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Complications in the spine associated with type 2 diabetes: The role of advanced glycation end-products

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Abstract

Type 2 diabetes mellitus (T2D) is an increasingly prevalent disease with numerous comorbidities including many in the spine. T2D is strongly linked with vertebral fractures, intervertebral disc (IVD) degeneration, and severe chronic spinal pain. Yet the causative mechanism for these musculoskeletal impairments remains unclear. The chronic hyperglycemic state in T2D promotes the formation of advanced glycation end-products (AGEs) in tissues, and the accumulation of AGEs may play a role in musculoskeletal complications by modifying the extracellular matrix, impairing cellular homeostasis, and perpetuating an inflammatory cascade via its receptor (RAGE). The AGE and RAGE associated alterations in extracellular matrix composition and morphological features of the vertebral bodies and IVDs are likely contributors to the incidence and severity of spinal pathologies in T2D. This review will broadly examine the effects of AGEs on tissues in the spine in the context of T2D, with an emphasis on the changes in the vertebrae and the IVD. Along with the clinical and epidemiological findings, we will provide an overview of preclinical rodent models of T2D that exhibit deficits in the IVD and vertebral bone. Elucidating the role of AGEs and RAGE will be crucial for understanding the disease mechanisms and translation therapies of musculoskeletal pathologies in T2D.

Keywords

Type 2 diabetes; Vertebral fracture; Intervertebral disc degeneration; Spinal pathologies; Advanced glycation end-products; AGEs

1. Introduction

1.1. Prevalence of T2D & spinal pathologies

Type 2 diabetes mellitus (T2D) is a highly prevalent disease with numerous comorbidities and an increasing global health burden. The prevalence of T2D is rising and is expected to

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reach 14% in the United States by the year 2030 (7.7% worldwide) [1,2]; in 2014 the annual global economic burden of T2D was between $612 billion and $1099 billion [3]. Worse yet, the economic burden of this disease disproportionately falls on minorities and low income households in developed countries [1]. T2D complications and comorbidities further exacerbate the economic burden of the disease. Major comorbidities include atherosclerosis, retinopathy, neuropathy, nephropathy, hypertension, cardiovascular disease, and peripheral vascular disease which together dramatically reduce life expectancy [4,5]. T2D also negatively affects the musculoskeletal system which subsequently impairs the patients' fitness and quality of life [6].

Neuropathic, immunological, and vascular complications related to T2D are also manifested in musculoskeletal tissues including muscle, tendons/ligaments, cartilage, and bone. T2D has been linked with muscle ischemia, infections and inflammatory myositis, and muscle denervation [7]. T2D patients suffer from reduced range of motion, increased incidence of injury [8], and increased tendon calcification [9]. In cartilage and bone, T2D increases the incidence of osteoarthritis [10], osteoporosis, osteopenia, and fracture risk [11]. The spine, because of its complex structure containing multiple tissue types, may have compounded susceptibility to the detrimental effects of diabetes. Indeed, T2D patients report more spinal pathologies including spinal stenosis [12], osteoporosis [11], vertebral fractures [11,13], lumbar disc degeneration [14], lumbar disc herniation [15], and poor post-operative outcomes of lumbar fusion [16]. These spinal pathologies can contribute to increased mortality and reduced overall quality of life. This review aims to survey the current state of knowledge on T2D associated pathologies in the spine with an emphasis on the vertebral bodies and the intervertebral discs. The vertebral bodies and the intervertebral discs are the primary load bearing and transmitting structures in the axial skeleton, both of which exhibit mechanical deficits at the material level in the presence of diabetes. The additional weight burden, a common comorbidity of T2D, along with the compromised mechanical behavior, may further amplify the disease and injury risk in these tissues. Moreover, these tissue-level deficits likely lead to vertebral fracture and intervertebral disc degeneration, which are known causes of low back pain [32,33] (Figure 1).

1.2. Vertebrae

Though diabetes is clinically recognized as a risk factor for osteoporotic fractures, it remains confounded with other factors including sex, age, and neurocognitive deficits [17]. Alterations to bone structure and quality occur in both the cortical and cancellous bone of individuals with T2D along with increased fracture risk. T2D patients exhibit elevated cortical porosity [18,19], and altered trabecular architecture [20], characterized by increased vBMD [21] and reduced Trabecular Bone Score (TBS) [22]. However, there is also an overall increase in lumbar bone mineral density (BMD) that is disproportionate with the incidence of fractures [20,23,24]. While the precise cellular mechanisms remain active areas of investigation, it is known that T2D enhances osteoclast function, impairs osteoblast function, and disrupts the osteocyte network [25].

Severe vertebral fractures in T2D patients are associated with higher mortality [6,26]. Despite increased lumbar BMD, postmenopausal women with T2D have more than a 3

times higher incidence of vertebral fractures [23,24]. BMD is a particularly discordant predictor of fractures in T2D patients. For example, a meta-analysis by Vestergaard showed higher BMD in T2D patients with increased risk of hip fracture [24]. Other studies have shown an increase in vertebral fracture in post-menopausal women with lower BMD [27], or a decoupled relationship between BMD and fracture risk [13]. The high prevalence of osteoporosis and vertebral fractures in post-menopausal women is not correlated with blood glucose levels [28]. In these cases, it is difficult to accurately evaluate a diabetic patients' fracture risk using BMD. Along with an increase in BMD, studies have shown compromised trabecular architecture of T2D patients. Using TBS to quantify the morphology of cancellous bone with DEXA or planar Xray [29], reduced TBS has been reported, indicating increased variability in trabecular architecture, in patients with T2D experiencing vertebral fractures [22]. While TBS improves the predictive fidelity of fracture risk in T2D patients, it is clear that more intricate factors such as bone matrix material quality are involved [30].

1.3. Intervertebral disc degeneration and injury

Low back pain affects up to 85% of the population and is the most common cause of disability worldwide [31]. Intervertebral disc (IVD) degeneration is associated with the development of low back pain [32, 33]. A number of factors including aging and IVD injury can lead to IVD degeneration [34,35]. With aging, IVDs exhibit decreased water content, increased mechanical stiffness, and decreased disc height; these features of IVD degeneration also appear in patients after IVD injury (such as herniation) [33]. T2D patients exhibit severe IVD degeneration [36,37] and increased disc herniation [15,38]. Studies have reported increased spinal pain in the presence of T2D and diabetic burden after adjusting for age, sex and BMI [39–44]. Moreover, diabetes is associated with severe chronic spinal pain [40]. Taken together, T2D is associated with higher incidence of reported musculoskeletal pain including neck and low back pain, while the mechanism remains unclear [10,45].

2. Advanced glycation end-products (AGEs) and its receptor (RAGE)

2.1. Advanced glycation end-products

One particularly notable consequence of T2D is the formation and accumulation of advanced glycation end-products (AGEs). AGEs are a family of heterogenous molecules formed by the Millard reaction, a spontaneous reaction between amino acid residues and extracellular sugars [46] that undergo non-enzymatic glycation or glycoxidation of proteins, lipids, or nucleic acids [47]. AGEs accumulate in diabetic tissues, likely caused by chronic hyperglycemia and impaired renal function [47]. The accumulation of AGEs occurs in the liver, collagenous tissues like cartilage and bone, as well as the blood vessels of T2D patients [46] causing detrimental changes to these tissues. In collagen rich tissues for example, AGEs can irreversibly increase the collagen cross-link density, which alters the biomechanical and biological properties of the tissue. In bone, increased collagen cross-linking has been shown to diminish biomechanical properties [48–50].

In post-menopausal T2D patients, urinary [11] and serum [51] pentosidine (an AGE) levels are positively correlated with increased incidence of vertebral fractures. While pentosidine

is a relatively small proportion (~1%) of AGEs in the body, serum pentosidine levels correlate with AGEs in bone [49]. Within the bone tissue, pentosidine levels are robustly correlated with total AGEs in cortical bone, but only modestly correlated in cancellous bone [52]. AGEs in bone impair mechanical properties from the nano-scale to the whole tissue level. Nano-indentation of human jawbones showed that pentosidine deteriorates creep deformation resistance and reduced time dependent viscoelastic recovery [53]. Increased cancellous bone fragility was observed in the hip of T2D males with elevated pentosidine levels in the bone [54]. Bone pentosidine levels in the vertebrae are correlated with reduced energy dissipation and failure load [55]. Mechanical alterations and increased bone fragility seen in patients with increased AGE levels are likely caused by effect of AGEs on the extracellular matrix and cell function [56]. Cellular and tissue culture models, as well as *in vivo* animal models have shown that the accumulation of AGEs can dramatically alter bone homeostasis.

The IVD, with its relatively low levels of tissue remodeling and turnover, is also highly susceptible to the accumulation of AGEs with aging [57]. In addition to forming crosslinks in the collagen network, the IVD is rich in glycosaminoglycans that are also susceptible to forming AGEs adducts [58]. Studies have shown that increased AGEs reduce water content in IVD tissues leading to lower T2 MRI relaxation times [59]. IncreasedAGE concentration *in vitro* impairs the viscoelastic behavior of mouse IVDs [60].

2.2. The AGEs/RAGE signaling axis in bone and in the intervertebral disc

The presence of AGEs in the extracellular matrix contribute to mechanical damage and induce pro-inflammatory signaling through the receptor for advanced glycation end-products (RAGE). RAGE is a multi-ligand proinflammatory cell-surface receptor for AGEs that perpetuates NF-κB signaling [46,61]. NF-κB is a protein transcription factor that upregulates pro-inflammatory cytokines such as a IL-6 and recruits inflammatory cells in addition to exacerbating RAGE signaling. RAGE also circulates in the serum and in the blood (e.g. soluble RAGE - sRAGE; and endogenous secretor RAGE - esRAGE), and they are elevated during inflammatory conditions and diabetes [46]. In the IVD, RAGE signaling correlates with elevated levels of carboxyl-methyl-lysine (another AGE) in the nucleus pulposus [62]. The increased RAGE expression is concomitant with elevated NF-κB signaling in degenerate discs [62]. *In vitro* cell and organ culture studies show that AGEs affect the IVD by reducing matrix synthesis in a RAGE-dependent manner [66,115].

AGEs/RAGE interactions affect bone remodeling by inhibiting bone formation and enhancing bone resorption. Cultured osteoblasts exposed to AGEs exhibit impaired proliferation and collagen adhesion [63,64]. AGEs and RAGE likely play a role in bone loss under diabetic conditions [65]. Osteoclasts are responsive to RAGE activation [65], and RAGE deficient osteoclasts show reduced integrin expression, suggesting that RAGE plays a role in promoting osteoclast attachment to the bone matrix [61]. RAGE depletion protects against diabetes-associated bone loss by suppressing osteoclastic activation [66]. RAGE KO (RKO) mice show decreased IL-6 and bone turnover (indicated by pyriodinoline) [65]. RKO mice with diabetes maintain the elevated bone mineral density, making it an ideal model

system to examine the effects of RAGE signaling in the modulation of bone matrix material quality in diabetes-mediated bone impairments [67].

AGE-enriched diets also elevate AGE accumulation in the musculoskeletal system; although, the diet appears to have differential effects on serum and tissue level AGEs in male and female rodents. Recent studies have assessed the IVD and vertebral bodies from mice on high AGE diets [68–70]. High AGE diet resulted in accumulation of AGEs in the IVD of female mice at 24 weeks, concomitant with annulus fibrosus damage and increased axial stiffness [70]. In addition to dietary models, the STZ-induced type 1 diabetes (T1D) mouse model show increased accumulation of AGEs in the spine associated with vertebral bone loss and IVD degeneration as well as increased TNFα expression and catabolic proteins, ADAMTS5 and MMP13 [71]. AGE accumulation has been shown to impact bone biomechanics in both cortical bone and cancellous bone at the matrix level, but this could also be biologically mediated by the osteocyte lacunar network. Osteocytes are the most abundant cells in bone and have been shown to regulate bone mechanical competence [30]. This can occur through modulation of the microstructure, directly or indirectly through osteocyte density, the osteocyte lacunar network, and proliferation [72]. Osteocyte density correlates with accumulation of microcracks and vertebral strength [72–74]. Osteocytes exposed to AGEs and hyperglycemia *in vitro* exhibit increased sclerostin, decreased RANKL, and increased cell apoptosis [75]. Others have shown that and glycolaldehyde-induced AGEs induce apoptosis and inhibit differentiation via increased TGFβ signaling in bone cells [76,77].

Mouse models of diabetes have shown alterations to osteocytes and the osteocyte lacunar network [78]. Otsuka Long-Evans Tokushima fatty rats showed altered osteocyte morphology in diabetic animals compared to controls [79]. High fat diet induced diabetic mice showed multiple alterations to the osteocyte lacunar network; a significant decrease in peri-lacunar mineralization heterogeneity with no change in mean peri-lacunar mineralization [80]. Osteocyte volume was significantly decreased with no change in overall number of dendritic processes and the network topology was profoundly modified in diabetic mice with increases in the mean node degree, mean node volume, and hub numbers, and a decrease in mean link length [80]. The alterations in the osteocyte lacunar network caused by diabetes likely have a profound effect on the biomechanical properties of diabetic bone.

3. Advanced glycation end-products in rodent models of type 2 diabetes

While large animal models of T2D are available [81,82], rodent models provide an inexpensive and readily available platform to analyze musculoskeletal alterations in diabetes and potential therapies. In particular, T2D animal models that exhibit elevated levels of AGEs may be especially suitable in studying the effects of AGEs on bone and intervertebral disc biology. Rodent models of T2D can be broadly separated into three categories; diet induced diabetes, single transgenic mutation, and polygenic mutations [81,83,84]. Additionally, some chemically induced (specifically streptozotocin (STZ)) rodent models of diabetes are used in musculoskeletal research, most often as a model of type 1 diabetes due to beta cell destruction [85]. Concomitant with the hyperglycemia, the STZ-induced

diabetic animals are also afflicted by abrupt and persistent pancreatic islet inflammation, insulitis, and insulin deficiency. While these models can exhibit AGE accumulation, the traumatic loss of physiological function make it more challenging to interpret the effects of AGEs and RAGE during disease. Low dose STZ injection combined with high fat diet has also been used as a model for T2D, though this model still results in significant beta cell dysfunction (86% reduction in cell area) [86]. For the purposes of this survey, we examined the following T2D rodent models that specifically evaluated the musculoskeletal alterations in the spine. We focus here on spinal phenotypes because some rodent models exhibit divergent musculoskeletal phenotypes in the appendicular and axial skeleton [87–89].

3.1. Genetic models of Type 2 diabetes

The leptin signaling pathway is a common target to genetically induce progressive T2D in rodents because leptin regulates metabolic homeostasis by controlling hunger and energy expenditure [90]. Rodents with a homozygous mutation on either the leptin gene or leptin receptor can become diabetic due to hyperphagia. Models that target this pathway include the Zucker diabetic fatty *fa*/*fa* (ZDF) rats, leptin-deficient ob/ob (Lepr ob/ob) mice and leptin-receptor deficient db/db (Lepr db/db) mice. It is important to note that data collected from rodent models without intact leptin signaling have to be interpreted carefully due to the association of diabetes with high leptin levels and the potential direct effects of loss of leptin signaling on the tissue of interest. To address this issue, genetic diabetic animal models without disruption in the leptin signaling pathway have been developed including the Zucker diabetic Sprague-Dawley (ZDSD) and University of California at Davis–type 2 diabetes mellitus (UCD-T2DM) rats.

3.1.1. Zucker diabetic fatty (ZDF fa/fa) rats—ZDF rats that are homozygous for the *fa gene* mutation develop progressive insulin resistance, glucose intolerance and beta-cell dysfunction. Male ZDF rats will spontaneously develop T2D between 9 and 11 weeks of age while female ZDF rats require a high fat diet (HFD) to show signs of T2D. AGE serum levels are elevated in 20 week male ZDF rats [91]. Current studies on the spine in ZDF rats investigated effects of diabetes on the vertebrae in male mice from 7 to 33 weeks [92–95]. At 7 weeks, the ZDF rats are obese but not diabetic and by 20 weeks, ZDF rats have elevated fasting blood glucose but are not obese.

Serum biomarkers are notably altered in 23 week old male ZDF rats on a HFD with reduced bone formation markers (P1NP and osteocalcin) and a decreased bone resorption marker (CTX) [96]. On both a standard and high fat diet, diabetic ZDF male rats had reduced BV/TV [92,94,96] and reduced trabecular thickness [94]. In diabetic ZDF rats, BMD appeared unaffected [95] or reduced [94,96]. Mechanical behavior of the vertebra are compromised in axial compression to failure of 33 week diabetic ZDF rats as indicated by reduced yield force, stiffness and ultimate load which remained significant after controlling for morphometry [94]. (See Table 1).

3.1.2. Leptin receptor deficient (Lepr db/db) mice—Lepr db/db mice experience hyperphagia due to loss of leptin signaling. Male and female mice by 4–8 weeks develop T2D characterized by obesity, hyperinsulinemia and hyperglycemia. Unlike the ZDF rats,

Lepr db/db mice exhibit obesity throughout their life. In addition, the diabetic phenotype can be amplified by high-fat or western diets. While there are some observations of increased levels of AGEs in the serum and other organs of Lepr db/db, the local tissue levels of AGEs are not always reported [97–99].

Lepr db/db mice commonly exhibit increased bone volume fraction (BV/TV) in the vertebra [89,100]. Yet sex-specific effects have been reported by other studies, such as in 17-week old female Lepr db/db mice that exhibited reduced bone formation rate and mineral apposition [101]. In these same 17 week old female mice, a bone formation serum marker (osteocalcin) and bone resorption serum marker (CTX) were also lowered. In addition, 11 week old male Lepr db/db mice had reduced trabecular thickness that contributed to a trending reduced bone volume fraction [102] and 30 week old Lepr db/db male mice had reduced BV/TV [103]. An increased BV/TV in 12 week old male and female Lepr db/db mice was attributed to increased trabecular number and decreased trabecular spacing [100]. Cortical vertebral bone structure has been shown to be impaired in these mice indicated by reduced cortical area fraction (Ct.Ar/Tt.Ar) and thickness (Ct.Th) in Lepr db/db female mice on a western diet and in both male and female mice with increase cortical bone surface fraction (Ct.BS/BV) [100,102]. The IVD is not grossly affected in terms of morphology, axial mechanics and degeneration by the Lepr db/db genotype at 12 weeks [100]; however, the segmental mechanics of a functional spinal unit (FSU) in torsion are impaired in these Lepr db/db mice [100] and reduced Safranin-O staining and increased cell apoptosis was observed in the coccygeal IVD of 30 week old male Lepr db/db mice [103]. (See Table 2).

3.1.3. Leptin-deficient (Lepr ob/ob) mice—Unlike ZDF and Lepr db/db rodents, Lepr ob/ob have a functional genetic mutation that prevent leptin production. The diabetic phenotype is similar to Lepr db/db defined by obesity, hyperglycemia and hyperinsulinemia; however, the impaired glucose and hyperglycemia tend to become normalized with aging. Limited data is available on the extent of tissue-specific AGE accumulation in the ob/ob animals.

Lepr ob/ob mice have increased trabecular bone area measured by histologically and radiographically [87,89,101], as well as an increased vertebral length, but reduced cortical thickness [87]. Increases in trabecular number and reduced trabecular spacing appear to account for the increase in lumbar bone area [87,101]. Although Lepr ob/ob have more lumbar trabecular bone, Turner et al. found that Lepr ob/ob mice have reduced mineralizing perimeter, bone formation rate and osteoblast number. Bone mineral content and density was unaffected in 10 week old [88] but was lowered in 24 week old Lepr ob/ob males [87]. While a number of studies have assessed the structure of the vertebral bodies of Lepr ob/ob mice, mechanical assessments are sparse. At 10 weeks of age, vertebrae from male Lepr ob/ob exhibit no differences in peak load when tested in compression. (See Table 3).

3.1.4. University of California at Davis-Type 2 diabetes mellitus (UCD-T2DM) rat—UCD-T2D rats develop T2D due to beta cell dysfunction with an intact leptin signaling pathway. The UCD-T2D rat is an animal model of adult onset diabetes with male and female UCD-T2D rats developing diabetes on average between 24 and 38 weeks,

respectively [104]. T2D in the UCD-T2D rat presents with obesity, hyperglycemia, and hyperinsulinemia.

The effects of the UCD-T2D phenotype on the intervertebral disc, vertebral bodies and vertebral endplates have been examined in this animal model at 24 weeks of age. Specifically, changes to the coccygeal IVD and endplate were evaluated with microCT, compositional analyses and mechanical testing [105], while the lumbar vertebra was assessed using microCT and mechanical testing [106]. The coccygeal IVD showed compositional changes indicative of degeneration such as increased AGEs, loss of proteoglycans and reduced hydration [105]. Pentosidine was measured using an ELISA assay, and it was increased by 29% in the AF and 104% in the NP [105]. Loss of proteoglycans was associated with an increase in endplate thickness and AGE accumulation was associated with diminished creep properties such as increased stiffness [105]. Despite the impairments to mechanical behavior and compositional changes to the IVD, the histological changes were unremarkable. The lumbar vertebra had deterioated morphological parameters with reduced bone volume fraction due to a decrease in trabecular thickness and increased trabecular spacing in addition to reduced tissue mineral density [106]. The lumbar vertebra also exhibited compromised mechanical properties in axial compression as indicated by reduced stiffness, yield force and ultimate load (normalized to bone mineral content) [106]. (See Table 4).

3.1.5. Zucker diabetic Sprague-Dawley (ZDSD) rats—

ZDSD rats are relatively new obese-diabetic rat model with an intact leptin signaling pathway. ZDSD rats have a longer pre-diabetic phase than the previously discussed models and develop overt T2D around 16 weeks. ZDSD rats experience obesity, hyperglycemia and insulin resistance during the pre-diabetic phase. As they develop overt T2D, ZDSD rats exhibit reduced body weight, hyperglycemia, elevated insulin resistance and reduced insulin levels. Male rats will spontaneously develop T2D while female rats require a diabetogenic diet. Because the UCD-T2DM strain is based on the ZDSD strain, we anticipate that the ZDSD animals to exhibit AGEs accumulation similar to their UCD-T2DM counter parts.

Male ZDSD rats exhibit reduced vertebral trabecular thickness in the diabetic (33 weeks) phase that leads to reduced bone volume fraction [94]. The mechanics of ZDSD male rats was impaired at 33 weeks in axial compression with reduced yield force, ultimate load and energy even when normalized to morphology [94]. While the diabetic phenotype of the ZDSD rat appears to negatively affect the vertebral bodies, the vertebral bodies from 20 week old female ZDSD rats on high fat diet appear to be grossly not affected. Female ZDSD rats were shown to have no differences in architecture, in areal bone mineral content, in bone mineral density, and in axial compression mechanics, despite reduced mineral apposition rate [107]. (See Table 5).

3.2. Dietary models of Type 2 diabetes

In addition to genetic models, dietary models such as high fat diet (HFD) can be used to induce T2D in wild-type rodents. A high fat diet can result in obesity, hyperglycemia and hyperinsulinemia allowing for the study of the effects of T2D independently of genetic

modifications [108]. While we know that C57BL/6J mice on a high fat diet are susceptible to T2D, it is important to note that not all studies utilizing the high fat diet model report the diabetic status of the animals.

We limited the scope of our review to studies that examined the effects of high fat diet in C57BL/6J mice. Most studies started the mice on a high fat diet at a young age, 4–5 weeks. Conflicting effects of HFD on the vertebral bodies have been reported with some studies showing increased spinal bone mineral content and areal bone mineral density after 19 weeks on HFD diet [109], no effect on bone mineral content after 12 weeks [110], reduced bone mineral content after 28 weeks [110] or no effect on bone mineral density after 12 weeks [111]. Initiating the HFD at 20 weeks old yielded similar results as starting at 5 weeks [111]. Reduced mechanical properties in axial compression with reduced ultimate load, yield force, stiffness and energy to ultimate load of the vertebral body was observed in addition to reduced trabecular bone volume fraction [111]. (See Table 6).

4. Discussion

Alterations in matrix composition and morphological features of the vertebral bodies and IVDs are likely contributors to the increased number and severity of spinal pathologies in T2D patients. Increasing clinical evidence shows elevated incidence of spinal pathologies in T2D patients; there is also emerging basic science research in *in vitro* and *in vivo* models that investigate putative mechanisms by which T2D affects the spine. The T2D associated changes in the intervertebral discs and vertebral bodies may be responsible for the compromised spinal mechanics that subsequently contribute to increased risk of low back pain, vertebral fractures, and other spinal pathologies. Although research into spinal structures outside the vertebral bodies and IVD is limited, osteoarthritis studies indicate that changes to the facet joints, muscles, and tendons/ligaments are likely and can contribute to the number of spinal pathologies observed in diabetic patients. In addition to increased spinal pathologies, individuals with T2D also experience impaired healing, adverse outcomes, and an increase in mortality [112].

AGEs and RAGE signaling are likely contributors to diabetic bone fragility and musculoskeletal complications. Increased levels of serum and bone AGEs support the hypothesis that AGEs are contributors to bone and collagen mechanical deficits. Modulation of AGEs and RAGE affect osteoblast, osteoclast, and osteocyte function disrupting bone homeostasis subsequently causing mechanical deficits in bone. AGEs are known to crosslink the organic component of bone matrix, but the AGE/RAGE axis may also exert biological control over other aspects of the bone's extracellular matrix. (See Fig. 1). It is also important to note that while AGEs and RAGE appear to be significant contributors to diabetic complications, other factors could also play a role in the diabetic skeleton. For example, the role of increased saturated fatty acids in bone marrow [19, 113], altered adipocyte differentiation [114], and increased inflammation can influence bone turnover and mechanics in T2D [113]. Additionally, there are substantial site-specific variations in the degree of AGE accumulation, and possibly RAGE expression, even in rodent models with hyperglycemia and/or increased AGEs-intake, and one must evaluate the AGEs status in the tissue of interest in order to determine its regional effects, especially since several models

have shown divergent effects on the axial skeleton and the appendicular skeleton [87–89]. Further investigations of the AGEs/RAGE signaling axis will help elucidate mechanisms of skeletal fragility in the spine.

5. Search methods

The data presented in sections 2.1 and 2.2 focuses on three main areas, AGEs correlation to vertebral fracture risk in humans, AGEs in bone and IVD biomechanics, and AGEs role in osteocyte function. Search terms included both the full term and corresponding abbreviations, e.g. Advanced Glycation End-products and AGEs; and Intervertebral disc and IVD. The search was completed between January 05, 2020 and January 14, 2021, search terms in PubMed and google scholar for these areas of interest include the following respectively; (Spinal Fracture) AND (AGEs OR Pentosidine) AND (Type 2 Diabetes), (Type 2 Diabetes) AND (AGEs OR Pentosidine) AND (Bone Biomechanics OR IVD Biomechanics), and (AGEs) AND (Type 2 Diabetes) AND (Osteocyte). Exclusions were made for review articles, type 1 diabetes, and animal vs human studies where applicable, search terms for additional background information in these sections not included.

The data presented in section 3 focuses on reviewing Type 2 Diabetes (T2D) animal models. Studies were included that utilized established T2D animal models whether or not the researchers verified diabetes in their animals. A list of relevant T2D animal models was compiled with exclusions for Type 1 diabetics and models with beta cell destruction. Studies focusing on Type 1 diabetes were excluded because the mechanism of disease differed from Type 2 diabetes. The search was completed between January 05, 2020 and January 14, 2021, keywords searched amongst paper utilizing the relevant animal models included were spine, vertebra or intervertebral disc in PubMed and google scholar.

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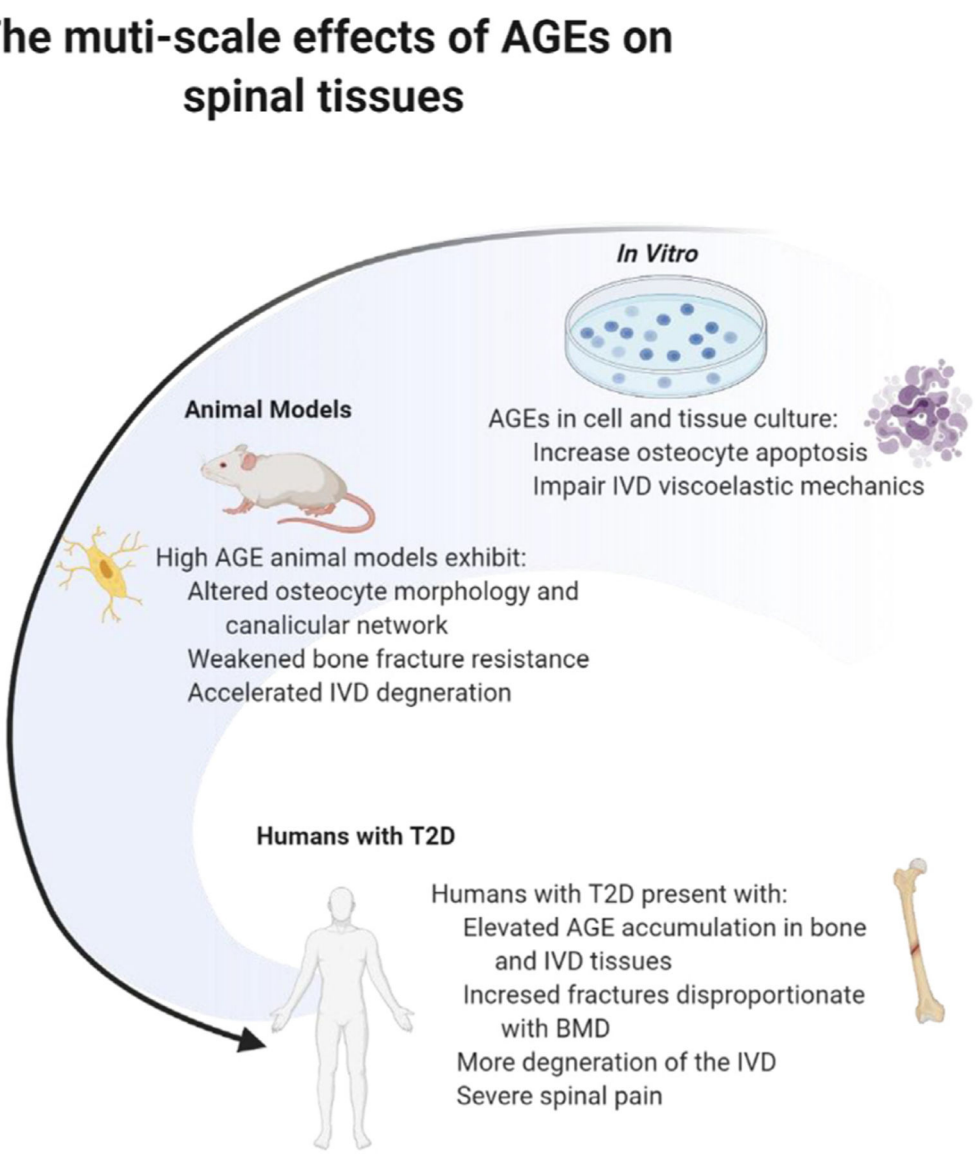

Fig. 1.

The multi-scale effects of AGEs on spinal tissues. AGE/AGEs = Advanced Glycation End-product(s). IVD = Intervertebral Disc. T2D = Type 2 Diabetes. Created with Biorender.com, Adapted from “From the Human Body to Micro-fluidics”, by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates.

Table 1

Reported bone phenotypes in Zucker diabetic fatty (ZDF) rats with a leptin recepter missense mutation (*fa/fa*).

	Age/Sex	Diet	Structure	Vertebral tissue composition	Mechanical behavior
Hamann,2011 and 2013	23 weeks/Male	HFD	Reduced BV/TV	Reduced total, trabecular, cortical/subcortical TMD	–
Reinwald, 2009	33 weeks/Male	Standard	Reduced BV/TV, Tb.th, vertebral height and CSA	Reduced whole vertebral aBMD, BMC	Reduced yield force, stiffness ultimate load and energy to ult. Load and post yield energy Reduced ultimate stress and modulus normalized to BV/TV
Prisby, 2008	13 and 20 weeks/Male	Standard	–	Reduced ash content at 20 weeks	–

Table 2

Reported bone and intervertebral disc phenotypes in leptin receptor deficient (Lepr db/db) mice.

	Age/Sex	Diet	Structure	Tissue composition	Mechanical behavior
Ducy, 2000	24 weeks/ Female	Standard	Increased BV/TV	–	–
Williams, 2011	11 weeks/Male	Standard	Reduced Tb·Th Reduced cortical bone perimeter, thickness Increased BS/BV	–	–
Natelson, 2020	12 weeks/	Standard	Increased BV/TV Reduced Tb.Sp Increased Tb·N	Reduced trabecular TMD (female only)	Reduced torsional failure strength Reduced angle to failure (female)
Natelson, 2020	12 weeks/	Western	Increased BV/TV Reduced Tb.Sp Increased Tb·N Reduced Tb·Th (female) Reduced Ct.Ar/Tt.Ar and Ct.Th (female) Increased Ct.BS/BV	–	Reduced torsional failure strength Reduced angle to failure (female)
Li, 2020	30 weeks/Male	Standard	Reduced BV/TV Reduced Tb·Th and Tb·N Increaed Tb.Sp Decreased Ct.Th	Bone: Reduced BMD Intervertebral disc: Reduced GAG in coccygeal IVD (histology)	–

Table 3

Reported bone phenotypes in leptin deficient (ob/ob) mice.

	Age/Sex	Structure	Tissue composition	Mechanical behavior
Ducy, 2000	12 and 24 weeks/	Increased bone area	–	–
Hamrick, 2004	24 weeks/Male	Increased vertebral length Increased Tb·N, bone area Reduced cortical thickness	Increased BMC and BMD	–
Ealey, 2006	10 weeks/Male		No effect on BMC or BMD	No effect on peak load
Tuner, 2013	15 weeks/Female	Increased lumbar bone area	–	–
Turner, 2013	24 weeks/Male	Increased bone area Increased Tb·N and reduced Tb·S	–	–

Table 4

Reported bone and intervertebral disc phenotypes in University of California at Davis- Type 2 diabetes mellitus (UCD-T2DM) rats.

	Age/Sex	Diet	Structure	Tissue composition	Mechanical behavior
Fields, 2015	24 weeks/	Standard	Increased endplate thickness	Intervertebral disc: Loss of GAG Reduced hydration Increased AGEs	Increased IVD stiffness
Acevedo, 2018	24 weeks/	Standard	Reduced BV/TV, Tb·Th Increased Tb.Sp	Bone: Reduced TMD	Reduced stiffness, yield force and ultimate load

Table 5

Reported bone phenotypes in Zucker diabetic Sprague-Dawley (ZDSD) rats.

	Age/Sex	Diet	Structure	Tissue composition	Mechanics
Gallant, 2014	20 weeks/Female	HFD	No differences on microCT	No differences inaBMC or BMD	No differences in axial compression
Reinwald, 2009	33 weeks/Male	Standard	Reduced BV/TV and Tb.th	–	Reduced yield force, stiffness, ultimate load and energy

Table 6

Reported bone phenotypes in High fat diet mouse models.

	Age/Sex	Diet Duration	Structure	Tissue composition	Mechanical behavior
Ionova-Martin, 2010	23 weeks/Male	19 weeks	–	Increased spine BMC and aBMD	–
Parhami, 2009	20 and 32 weeks/Male	12 and 28 weeks, respectively	–	Reduced vertebral BMC at 32 but not 20 weeks No differences in tissue mineral density	–
Inzana, 2013	17 and 32 weeks/Male	12 weeks	Reduced BV/TV No difference in Tb·Th, Tb·N, Tb.Sp, Conn.d Reduced cortical area No effect on cortical thickness	No effects on BMD	Reduced yield force, stiffness, ultimate load and energy to ultimate load