established in 2006 and managed to analyse data from a cohort of 293 T1D patients under the age of 20 years. On average, the children were diagnosed with T1D at the age of 7.6 years, and 46.4% of them were male, while the remaining 53.6% were females. In contrast to previously stated studies, 39.6% of the patients were Chinese, 35.8% Malays, and 19.8% of the patients were Indians. Of 277 patients, 147 (53.1%) reported a positive family history of diabetes among first-degree relatives. However, despite an extensive investigation into the epidemiology of the cohort, the incidence rate could not be determined. This was primarily due to under-reporting of T1D cases by physicians as the participation was still not nationwide.

Between juvenile and adult-onset T1D, it could be concluded that females slightly outnumbered males in the incidence of T1D. Since most of the other parameters were inconsistent, it is crucial to establish a nationwide

study or cohort to determine the epidemiology of T1D in Malaysia.

CLINICAL PRESENTATION OF T1D

Although traditionally, T1D has been defined as juvenile-onset, the disease can occur at any age, and up to 50% of cases occur in adulthood.[12] This, in turn, may lead to adults being initially misclassified as having T2D. Children with T1D classically present with characteristic symptoms of polyuria and polydipsia. An approximately one-third of them develop diabetic ketoacidosis (DKA). However, the clinical presentations may differ in adult patients as the onset of T1D may be more variable.

The signs and symptoms of severe insulin deficiency and hyperglycaemia in T1D include polyuria, polyphagia, polydipsia, weight loss and fatigue. At very low levels of insulin, lipolysis will occur where the body will divert to fat as its source of energy. Ketone bodies that are produced from the metabolism of fat will consequently accumulate in the blood, leading to metabolic acidosis and compensatory respiratory alkalosis due to hyperventilation. Without medical intervention, this will result in cerebral oedema, mental confusion, unconsciousness, coma and ultimately, death.[1]

T1D patients may also first present with complications of diabetes which are now one of the leading causes of disability and death in many developed and developing countries. In Malaysia, several studies have examined the clinical characteristics with different outcome variables of local patients with T1D. In one of the earliest reports which looked into the clinical features of T1D patients in Malaysia, Lim discovered that 31% of patients presented with acute onset of polyuria and polydipsia, while 28% experienced pruritus vulvae.[5] These patients also had a high random mean blood glucose level at diagnosis (22.9 mmol/L). Approximately 88% of them had a relative weight of less than one at diagnosis, which was categorised as underweight.[5] In another study, polyuria and polydipsia were also the most commonly reported symptoms among newly diagnosed T1D patients. On the contrary, nausea and vomiting were the most frequently presented symptoms in previously diagnosed T1D patients.[13] Zaman Huri *et al.* established the biochemical profiles of patients who presented with DKA at the time of admissions which were more or less similar. However, the level of haemoglobin A1c (Hb1Ac) was not measured. The concentrations of urine ketone were found to be significantly higher in previously diagnosed compared to newly diagnosed patients, although no statistical analysis was performed for all of these findings.[13]

Ismail *et al.* found that glycaemic control in adult T1D patients was generally poor with a mean geometric mean HbA1c of 8.9%. About 62% of patients had HbA1c greater than 8%, while only 26% had HbA1c less than 7.5%.[6] Interestingly, Chinese patients were found to have better glycaemic control with significantly lower HbA1c levels than Malay or Indian patients. Age was negatively correlated with glycaemic control, but the effect disappeared when other factors were included in the analysis.

In another study that evaluated various determinants of complications in patients with diabetes, Nazaimoon *et al.* found that T1D patients who experience microalbuminuria were significantly older and has higher BMI as well as blood pressure. Meanwhile, patients without retinopathy were noted to be substantially younder, had shorter period of diabetes and lower systolic blood pressure.[14]

From the reports previously mentioned, data on clinical presentations of patients was limited and restricted by each study objectives. The mean age at diagnosis of patients involved was between 18 and 24 years. Therefore, these adult patients might not presented with the classic symptoms seen in children with T1D. One of the most comprehensive data on clinical features of young patients diagnosed with T1D in Malaysia was reported by the DiCARE. The majority of these patients (42.3%) were between the 10-15 age group at diagnosis. Almost all patients (94.9%) diagnosed were symptomatic, and as similarly reported by Lim, more than half (58.3%) of these symptomatic patients had DKA.[11] Among the non-DKA patients, 92.0% experienced polyuria or polydipsia, and 67.3% had weight loss. Close to 59% of patients were of normal weight, followed by 29.8% underweight and

11.8% overweight. Only 2.7% and 9.2% had their insulin autoantibodies, and C-peptide levels measured, respectively, which may reflect the unavailability of these tests in centres that participated. This was the only study that included the measurement of insulin autoantibodies compared to the previously mentioned studies.

GENETICS OF T1D

T1D is a polygenic disease influenced by environmental factors, whereby the relative effect of both factors may change with age. In susceptible children, the development of T1D is believed to involve an unknown environmental trigger that drives the breakdown of peripheral tolerance with genetic risk factors contributing to the different stages of disease development.[15] Close to 60 genetic loci have been associated with susceptibility to T1D.[16] From numerous studies, it is now known that the most significant susceptible locus for this disease maps to the human leukocyte antigen (HLA) region on chromosome 6p21. HLA genes account for 30%-50% of the T1D genetic risk, and HLA class II haplotypes DRB1*0301-DQB1*0201 (DR3-DQ2) and DRB1*0401-DQB1*0302 (DR4-DQ8) are the most prominent associated genes reported in patients with T1D. In Malaysia, there is limited data on the association of genetic susceptibility to T1D. One study had reported HLA-DRB1*0301 to be an independent genetic marker for T1D susceptibility in Malays (RR = 8.36), similar to other findings involving Caucasians and Chinese population.[17,18] Additionally, the occurrence of DQA1*0501 and DQB1*0201 were found to be significantly higher in patients compared to controls.[19] However, these two markers were no longer significant as independent risk factors in logistic regression model. HLA-DQB1*0601 was found to be a protective allele against T1D in this cohort, similar to findings of other studies.[20,21] Nevertheless, more research is needed to describe the HLA allele frequencies among Malaysians with T1D involving multi-ethnic groups.

DIAGNOSIS AND IMMUNE PHENOTYPE OF T1D

Along with presenting clinical symptoms, T1D can be diagnosed based on fasting and/or random venous plasma glucose concentration. The World Health Organization has also recommended using the HbA1c as part of the diagnosis of T1D.[22] Although HbA1c measurement has less day-to-day variance than fasting plasma glucose, the test is more expensive, thus developing countries may have limited access to it.

Even though they do not directly contribute to the pathogenesis of T1D, autoantibodies against ß-cell proteins and peptides are now widely accepted as the hallmark of the disease. These autoantibodies mainly target insulin, tyrosine phosphatase-like protein or islet antigen-2 (IA-2), glutamic acid decarboxylase (GAD) and zinc transporter-8 (ZnT8). More than 90% of newly diagnosed diabetic patients have more than one of these autoantibodies.

Previous studies have suggested that about 80%-90% of T1D patients have detectable autoantibodies at disease onset, and about 2% of the general young population has a background autoantibody presence.[23,24] However, there are ethnic and geographic differences in the prevalence of autoantibodies among patients with T1D.[25–28] Based on a 1999 study by Nazaimoon *et al.*, 35.3% of T1D patients had positive GADA and presented with significantly lower BMI, with decreased levels of fasting and post-glucose C-peptide compared to those who were GADA-negative. Other factors such as gender, age of onset or family history of diabetes did not affect GADA positivity. The frequency of GADA positivity was significantly higher in the newly onset T1D patients compared to those who had a long-standing disease,[29] similar to another study.[30] No significant differences were observed in the prevalence of GADA between the three analysed ethnic groups. The autoantibody was present in 30.8% of Malays, 36.4% of Chinese and 39.4% of Indian T1D patients.

Conversely, in a recent study, anti-islet cell antibody (ICA), GADA and anti-insulinoma associated antigen 2 antibody (IA2A) were associated with ethnic groups and age, and only IA2A was associated with gender.[8] Here, the autoantibodies were not associated with disease duration and HbA1c level. The levels of ICA, GADA and IA2A were found significantly higher in patients aged below ten years old compared to older patients. It was observed in this study that Chinese patients had significantly higher

levels of ICA and GADA compared to Malays. ICA levels were also significantly higher in Indian patients compared to Malays. These observations were in accordance with previous studies showing the varying prevalence of DAA in different populations.[31–33] Overall, between 47% and 59% of adult Malaysian T1D patients were seropositive for at least one autoantibody from several studies.[8,28,32] Anti-ICA was the most commonly detected autoantibody in these cohorts, followed by GADA, IA2A and anti-insulin antibody (IAA). Multiple autoantibody positivity was reported in as high as 74% of patients by Mahayidin *et al.*

Specifically, the combination of ICA and GADA was the highest seen in 54 (59.3%) patients, whereas the combination of ICA + GADA + IA2A was the most commonly seen triple positivity in 25 (28%) patients. Only one patient showed simultaneous positivity of 4 autoantibodies.[8] In another study, about 29% of T1D patients were positive for two autoantibodies, and 14.3% had three autoantibodies positivity. However, the combinations of positive autoantibodies among these study subjects were not mentioned by Yeow *et al.*[34] On the contrary, Nazaimoon *et al.* reported that IAA was the most frequently detected (47.4%) antibody, followed by GADA (33.8%) and IA2 in only 8.9% of patients. There were only three patients (1.4%) found to be ICA positive.[30]

A further 17 out of 42 (40.5%) T1D patients identified by Yeow *et al.*, were clinically dependent on insulin and had tested negative for these autoantibodies.[34] Absence of pancreatic autoantibodies was also observed in about 32% of patients with near or complete β-cell destruction in another study.[30] These patients were diagnosed with idiopathic T1D, of which disease is not associated with autoantibodies, and cases are most commonly observed in Asian ancestry. In addition, Yeow *et al.* also identified 6 patients with latent autoimmune diabetes of adulthood (LADA) where positive autoantibodies but detectable C-peptide level were detected in these patients. Despite after more than 3 years of diagnosis, 5 of them had fasting C-peptide >250 pmol/L, indicating a slow autoimmune β-cell destruction. It was also reported that another 5 patients had C-peptide of <250 pmol/L and were seronegative for autoantibodies but were not clinically insulin dependent.[34] Thus, from a clinical standpoint, a low level of C-peptide measurement may not always translate for the need for insulin treatment, although it is helpful for classifying T1D.

Several studies have reported elevated Lp(a) in T2D and whether similar observations can be attained in T1D remain unclear. Nawawi *et al.* reported that 5 out of 26 (19.2%) T1D patients aged between 16 and 49 years old, had significantly elevated serum Lp(a) compared to controls. The serum concentrations of Lp(a) were also significantly higher in different subgroups compared with the controls except for the hypertriglyceridemia subgroup. Intriguingly, the concentration of serum Lp(a) was found to be higher in T1D patients compared to those with T2D.[35] It has been proposed that elevated Lp(a) concentrations in T1D is genetically determined and has an immunological component involved, of which the underlying mechanism is still unclear.[36] More research is therefore needed to investigate the exact role of Lp(a), and its relevance in T1D as this study only involved 20 patients of the Malay ethnic group in Malaysia.

Though least studied in Malaysia, LADA can occur in 10-25% of adult patients with T2D phenotype.[37] Although the presence of multiple autoantibodies is highly predictive of T1D, 10-15% of patients with LADA may also exhibit seropositivity for these pancreatic autoantibodies, specifically GADA. Regardless of age, GADA positivity has been shown to be the most consistent, and it was also shown to be continually positive in about 35% of LADA patients after 3 years. Salem *et al.* reported 33 LADA patients (2.9%) with GADA titre above the cut-off point of 5 μ/mL. These patients also did not require insulin for the previous 12 months. However, it was revealed that 70% of LADA patients were dependent on insulin, while only 43% of GADA-negative diabetic patients were on insulin treatment. Signifying decreased β-cell function, it was also found that HbA1c was higher in LADA patients compared to GADA-negative diabetic patients.[38] Hence, apart from aiding the diagnosis of T1D, GADA positivity

may also assist in classifying LADA, especially in adult patients initially diagnosed as T2D.

MANAGEMENT OF T1D

The main goal of T1D therapy is to achieve good glycaemic control to delay the occurrence of chronic diabetes complications and avoid the recurrent acute complication of DKA. All T1D patients require exogenous insulin replacement due to failure of endogenous insulin synthesis following the destruction of β-cells of the pancreas. From a survey conducted in 2001-2002 among T1D patients from the Western Pacific Region, 65.4% of Malaysian children (<18 years old) had one or two daily insulin injections. About 11.4% received three daily injections, while 23.2% received four or more daily injections. From that survey, none was reported to be on insulin pump.[39] Generally, older patients responded better to insulin therapy and yielded better glycaemic control than younger patients.[34]

Multiple daily injections and insulin pump are two methods of insulin therapy for achieving good glycaemic control. The insulin pump has been widely used in paediatric age group since the year 2000. A retrospective cohort study involving eighteen T1D patients with a mean age of 14.6 ± 5.5 years old was carried out in a tertiary university hospital in Malaysia following the introduction of insulin pump therapy in children and adolescents in 2004. Patients who switched to insulin pump therapy were shown to have significantly lower HbA1c levels than while they were on multiple daily injections.[40]

A study among 57 children with T1D in a tertiary centre in Malaysia found that their adherence to insulin therapy was poor as reflected by the HbA1c level of ≥7.5% in more than 90.0% of subjects.[41] However, the study which was based on one-year records, was unable to identify the predictors of poor adherence to insulin therapy. An earlier study involving 329 young (< 40 years old) Malaysians with T1D has also found that the overall glycaemic control was generally poor, with a mean HbA1c of 8.9%. Ethnicity, household income, and access to diabetes care facilities as well as trained educators were significant factors affecting the glycaemic control.[6]

Patient education is a crucial element in achieving better glycaemic control among T1D patients. In Malaysia, the ratio of trained dieticians to the whole population is very low, limiting the ability for a proper consultation and follow-ups of diabetic patients. One of the strategies to overcome this limitation is by implementing a short yet comprehensive structured education programme to enhance self-care practices among diabetes patients with poor glycaemic control. The frequency of self-monitoring of blood glucose (SMBG) among Malaysians with T1D was reported to be 26 times per month, which was among the lowest compared to an average of 66 times per month among patients from the other Western Pacific Region countries.[39] Tan *et al.* have conducted a 12-week-programme that involved two monthly face-to-face sessions and one telephone follow-up. Following the longitudinal study, significant improvement in SMBG, HbA1c level, knowledge and treatment compliance were observed as compared to the control group.[42] A tight collaboration of an interdisciplinary team (i.e. physicians, nurses and diabetes educators), the patient and their family, as well as support systems involving school or work is imperative in the management of T1D. By promoting healthy living and good glycaemic control, complications from the disease can be prevented.

COMPLICATIONS OF T1D

Hypoglycaemia is a common manifestation among T1D on insulin therapy. Among T1D patients in Malaysia, hypoglycaemia was reported to be between 20 to 36 events per 100 patient-years.[7,39] In a 4-week prospective study among 113 patients, 50% reported having ≥ 1 hypoglycaemic events, almost 25% reported ≥ 1 nocturnal hypoglycaemic events, and 11% reported ≥ 1 severe hypoglycaemic events requiring the assistance of another person.[7]

The events of DKA among T1D patients in Malaysia was the highest reported among the Western Pacific Region countries, at the rate of 26.3 per 100 patient-years. On the other hand, the rate of chronic complications such as nephropathy and hypertension were the lowest being reported.[39] Nephropathy, as reflected by albuminuria, was

seen in 13.2% of T1D patients under the age of 25 years old.[34] This was in agreement with another study involving 329 young T1D (< 40 years) in Malaysia that reported microalbuminuria was seen in 13.4% of them. These patients were found to be older, had elevated blood pressure, as well as higher BMI and WHR. The percentage of microalbuminuria was up to 10% even in those diagnosed less than five years and doubled to 23% in those diagnosed for more than 10 years.[14] Retinopathy was detected in 12% of this cohort. The majority had background retinopathy (55%), followed by proliferative (33%) and pre-proliferative (13%) retinopathy.[14]

A retrospective cohort review from the DiCARE found that DKA was a common presentation at diagnosis in those below 20 years old with T1D. The percentage of DKA at diagnosis was 54.5% in the year 2000 and steadily increased to 66.7% in 2009.[43] These figures were similar to one of the earliest published data on young diabetes in Pahang, which reported 69% of T1D patients presented with DKA. Sixty-five percent of them had experienced more than one previous episodes of DKA.[5] Infections were identified as the main trigger of DKA in diabetes patients in Malaysia. DKA was found to be more common in those with normal body weight. However, demographic factors such as age, gender and ethnicity were not associated with DKA.[43]

In addition, about 30% of T1D patients aged less than 25 years old had dyslipidaemia, and 16% were overweight or obese. Statins and antihypertensive medications had to be initiated in more than 10% of them from a study conducted in a hospital in north Peninsular Malaysia.[34] Elevated serum total cholesterol (≥ 5.2 mmol/L) in 60%, elevated LDL-cholesterol (≥ 2.60 mmol/L) in 80% and low HDL-cholesterol (≤1.15 mmol/L) in 27% were reported in a multi-centre study involving 269 young (<40 years old) T1D patients. Ethnicity was identified as a determinant factor for triglycerides, LDL- and HDL-cholesterol levels, where better lipid profiles were seen among the Chinese.[44]

A cohort study that enrolled 665 T1D patients captured from a 2009 national registry found that 105 patients died within 5 years. The mortality rate was 1.6 persons per 100 person-years. Cardiovascular and infections were identified as significant causes of death. Male gender, elderly and underlying ischaemic heart disease were identified as significant risk factors of mortality in T1D patients in Malaysia.[9]

CONCLUSION

Though its peak incidence is between the ages of 10 and 14, T1D clinical presentation can occur at almost any age. In Malaysia, most studies have reported adult-onset T1D, with a mean age at diagnosis ranging from 22 to 30.2 years. The DiCARE registry, on the other hand, had provided a comprehensive investigation of T1D incidence among children and adolescents. On average, these patients were diagnosed at the age of 7.6 years. Nevertheless, there was a female preponderance of patients with T1D in the local population, along with Chinese ethnicity constituting the most reported cases followed by Malays and Indians. Polyuria and polydipsia were the most common clinical presentations reported among Malaysian patients with T1D. More than half of these symptomatic patients had DKA, of which events were the highest reported among the Western Pacific Region countries.

This may explain the corresponding poor overall glycaemic control seen. However, the rate of chronic complications, such as nephropathy was lower. To support the diagnosis of T1D, markers of autoimmunity such as DAA were measured in several local studies. The prevalence of DAA was shown the highest for ICA, followed by GADA, IA2A and anti-insulin antibody. Most Malaysian children had one or two daily insulin injections as part of T1D therapy. Additionally, ethnic background, household income and access to diabetes care facilities were noted as significant factors influencing glycaemic control. Given the increasing incidence of T1D as reported recently,[2] this autoimmune disease may become a public health burden among the younger population in Malaysia in the near future. The corresponding increase in diabetes-related health expenditure is expected to contribute the most burden since T1D is a long-term condition. And since T1D development is multifactorial, research is still lacking in Malaysia in order to understand

the complex interplay of genetic and environmental factors contributing to disease onset. In-depth analyses of the human immune responses are crucial to the outlook and future success of immune tolerance induction in preventing β-cell loss. Consequentially, with the emerging phenomenon of early-onset T2D among Malaysians, staging T1D pathogenesis provides a critical measure in better classification and management of the disease by assisting to dissect the progressive autoimmunity process.

ACKNOWLEDGEMENT

We would like to thank the Director-General of Health Malaysia for his permission to publish this article. AMG research work was financially supported by the Universiti Malaysia Pahang under research university grants UMP Fundamental Research Grant RDU200342 and UMP Sustainable Research Collaborative Grant RDU200709.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

REFERENCES

1. Kahanovitz L, Sluss PM, Russell SJ. Type 1 diabetes-a clinical perspective. Point Care. 2017;16(1):37–40.
2. Atlas IDFD. 463 PEOPLE LIVING WITH DIABETES million. 2019.
3. Patterson CC, Karuranga S, Salpea P, Saeedi P, Dahlquist G, Soltesz G, et al. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract [Internet]. 2019;157:107842. Available from: https://doi.org/10.1016/j.diabres.2019.107842
4. DOS Malaysia. Current Population Estimates Malaysia 2019 [Internet]. Department of Statistics Malaysia. 2019. p. 2, 7, 10. Available from: www.dosm.gov.my
5. Lim TO. Prevalence, age at diagnosis, clinical characteristics and treatment of diabetes in the young in Pahang, Malaysia. Diabetes Res Clin Pract. 1991;12 (3):201–7.
6. Ismail IS, Wan Nazaimoon WM, Wan Mohamad WB, Letchuman R, Singaraveloo M, Pendek R, et al. Socioedemographic determinants of glycaemic control in young diabetic patients in peninsular Malaysia. Diabetes Res Clin Pract. 2000;47(1):57–69.
7. Hussein Z, Kamaruddin NA, Chan SP, Jain A, Uppal S, Bebakar WMW. Hypoglycemia awareness among insulin-treated patients with diabetes in Malaysia: A cohort subanalysis of the HAT study. Diabetes Res Clin Pract [Internet]. 2017;133:40–9. Available from: https://doi.org/10.1016/j.diabres.2017.08.007
8. Mahayidin H, Zakariah SZ, Ishah NA, Wee XA, Nor NM, Arip M. Diabetes-associated autoantibodies among young diabetes mellitus patients in Malaysia. Malaysian J Med Heal Sci. 2020;16(2):118–25.
9. Bujang MA, Tiong XT, Saperi FE, Ismail M, Mustafa FI, Abd Hamid AM. The all-cause mortality and risk factors for mortality within five years among prevalent Type 1 Diabetes Mellitus Patients. Int J Diabetes Dev Ctries. 2019;39(2):284–90.
10. Tan SMK, Shafiee Z, Wu LL, Rizal AM, Rey JM. Factors associated with control of type I diabetes in Malaysian adolescents and young adults. Int J Psychiatry Med. 2005;35(2):123–36.
11. Zain FM, Hong JYH, Wu LL, Harun F, Rasat R, Jalaludin MY, et al. 2nd Report of Diabetes In Children and Adolescents Registry (DiCARE) 2006 - 2008. 2012;1–73.
12. Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. Lancet Diabetes Endocrinol [Internet]. 2018;6(2):122–9. Available from: http://dx.doi.org/10.1016/S2213-8587(17)30362-5
13. Huria HZ, Foonga GTK, Widodoa RT, Pendekb R. Different characteristics of diabetic ketoacidosis between type 1 and type 2 diabetes patients in Malaysia. Asian Biomed. 2009;3(2):201–5.
14. Wan Nazaimoon WM, Letchuman R, Noraini N, Ropilah AR, Zainal M, Ismail IS, et al. Systolic hypertension and duration of diabetes mellitus are important determinants of retinopathy and microalbuminuria in young diabetics. Diabetes Res Clin Pract. 1999;46(3):213–21.
15. Rewers M, Ludvigsson J. Environmental risk factors

for type 1 diabetes. Lancet. 2016;387(10035):2340–8.
16. Robertson CC, Rich SS. Genetics of type 1 diabetes. Curr Opin Genet Dev [Internet]. 2018;50(Figure 1):7–16. Available from: https://doi.org/10.1016/j.gde.2018.01.006
17. Penny MA, Jenkins D, Mijovic CH, Jacobs KH, Cavan DA, Yeung VTF, et al. Susceptibility to IDDM in a Chinese population: Role of HLA class II alleles. Diabetes. 1992;41(8):914–9.
18. Kockum I, Wassmuth R, Holmberg E, Michelsen B, Lernmark A. HLA-DQ primarily confers protection and HLA-DR susceptibility in type I (insulin-dependent) diabetes studied in population-based affected families and controls. Am J Hum Genet. 1993;53(1):150–67.
19. Rohana AG, Loh KC, Tin SK, Soh CH, Nazaimoon WMW, Fong KY, et al. HLA-DQ A1, -DQB1 AND -DRB1 gene polymorphism - In Malay Type 1 diabetes mellitus patients and their use for risk prediction. Med J Malaysia. 2011;66(2):133–7.
20. Guja C, Guja L, Nutland S, Rance H, Sebastien M, Todd JA, et al. Type 1 diabetes genetic susceptibility encoded by HLA DQB1 genes in Romania. J Cell Mol Med. 2004;8(2):249–56.
21. Mosaad YM. HLA-DQB1* alleles and genetic susceptibility to type 1 diabetes mellitus. World J Diabetes. 2012;3(8):149.
22. Kazi AA, Blonde L. Classification of diabetes mellitus. Vol. 21, Clinics in Laboratory Medicine. 2001. 1–13 p.
23. Of D, Mellitus D. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37 (SUPPL.1):81–90.
24. Knip M, Korhonen S, Kulmala P, Veijola R, Reunanen A, Raitakari OT, et al. Prediction of type 1 diabetes in the general population. Diabetes Care. 2010;33(6):1206–12.
25. Dzidzonu DK, Skrivarhaug T, Joner G, Moger TA. Ethnic differences in the incidence of type 1 diabetes in Norway: a register-based study using data from the period 2002–2009. Pediatr Diabetes. 2016;17 (5):337–41.
26. Singh S, Usha, Singh G, Agrawal NK, Singh RG, Kumar SB. Prevalence of autoantibodies and HLA DR, DQ in type 1 diabetes mellitus. J Clin Diagnostic Res. 2016;10(7):EC09-EC13.
27. Cheng BW, Lo FS, Wang AM, Hung CM, Huang CY, Ting WH, et al. Autoantibodies against islet cell antigens in children with type 1 diabetes mellitus. Oncotarget. 2018;9(23):16275–83.
28. Trisorus C, Aroonparkmongkol S, Kongmanas HB, Sahakitrungruang T. Prevalence of islet autoantibodies in Thai juvenile-onset type 1 diabetes. Pediatr Int. 2018;60(11):1002–7.
29. Wan Nazaimoon WM, Faridah I, Singaraveloo M, Ismail IS, Wan Mohamad WB, Letchuman R, et al. Prevalence of glutamic acid decarboxylase antibodies amongst young Malaysian diabetics. Diabetes Res Clin Pract. 1999;43(1):59–66.
30. Nazaimoon WM, Azmi KN, Rasat R, Ismail IS, Singaraveloo M, Mohamad WB, et al. Autoimmune markers in young Malaysian patients with type 1 diabetes mellitus. Med J Malaysia. 2000;55(3):318–23.
31. Andersson C, Vaziri-Sani F, Delli A, Lindblad B, Carlsson A, Forsander G, et al. Triple specificity of ZnT8 autoantibodies in relation to HLA and other islet autoantibodies in childhood and adolescent type 1 diabetes. Pediatr Diabetes. 2013;14(2):97–105.
32. Decochez K, Tits J, Coolens J, Van Gaal L, Krzentowski G, Winnock F, et al. High Frequency of Persisting or Levels After Diagnosis of Type 1 Diabetes Presenting Before 40 Years of Age. Diabetes Care. 2000;23(6):838–44.
33. Garnier L, Marchand L, Benoit M, Nicolino M, Bendelac N, Wright C, et al. Screening of ZnT8 autoantibodies in the diagnosis of autoimmune diabetes in a large French cohort. Clin Chim Acta [Internet]. 2018;478(October 2017):162–5. Available from: https://doi.org/10.1016/j.cca.2017.12.043
34. Yeow TP, Aun ESY, Hor CP, Lim SL, Khaw CH, Aziz NA. Challenges in the classification and management of Asian youth-onset diabetes mellitus-Lessons learned from a single centre study. PLoS One. 2019;14(1):1–14.
35. Nawawi HM, Muhajir M, Kian YC, Mohamud WNW, Yusoff K, Khalid BAK. Type of diabetes and waist-hip ratio are important determinants of serum lipoprotein (a) levels in diabetic patients. Diabetes Res Clin Pract. 2002;56(3):221–7.
36. Kronenberg F, Auinger M, Trenkwalder E, Irsigler

K, Utermann G, Dieplinger H. Is apolipoprotein(a) a susceptibility gene for Type I diabetes mellitus and related to long-term survival? Diabetologia. 1999;42 (8):1021–7.
37. Naik RG, Palmer JP. Latent autoimmune diabetes in adults. Type 1 Diabetes Adults Princ Pract. 2007;54(December):17–32.
38. Salem SD, Saif-Ali R, Muniandy S, Al-Hamodi Z, Ismail IS. Comparison of adults with insulin resistance (IR) in latent autoimmune diabetes versus IR in glutamic acid decarboxylase antibody-negative diabetes. Ann Acad Med Singapore. 2014;43(2):107–12.
39. Craig ME, Jones TW, Silink M, Ping YJ. Diabetes care, glycemic control, and complications in children with type 1 diabetes from Asia and the Western Pacific Region. J Diabetes Complications. 2007;21(5):280–7.
40. Ooi HL, Wu LL. Insulin pump therapy in children and adolescents with type 1 diabetes: Improvements in glycemic control and patients' satisfaction - hospital UKM experience. Med J Malaysia. 2011;66 (4):308–12.
41. Ying CL, Shah NM. Adherence to insulin treatment in children with type I diabetes mellitus at a hospital in Malaysia. Asian J Pharm Clin Res. 2017;10 (11):356–61.
42. Tan MY, Magarey JM, Chee SS, Lee LF, Tan MH. A brief structured education programme enhances self-care practices and improves glycaemic control in Malaysians with poorly controlled diabetes. Health Educ Res. 2011;26(5):896–907.
43. Hong JYH, Jalaludin MY, Mohamad Adam B, Fuziah MZ, Wu LL, Rasat R, et al. Diabetic ketoacidosis at diagnosis of type 1 diabetes mellitus in Malaysian children and adolescents. Malaysian Fam Physician. 2016;10(3):11–8.
44. Ismail IS, Nazaimoon W, Mohamad W, Letchuman R, Singaraveloo M, Hew FL, et al. Ethnicity and glycaemic control are major determinants of diabetic dyslipidaemia in Malaysia. Diabet Med. 2001;18 (6):501–8.