THE EFFECT OF HIGH ADVANCED GLYCATION END PRODUCTS (AGE) IN FOOD ON BACK PAIN: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: The production of Advanced Glycation End-products (AGEs) is the result of the glycation process that occurs during the reaction of sugar with protein or fat. Limited information can be found on the association of AGEs with back pain; however, there are studies on the AGE rich diet which can induce the degeneration of intervertebral discs (IVD). Therefore, this study aimed to review the effect of high AGEs in food on the development of back pain. **Methods:** This study has been done via systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A thorough literature search was performed using SCOPUS, Science direct, SAGE journal, and manual search. Articles focused on study of AGEs and its relation to it such as the role of AGEs and its receptor and mechanism of exogenous AGEs in spine were included. Since the back pain is the main concern of this study, any articles which related to disc degeneration, diet and back pain is also accepted. The articles should be written in English and published between 1999

and 2019. Besides, any human or animal study were also included. This study excluded articles which are not written in English, published before 1999, focused on endogenous AGE, treatment or intervention of AGE-related disease. **Results:** 4 studies were included for review. The detailed analysis of the data from these studies indicated that there is an association between high content of AGEs in food and the degeneration of IVD which leads to the development of back pain. However, most of the studies suggested that the degeneration of IVD is strongly dependent on sex with a higher prevalence among females. **Conclusion:** This review supports the hypothesis that a high AGE diet is correlated with the development of back pain through IVD degeneration in mice. As animal IVD has shown to mimic human IVD, these results are suggested to apply similarly to humans. Further research should be conducted for a more comprehensive understanding of the effect of AGEs on IVD to help in the development of effective strategies and interventions to prevent back pain, especially among women.

KEYWORDS: Advanced Glycation End products, back pain, intervertebral disc, dietary AGEs, disc degeneration

INTRODUCTION

Back pain is a common health-related condition that can affect the quality of life and interfere with work performance. Low back pain is a leading factor of disability around the world. According to the Global Burden of Disease (GBD) 2016, in 2016 low back pain was among the 5 leading causes of years lived with disability (YLD) (Hoy et al., 2014). With the prevalence of up to 84%, low back pain (LBP) is considered the most common problem affecting the adult population (Allegri et. al, 2016).

LBP is usually defined as pain, muscle tension or stiffness localized at the lower region of the back body. The definition of chronic low back pain (CLBP) is pain that lasts more than three months, even after an initial injury or a treated underlying cause of acute low back pain (National Institute of Neurological Disorders and Stroke, 2019) and it represents the leading cause of disability worldwide that affects quality of life and work performances (Koes, van Tulder & Thomas, 2006; Allegri et al, 2016). LBP may originate from the spinal structure, age-related degenerative processes in the intervertebral disks and facet joints and disc herniation (Deyo & Weinstein, 2001).

Symptoms of LBP which are caused by specific pathophysiological mechanisms such as hernia nuclei pulposi, infection, osteoporosis or fracture is defined as specific LBP while non-specific LBP is defined as idiopathic caused (Koes, van Tulder & Thomas, 2006). There are many risk factors that contribute to LBP such as heavy lifting and twisting, bodily vibration, obesity, and poor conditioning, however LBP is common even in people without these risk factors. Moreover, LBP is more prone in individuals aged more than 30 years old (Deyo & Weinstein, 2001). Besides, a few studies have been done on the Advanced Glycation

End-products (AGEs) and its effect towards back pain. It is believed that AGEs may be one of the contributing factors of back pain.

According to Diamanti-Kandarakis, Palimeri & Palioura (2015), Advanced Glycation End products (AGEs) is a complex group of compound which is produced endogenously during the process of aging and also under the conditions of hyperglycemia and oxidative stress. AGEs are also known as glycotoxins and it can be derived from exogenous origin such as from certain foods like meat, certain cheeses and fried eggs, specific cooking methods, smoking and also from the result of Maillard reaction or the "browning effect". Besides supporting the statement, Stirban and Tschope (2015) also mentioned that the amount of AGEs in food depends on how the food is prepared.

According to Kutlu (2016), the Maillard reactions produce harmful substances called advanced glycation end products. The spontaneous and non-enzymatic reaction between proteins and lipids with other reducing sugar is known as the glycation process. This process produces a product in the form of ketoamines. The disintegration via oxidative and non-oxidative mechanism transforms the unstable ketoamines into AGEs. Smoking and cooking food at high temperatures induce the production of exogenous AGEs known as glycotoxins.

The rapid increase in western lifestyle as well as the increasing consumption of highly processed food and sugar, smoking and a lack of physical activity increases the incidence of chronic diseases among young and middle-aged people (Ott et al., 2014). The incidence of chronic disease among people is associated with the accumulation of age-related modified biomolecules. Generally, cellular defense mechanism in the body will repair or remove the unfunctional cell. However, the endogenous repair and degradation system is impaired during the aging process which will lead to the accumulation of damaged cells (Ott et al., 2014).

The accumulation of damaged cells is normal in the process of normal aging. The increasing level of damage and accumulation leads to neurodegenerative and vascular disease in older people. Besides, the higher production of oxidative stress during aging will promote protein modifications and lead to the impairment of normal defense mechanism. With the increased intake of glucose and fat, the development of the chronic disease will also accelerate. Cellular modifications through different precursors lead to the formation of AGEs in the body (Ott et al., 2014).

This study is conducted to review the effects of high AGE in food on back pain. Moreover, the information about the role of dietary AGEs on spinal pathology such as intervertebral discs is studied; hence this systematic review is essential to answer how AGEs lead to back pain.

METHODS

Study Design: A Systematic Review

This study has been done via systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaf & Altman, 2009). PRISMA is a protocol used in order to complete the framework of this systematic

review. According to PRISMA guidelines, the first step was the identification process in which articles to be included in this study was selected based on keywords searched through several databases. Next, the articles were then screened by removing duplicates to identify the numbers of articles which are eligible to be used in this study following the inclusion and exclusion criteria. After assessment of eligibility was done, the included articles were then used for review.

Search Strategy

The sources of this study are from databases that were accessible from the International Islamic University Malaysia library which is SCOPUS, Science Direct, SAGE journal and also manual search such as Google. The following keywords are used; "advanced glycation end products AND back pain", "advanced glycation end products AND disc degeneration", "advanced glycation end-products OR RAGE AND back pain", "AGE AND back pain", "advanced glycation end products AND food".

Inclusion Criteria

The criteria required in order to be included in the review is that the paper focuses on the study of advanced glycation end products (AGEs) and relations to it such as the role of AGE and its receptor and the mechanism of exogenous AGE in the spine. In addition, the paper that is related to disc degeneration, diet and back pain was also included since back pain is the main concern of this study. Journals or articles that were written in English; published between 1999 and 2019 and involved animal or human as participants were also included. The articles which were not published in English were excluded. The studies that focused on endogenous AGE, treatment or intervention of AGE-related disease were also excluded because the main focus of this study was to investigate the effect of AGE on back pain and how AGE contribute to back pain or disc degeneration.

Study Selection

The studies selected were reviewed if it fulfills the inclusion criteria. The studies that match the exclusion criteria were omitted to prevent bias in the result section. The study selection is important to avoid any misinterpretation, misjudgment and misleading of the information in the paper.

Data Item

Data extraction was performed for each included studies. The data that were extracted included author, publication year , title, type of sources, purpose of the study, study design,

subjects information, study duration and measurement (amount of dietary AGEs and assessment of AGEs).

Quality Assessment

Risk of Bias in Systematic Review (ROBIS) was used as a tool in assessing the risk of bias of the study. The tool is completed in 3 phases; (1) assess relevance which is optional, (2) identify concerns with the review process and (3) judge a risk of bias in the review.

Summary Measure

The primary measure of this study was to determine the effect of high content of exogenous AGE and how exogenous AGE is produced (sources of exogenous AGEs). Meanwhile, the primary outcome for this study is how the accumulation of AGEs in the IVD can lead to development of back pain.

Data Analysis

The analysis of the study was to (1) identify the major sources of exogenous AGE and (2) evaluate the accumulation of AGE that induces disc degeneration.

RESULTS

Selection of sources of evidence

Based on the open access and three databases chosen; a total number of 1465 of sources of evidence was yielded. After the duplicates were removed, searches identified 1093 articles, 1016 articles excluded based on title, 77 abstract and full-text articles were identified and retrieved

for assessment, and 4 articles met the inclusion criteria and were included in the review (Figure 1).

Acceptance and rejection status of sources of evidence

A list was made on the rejection and acceptance of the articles based on eligibility criteria. Out of 77 articles, 5 articles were rejected because the articles were not published in English, 1 article was not accessible and another 67 articles were purely irrelevant because not related to the purpose of the study and had no relation between AGEs and back pain.

Characteristics of sources of evidence

All of the papers included for the review were research articles. Four studies highlighted the effect of dietary AGEs on spine in which three studies considered sex and age as major dependents of the back pain caused by dietary AGEs; while 1 study focused on the role of AGE and effect on spine regardless of age and sex (Table 1). All of the studies used C57BL/6 mice as subjects and the length of the study was between 6 to 18 months. In 3 studies, the level of AGE ingested by the mice was the same. However, the study by Illien-Junger et al. (2015), varied as they used Methylglyoxal (MG) and Carboxymethyl-lysine (CML) as the AGEs marker in the serum and food.

Quality Assessment/Risk of Bias

The first phase of ROBIS which is assessing relevance was skipped as the included studies for this review were in level II of level of evidence rating. The risk of bias was assessed from phase 2 which is identifying concerns with review process (Table 2, 3, 4, 5). After the risk of bias was assessed, the risk of bias was summarized in phase 3 (Table 6).

Table 2. Study Eligibility Criteria

DOMAIN 1: STUDY ELIGIBILITY CRITERIA

Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	PY
1.2 Were the eligibility criteria appropriate for the review question?	Y
1.3 Were eligibility criteria unambiguous?	PN
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y
	Y

1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	
Concerns regarding specification of study eligibility criteria **Rationale for concern:** **Considerable effort has been made to clearly specify the review question and objectives, and to pre-specify and justify appropriate and detailed eligibility criteria that have been adhered to during the review**	LOW

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Table 3. Identification and Selection of Studies

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y
2.2 Were methods additional to database searching used to identify relevant reports?	Y
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	PY
2.4 Were restrictions based on date, publication format, or language appropriate?	PY
2.5 Were efforts made to minimise error in selection of studies?	PN
Concerns regarding methods used to identify and/or select studies **Rationale for concern:** **Most of the signalling questions were answered as "Yes" or "Probably Yes" and so no potential areas of bias were identified.**	LOW

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Table 4. Data Collection and Study Appraisal

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL

Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:	
3.1 Were efforts made to minimise error in data collection?	N
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	PY
3.3 Were all relevant study results collected for use in the synthesis?	Y
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	N
3.5 Were efforts made to minimise error in risk of bias assessment?	N
Concerns regarding methods used to collect data and appraise studies **Rationale for concern:** **Lack of formal quality assessment means that the risk of bias in the included studies is unclear. There were insufficient study details available to allow the reader to interpret the results. There is therefore a high risk of bias in both the data collection and study appraisal process for this review**	HIGH

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Table 5. Synthesis and Findings

DOMAIN 4: SYNTHESIS AND FINDINGS	
Describe synthesis methods:	
4.1 Did the synthesis include all studies that it should?	PY
4.2 Were all pre-defined analyses reported or departures explained?	NI
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y N
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	PN
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	PN
4.6 Were biases in primary studies minimal or addressed in the synthesis?	
Concerns regarding the synthesis and findings **Rationale for concern:** **There is insufficient information reported to make a judgement on risk of bias.**	UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Table 6. Summarization of Concerns Identified

Domain	Concerns	Rationale for concerns
1.Concerns regarding specification of study eligibility criteria	LOW	Considerable effort has been made to clearly specify the review question and objectives, and to pre-specify and justify appropriate and detailed eligibility criteria that have been adhered to during the review
2. Concerns regarding methods used to identify and/or select studies	LOW	Most of the signalling questions were answered as "Yes" or "Probably Yes" and so no potential areas of bias were identified.
3. Concerns regarding methods used to collect data and appraise studies	HIGH	Lack of formal quality assessment means that the risk of bias in the included studies is unclear. There were insufficient study details available to allow the reader to interpret the results. There is therefore a high risk of bias in both the data collection and study appraisal process for this review
4. Concerns regarding the synthesis and findings	UNCLEAR	There is insufficient information reported to make a judgement on risk of bias

Table 7. Table Risk of Bias

RISK OF BIAS IN THE REVIEW

Describe whether conclusions were supported by the evidence:	
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4? **B. Was the relevance of identified studies to the review's research question appropriately considered?** **C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?**	Y Y PY
Risk of bias in the review **Rationale for risk:** **The findings of the review are likely to be reliable. Phase 2 did not raise any concerns with the review process or concerns were appropriately considered in the review conclusions. The conclusions were supported by the evidence and included consideration of the relevance of included studies.**	Risk: LOW

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Synthesis of the results

All of the studies discussed the role of AGEs which lead to degeneration of disc with a majority of them focusing on sex-dependent disc degeneration (Table 2).

1. **Sources of exogenous AGEs**

   Two studies (1,4) stated that exogenous AGEs are produced during the preparation of food where food is processed at high temperatures. One of them (4) noted that the food prepared for the sample with H-AGE content has a similar AGE level with bread crust which can increase the accumulation of AGE in young rats. Besides, the other two studies (2,3), suggested that western lifestyle diet contains high amount of AGEs, especially the high processed food.

2. **Accumulation of AGEs in Intervertebral Disc (IVD)**

   Serum AGEs level was reported to be higher in all of the studies. The dietary AGEs were produced via processing food at high temperatures. Two studies (3, 4) reported decrease in trabecular bone volume of H-AGE mice. Studies 1 and 4 noted a significant decrease in trabecular BMD and it is suggested in study 4 that aging is an additional risk for the reduction of trabecular BMD.

Morphological changes were reported in 2 studies (2, 3) which is in study 2, the annulus fibrosus (AF) collagen fiber appeared brighter in H-AGE group indicating the damage of collagen molecules in H-AGE female mice. Study 3 reported increased calcification of EP and IVD in mice fed with high AGE diet.

Three studies (1, 2, 4) showed that serum AGE was higher in H-AGE fed female mice compared to L-AGE female mice and the other study (3) also shows a significant increase of serum AGEs level in mice fed with high AGEs food. All studies demonstrated significant increase in AGEs in IVD of mice that were fed with high AGE diet.

3. AGEs induce degeneration

All studies described that the accumulation of AGEs in IVD, independent from diabetes and hyperglycemia lead to the alteration of spinal structure. Three studies (1, 2, 4) suggested that dietary AGE induced disc degeneration is more prone to females. Study 3 explained, high amount of AGEs ingested caused early pathological change in the spine which will result to the acceleration of spine degeneration by obstructing the nutrition pathways.

DISCUSSION

This study investigated how dietary AGEs affect the degeneration of IVD which contributes to back pain. AGEs were first identified in the cooked food as the end products of reaction that occur between sugar and protein or fat which are known as glycation process (Maillard reaction). The formation of AGEs in the human body was first recognized 40 years ago (Sharma et al., 2015) and studies have shown increased interest towards AGEs especially in recent years due to its association with many chronic diseases (Luevano-Contreras and Chapman-Novakofski, 2010).

AGEs can be found in collagen and other connective tissue protein and it can accumulate in tissues and suppress the expression of aggrecan via acceleration in the RAGE (Yokosuka et al., 2006). Besides, AGE accumulation also occurs because of normal aging. Common AGEs that are associated with the changes of protein structure including CML, pentosidine and glucosepane while reactive AGE precursors which are linked to cellular injury are MG and its derivatives and MG-H1 (Sharma et al., 2015; Luevano-Contreras and Chapman-Novakofski, 2010).

From the results obtained in the reviewed papers, the first finding is the characteristics of intervertebral disc degeneration is characterized by loss of IVD height, structural defects, loss of water and glycosaminoglycan (GAG) content, chronic inflammation and catabolic metabolism (Illien-Junger et al., 2018). There are multiple ways of how AGE accumulation can induce structural disruption and painful IVD degeneration. IL-1β, AGE-RAGE complex and NLRP3

inflammasome are among the factors that can induce accumulation of AGE in tissue. These 3 factors accelerate degeneration by promoting inflammation and stimulating degradation of ECM (Yu Song et al., 2017).

Besides, AGE MG-H1 was associated with ectopic calcifications (EC), endochondral ossifications and induced hypertrophy in human IVD. The induction of EC resulted in slightly increased RAGE expression in NP and increased the expression of COL 10; marker for hypertrophy and osteopontin (OPN); marker for osteogenic differentiation. AGE also can lead to focal area defects and structural disruptions which distinguish ageing from IVD degeneration and result in painful back pain (Illien-Junger et al., 2016; Kindschuh et al., 2016).

Second finding reported that human diet which is high in AGE is determined by CML and MG levels prepared by different cooking methods (Nerlich et al., 2007; Sharma et al., 2015). Recent studies indicated that food high in protein and fat such as meat groups contained higher amount of MG which tend to contain more AGE (Sharma et al., 2015). Western diet is also a plentiful source of exogenous AGE. Diet which contains AGE depends on nutrient composition and the way food is processed. CML is also one of the first to be characterized in milk and milk products and reported as one of the most abundant AGE in food (Luevano-Contreras and Chapman-Novakofski, 2010).

From the findings, it is concluded that chronic exposure to dietary AGE can negatively influence spinal structure, independently from diabetes and hyperglycemia. Although AGE accumulations occur endogenously and accelerated ageing, the consumption of poor diet (diet high in AGE) can worsen the condition. The early pathological change can be observed through the elevated cortical thickening in vertebrae, calcification of endplate, reduced IVD height and GAG content and increased the expression of COL 10 (Illien-Junger et al, 2015a). The presented data suggested food quantity and quality play an important factor in maintaining spinal health.

Although the findings indicated that high AGE diet leads to IVD degeneration, age and sex of the subjects are believed to become the risk factors that accelerate the accumulation of AGE and degeneration of IVD (Krishnamoorthy et al., 2018; Illien-Junger et al., 2015b; Illien-Junger et al., 2018). The studies showed that young female mice were more prone to degeneration of IVD compared to male mice. Sex hormones may play a role in the AGE-mediated changes in vertebral structure and function. Aged mice are another risk factor to the accumulation of AGE in the spine which leads to degeneration because of the less effective elimination of excess AGE through renal excretion. Thus, an aged human is believed to have impaired function of renal and contribute to the accumulation of AGE in the body.

CONCLUSIONS

This study aimed to review the effect of high dietary AGE on back pain, however, the study on dietary AGE and back pain is limited. Consequently, there was a lack of arguments to support

the research and back up the study altogether. The overview of the studies accepted that the ingestion of high AGE food can lead to the degeneration of IVD through the alteration of spinal structure and function. Therefore, it is proven that a high-AGE diet correlated with the development of back pain through degeneration of IVD in mice which mimics the IVD of human; suggested that the result could be the same in human IVD.

CONFLICT OF INTEREST

No conflict of interest to declare.

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Table 1. Characteristics of sources of evidence

NO	AUTHOR (YEAR)	METHODOLGY ADOPTED	INTERVENTION	SOURCES OF HIGH EXOGENOUS AGEs	ACCUMULATION OF AGEs THAT INDUCE BACK PAIN	KEY FINDINGS/RESULTS	GAPS IN THE RESEARCH
1	Kindschuh et al. (2016)	Clinical study	Pair-fed isocaloric diet containing low AGEs amount or high Ages amount	Processing food at high temperature	● accumulate in bone where they crosslink collagen ● gender effect	● serum AGE level significantly increase in femal e HAGE mice ● AGEs effect on vertebral bone may be hormonally mediated ● Significant alterations to the elastic comp	Further research for AGE effect and cellular modifications to validate the link between changes in bone quality, quantity and function.

END …

						ressive and shear properties of vertebra ● Changes in trabecular architecture and density ● Statistically significant, $p<0.01$	
2	Krishnamoorthy et al. (2018)	Longitudinal study	Isocaloric diet group receiving low AGE food or high AGE food-generated via high temperature heating	-Human western diet (crispy McDonalds chicken) -microwaved skinless chicken breast	● Accumulation of AGEs in female IVD tissue ● Altered biomechanical properties ● Altered annul	● Loss IVD integrity and advancing the pathogenesis of the degenerative process	- Did not identify any qualitative histological differences in NP or endplate of any group - Large differences in food consistency. Not

END …

					us fibrosus organization ● Impaired collagen quality ● Gender effect	● Significant alteration in collagen quality ● Functional changes of IVD ● Increase susceptibility to enzymatic digestion ● Statistically significant, $p<0.05$	clear whether consistency affected food consumption. -causes for the sex-dependent effects of dietary AGEs warrant future investigation because estrogen regulate cell metabolism
3	Illien-Junger et al. (2015)	Longitudinal study	Low AGEs diet. Produced without the use of heat. High AGEs diet supplemented	Western style diet	● Chronic AGEs affected bone structure ● Chronic	● Significantly increased vertebral cortical	-AGE-derivatives were only quantified in serum

END …

			with AGEs. Identical in caloric and nutritional content.		AGEs reduced IVD height ● Ectopic calcification detected ● High COL-X staining in IVD cells ● Low GAG content within NP ● Increased MG-derivatives in vertebrae and EPs	thickness ● Significantly decreased IVD height ● Increased calcification of EP and IVD ● Hypertrophic differentiation of NP cells ● High AGEs accelerated degenerative change in spinal ● Compact vertebral EP cause	

END …

						d diminished nutrient and oxygen content ● Decreased cell density suggested poorer bone quality ● Statistically significant, $p<0.05$	
4	Illien-Junger et al. (2018)	Longitudinal study	Low AGEs diet. High AGEs diet. Identical in caloric and nutritional content.	-Produced in food processed (under dry heat) -Bread crust -High-fat diet	● Elevated serum AGE levels ● Decreased vertebral mechanical	● H-AGE diet caused change in bone mechanical structure and	-Different in food consistency, not able to determine the amount of food ingested

END …

					properties ● Decreased in bone quality ● Impairing osteoclastic bone resorption and osteoblast proliferation and differentiation	mechanics ● Aging dominated dietary effects of AGEs ● Young female may be at risk ● High AGE diet may result in an accelerated bone aging phenomena ● Sex hormone may play a role ● Statistically significant,	

						$p<0.05$	

Note. AGEs: Advanced Glycation End Product , IVD: Intervertebral Disc , NP: Nucleus Pulposus , MG: Methylglycoxal , EP: Ectopic , COL-X: Collagen 10 alpha-1 , GAG: Glycosaminoglycan

Table 2: Synthesis of the Results

AUTHOR (YEAR)	TITLE	TYPE OF SOURCES	PURPOSE	LEVEL OF EVIDENCE/STUDY DESIGN	SUBJECTS	LENG OF ST
Kindschuh et al. (2016)	Effects of Long-Term Exposure of Exogenous Advanced Glycation Endproducts on Vertebral Bone Microarchitecture; Sex-Differences on Structure Derived Mechanical Properties	Research article	To investigate the sex-dependent effect of of exogenous AGEs on vertebral bone quantity, quality and mechanical behaviour	Level II Cohort Study	C57BL/6 mice (Female, n=8/group) (Male, n=4/group)	6 mon
Krishnamoorthy et al. (2018)	Dietary advanced glycation end-product consumption leads to mechanical stiffening of murine intervertebral discs	Research article	To assess the effect of dietary AGEs on structure and function of IVDs in female and male mice	Level II Cohort Study	C57BL/6J mice (Female, n=21) (Male, n=23)	6 mon
Illien-Junger et al. (2015)	Chronic Ingestion of Advanced Glycation End Products Induces Degenerative Spinal Changes and Hypertrophy in Aging Pre-Diabetic Mice	Research Article	Investigated the role of specific AGEs precursors on IVD and vertebral pathologies in aging C57BL6 mice that were fed isocaloric diet with standard or reduced amount of Ages precursors	Level II Cohort Study	C57BL/6 (dMG^-, n=12) (dMG^+, n=9)	18 mo
Illien-Junger et al. (2018)	Dietary advanced glycation end products have sex- and age-dependent effects on	Research Article	To test the overall hypothesis that high dietary AGE ingestion, independent	Level II Cohort Study	C57BL/6J (Female, n=10/group) (Male, n=10/group)	6 mon 18 mo

END …

	vertebral bone microstructure and mechanical structure in mice		from diabetes, will result in accumulation of AGEs in spinal tissues and induce vertebral changes in young female mice			

Figure 1. Selection process of articles included in the study