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REVIEW ARTICLE

Diabetes mellitus as a risk factor for intervertebral disc degeneration: a critical review

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Abstract

Purpose To examine to what extent diabetes mellitus (DM) is implicated as a distinct mechanism in intervertebral disc degeneration (IVDD).

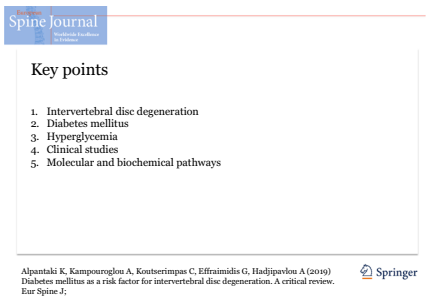
Methods The published clinical and laboratory data relevant to this matter are critically reviewed. A total of 12 clinical studies evaluate the association between DM and degenerative changes such as IVDD, spinal stenosis (SS) and IVD herniation. A total of 34 laboratory research papers evaluate the association between DM and IVDD.

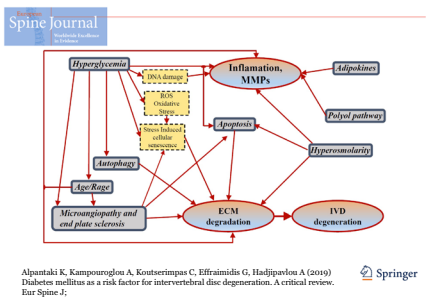
Results There are 7 studies that correlate DM with IVDD, 4 of them showing that DM is a significant risk factor for degeneration, and 3 of them failing to establish any association. Three studies demonstrate significant association between DM and SS. However, 2 of these studies also include patients with IVD herniation that failed to demonstrate any correlation with DM. Two other studies indicate a significant association between DM and lumbar disc herniation. Multiple different mechanisms, acting independently or interactively, cause tissue damage leading to IVDD including: microangiopathy of the subchondral vertebral endplate, cellular senescence, cell death (through apoptosis or autophagy), hyperglycaemia, advance glycation end products, adipokines, and cytokines (through oxidative, osmotic, and inflammatory mechanisms).

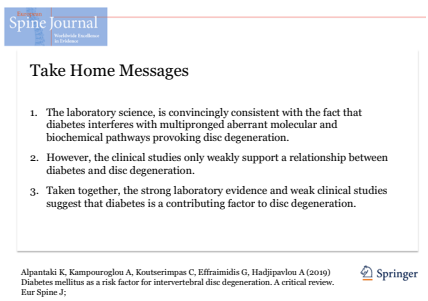
Conclusion The clinical evidence is not consistent, but weakly supports the relationship between DM and IVDD. However, the laboratory studies consistently suggest that DM interferes with multipronged aberrant molecular and biochemical pathways that provoke IVDD. Taken as a whole, the strong laboratory evidence and the weak clinical studies implicate DM as a distinct contributing factor for IVDD.

Graphic abstract

These slides can be retrieved under Electronic Supplementary Material.







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Keywords Intervertebral disc degeneration · Diabetes mellitus · Hyperglycaemia · Clinical studies · Molecular and biochemical mechanisms

Introduction

Diabetes mellitus (DM) and intervertebral disc degeneration (IVDD) are both common conditions. DM, with a prevalence of 8% in the general population, is a multiorgan disorder that affects all types of connective tissues, including bone and cartilage [1]. Diabetic patients experience different age-related changes in their cartilage matrix than non-diabetics [2]. Clinical and laboratory studies suggest that DM may contribute to the development and deterioration of bone cartilage in osteoarthritis [3].

IVDD is an age-dependent, cell-mediated molecular degradation process under genetic influence. IVDD is accelerated primarily by nutritional and mechanical factors, and secondarily by toxic or metabolic influences. These factors mediate degeneration by triggering multiple chemical reactions. These changes can affect the morphology of the disc, manifested as thickening of the vertebral endplate, cracks and fissures in the matrix, delamination and tears in the annulus fibrosus (AF), and in the biomechanical function of the disc. The end result of disc degeneration is characterized by collapse of the IVD space and osteophyte formation. Although IVDD has been extensively studied, the order and the causal relationships of biochemical, molecular, and cellular events occurring in the disease process have not been entirely clarified [4].

In this framework, we examine whether and how DM, with its generalized adverse metabolic effects in almost every tissue, could also be a culprit of IVDD. The purpose of this article is to evaluate the published data of the effects of DM on IVDD.

Methods

To determine the relationship between DM and IVDD, we reviewed the relevant clinical and laboratory publications, using PubMed and the US National Library of Medicine through December 2018, with the search criteria: "intervertebral disc" and "diabetes mellitus".

The initial electronic search revealed 136 articles. Three independent researchers examined each paper to include or exclude in the study. The present review is limited to papers published in English language peer-reviewed journals. Case reports, literature reviews, and technical notes were excluded. With these inclusion criteria, 12 clinical studies from 9 different countries and 34 laboratory research papers investigated the relationship between DM and IVDD.

Results/discussion

Clinical studies

All 12 studies (see Table 1) use correlation methods to examine the association between DM and degenerative changes such as IVDD, spinal stenosis (SS), and IVD herniation. These three entities are different evolutionary states of the same degenerative process that begins as IVDD. Disc degeneration appears to be a prerequisite of disc prolapse and degenerative SS [4].

There are 7 studies that investigate the association of DM with IVDD. Of these, 4 studies (one cross-sectional control [5], two retrospective studies [7, 8], and one cross-sectional insurance industry-based retrospective study [6]) show that DM is a significant risk factor for IVDD. The severity of IVDD seems to be directly correlated with the duration of the disease and its bad management. However, retrospective studies are well known for their inherent incomplete documentation and weak persuasive power [17]. There are also other important hedges that limit the contribution of these studies. For instance, one study with a large number of patients is an insurance industry database study in which diabetes was one of several other potential risk factors, leaving room for coding errors and code bias [6]. Three studies also targeted other associated pathologies [5, 6, 8].

The other 3 studies [9–11] show that DM is not a statistically significant risk factor for IVDD. One of these studies, a cross-sectional study in an elderly population, with its primary goal the degree of association between IVDD and cardiovascular disease, failed to demonstrate any connection between IVDD and DM. However, this is a poor-designed study which primarily intended to investigate associated risk factors between cardiovascular disease status and IVDD. Glycosylated haemoglobin (elevated in hyperglycaemia), as a biochemical marker for DM, was included among other factors as secondary objectives in their study [9]. Two other studies were conducted in twins (one case control and one cross-sectional) [10, 11] and also failed to demonstrate any significant correlation between IVDD and DM.

Of the remaining 5 studies, there is 1 study dealing solely with SS and 2 studies with both SS and IVD herniation (one prospective control [12], one case control [13], and one cross-sectional control [14]). All three studies showed a significant association between DM and SS, promoting DM as a risk factor for the development of lumbar SS. However, there are important caveats lessening their contribution. One statistically significant ($p < 0.0001$) study [12] shows that diabetic women are associated with SS. However, the

Table 1 Correlation between intervertebral disc degeneration, spinal stenosis, disc herniation, and diabetes mellitus

No.	References	Study design/level of evidence	Population	Methods	Outcomes	Strength/limitation
1.	Agius et al. [5]	Cross-sectional, 2 branches with control/II	100 pts DM versus 86 pts non-DM	Relationship between BMD, IVD height, BP, OVF risk versus DM	No significant independent association between DM and BMD Significant association between narrowed IVD and DM DM is a significant risk factor for IVDD and is not associated with BMD and OVF	*Strength* Limited sample but has 90% statistical power. High quality data *Limitation* IVDD not the only target. Significant age difference between 2 groups. Control group may not truly represent general population
2.	Jakoi et al. [6]	Cross-sectional retrospective (Insurance industry database study)/III	280,399 pts with IVDD of which 14,114 pts with DM	IVDD correlation with DM, obesity, and smoking	DM, obesity, and cigarette smoking each are significantly associated with IVDD	*Strength* Large sample size *Limitation* Retrospective analysis of an insurance industry database study leaving room for coding error or code bias. Difficult to know if physicians were coding appropriately for IVDD. Data from a large private insurer (Humana) with customers nationwide, but no other insurers
3.	Liu X, 2018 [7]	Retrospective study/III	150 pts without DM (group A) and 622 pts with DM (well-controlled group–group B, $n=380$) and a bad-controlled group 242 pts	IVDD in pts without DM versus pts with well-controlled and bad-controlled DM	Patients with DM show more severe IVDD from L1–L2 to L5–S1 after removal of age effects ($p<0.05$). DM duration > 10 years and a poor control of DM are predisposing risk factors for IVDD The longer the duration or poor control of DM the more severe the associated IVDD	*Strength* Satisfactory sample size *Limitation* Include pts with low back pain seeking therapy. Does not analyze the age differences between the groups. Retrospective study
4.	Steelman et al. [8]	Population retrospective case control study/III	160,911 pts with IVDD and 315,225 age and sex-matched controls in military members	IVDD associated risk factors: DM, obesity, smoking, hip and knee arthritis	The authors were able to identify a significant association between IVDD and: (a) DM an OR of 1.469 (CI), 1.350–1.598 (b) Hip and knee arthritis of OR 2.295 (CI), 2.685–3.187 (c) Tobacco dependency of OR 1.799 (CI), 1.308–1.36 (d) Obesity of OR 1.556 (CI 1.497–1.618)	*Strength* Large sample size *Limitation* IVDD not the only primary target. Retrospective study

Table 1 (continued)

No.	References	Study design/level of evidence	Population	Methods	Outcomes	Strength/limitation
5.	Hangai et al. [9]	Cross-sectional elderly population/III	231 pts without DM versus 36 pts with DM	IVDD versus DM (HbA1c) Primary study: Association between IVD and CV risk factors. Secondary study: Association between high BMI, high LDL, smoking, drinking, DM	No significant independent association between IVDD and DM, HbAc1 used as a biochemical marker for DM	*Strength* Satisfactory sample size *Limitation* IVDD not the primary target. DM diagnosed only based only on HbA1c
6.	Fabiane et al. [10]	Cross-sectional control, twins, DM and IVDD incidence; twins discordant for DM, IVDD incidence/II	956 twins; 33 twins discordant for DM	IVDD versus DM, BMI, age, smoking, alcohol	6.6% of twins had DM IVDD score was higher in DM twins (14.9 vs. 13.1, $p=0.04$) but not an independent risk factor when age and BMI included. (80% power at 0.1 significance) Discordant twin analysis ($n=33$ pairs) showed no significant difference in IVDD between diabetic twins unaffected twins	*Limitation* IVDD not the only primary target. Limited sample size. Predominance of females in the sample. The limited differences in HbA1C between cases and controls are suggestive of pre-diabetes in controls.
7.	Videman et al. [11]	Case control, MZ twins discordant for DM/III	9 pairs of monozygotic twins discordant for DM	DM versus BMD and IVDD MRI scans	IVDD did not differ between DM pts and their twins; after controlling for smoking, femoral neck BMD was 2.5% lower in DM than their twins ($p=0.09$)	*Limitation* IVDD not the only primary target. Small number of subjects
8.	Asadian et al. [12]	Cross-sectional, prospective, 3 branches with control group/II	110 pts with SS, 110 pts with IVD herniation. Control 110 pts without spinal pathology	SS and IVD herniation versus DM Association between DM, SS and IVD herniation	32 (29.1%) in the SS group, 7 (6.4%) in the IVD herniation group, and 11 (10%) in the control group DM in women with SS and women with IVD herniation was 35.9% and 10.3%, respectively, versus 10.9% in the control group Statistically significant in the SS group versus controls ($p<0.0001$). No significant difference was found in men	*Strength* High statistical power *Limitation* Bias due to greater number of women and underpower men. The IVD herniation group was younger than the other two groups, with too few participants in the > 60 age group, which might bias the diabetes prevalence assessment Poor correlation of the control group. Not investigate the duration of diabetes and the type of diabetes treatment

Table 1 (continued)

No.	References	Study design/level of evidence	Population	Methods	Outcomes	Strength/limitation
9.	Anekstein et al. [13]	Case control cross-sectional/III	395 pts with SS, IVD herniation, OVF	Correlation between SS, IVD herniation, or OVF versus DM	The prevalence of DM in SS: 28% OVF: 6,5%, disc herniation: 12.1% DM is a statistical significant risk factor for SS ($p=0.001$) Prevalence of DM between SS and IVD herniation group is more pronounced in the younger age group	*Strength* Satisfactory sample size *Limitation* SS, IVD herniation, and OVF might simultaneously exist in the same patient
10.	Maeda et al. [14]	Cross-sectional, symptomatic SS in the general Japanese population/III	968 participants (319 men, 649 women), age 21–93 y, 92 symptomatic SS versus 876 asymptotic SS.	Association of DM with symptomatic SS versus asymptomatic SS Comparison between moderate and severe MRI SS. DM assessment using HbAc1	DM is significantly associated with moderate SS (multiple logistic regression analysis p 0.0009). No significant association in subjects with severe SS (p 0.42) MRI used to evaluate stenosis Classification Canal narrowing Normal, Grade 1 No narrowing Mild, Grade 2 1/3 Moderate, Grade 3 1/3–2/3 Severe, Grade 4 > 2/3	*Strength* Satisfactory sample size *Limitation* DM assessment using HbAc1
11.	Jhawar et al. [15]	Case control, prospective longitudinal study/II	98.407 female nurses	Primary target: Correlation between CV risk and IVD herniation Secondary target: DM, cholesterol, hypertension, obesity, smoking	Multivariate relative risk for DM is 1.52 IVD herniation is highly associated with DM, high cholesterol, hypertension, smoking, and myocardial infarction before the age of 55	*Strength* Satisfactory sample size *Limitation* DM not the primary target
12.	Sakellaridis [16]	Prospective, control study/II	102 operated pts with IVD herniation versus 98 pts without IVD herniation operated for other reasons	IVD herniation association with DM	DM in 32% of pts with IVD herniation versus 13% of pts without IVD herniation DM predisposes to IVD herniation with compressive radiculopathy (32%) Yates-corrected $\chi 2=10.28$. $p=.0013$	*Strength* Prospective, high statistical power. Sciatica attributed to IVD herniation and not to diabetic neuropathy *Limitation* Larger sample size would have been more convincing

DM diabetes mellitus, *Pts* patients, *BMD* bone mineral density, *BP* back pain, *Fx* fracture, *OVF* osteoporotic vertebral fracture, *IVD* intervertebral disc, *IVDD* degenerative disc disease, *SS* spinal stenosis, *HbA1c* glycosylated haemoglobin, MZ monozygotic, *CI* confidence interval, *OR* multivariable adjusted odds ratios

lack of statistically significant association reported in men is likely because the male sample is underpowered ($n=96$) and the female sample is robust ($n=234$). This introduces a bias in the interpretation of the study results [12]. In another cross-sectional study of symptomatic clinical lumbar SS patients [14], there is a significant association, but only between its moderate form ($p<0.0009$) and not with its more severe stage. This is an unexpected finding that is difficult to explain.

The relationship between DM and SS is corroborated by a recent laboratory study, in which harvested decompressive laminectomy tissues from patients with lumbar SS exhibited a significant greater degree of elastin loss and less homogenous fibre orientation in diabetic patients as opposed to non-diabetics. Patients with lumbar disc herniation exhibited less elastin degradation and less fibrosis as opposed to diabetic patients [18]. These findings suggest that DM, apart from its degenerative effect on IVD [1, 3], may also play a direct role in the development of SS.

Two studies were specifically designed for lumbar disc herniation patients. One based on a case control prospective longitudinal population [15], and the other a prospective control [16], showed a statistically significant association between DM and lumbar canal herniation. However, lumbar disc herniation was also the objective in two other studies, as mentioned earlier: one retrospective case control [13] and the other cross-sectional prospective control [12] that also targeted SS patients, which failed to establish any association.

The reports correlating DM with the clinical (pain) and imaging appearance of IVDD (vertebral space reduction, disc herniation, and SS) are few, difficult to compare, and use different evaluating criteria. In one study, back pain was not entirely attributed to IVDD [13]. It goes without saying that blaming lower back pain simply on IVDD is controversial. Imaging structural abnormalities (narrowing of the disc space, black discs, herniation, annular tear, etc.) has a weak prediction for back pain [19]. Pain, although not always present, may originate in structural changes of disc degeneration such as tear, fissure, and delamination of AF. These defects, however, not always can be invaded by vascular granulation tissue carrying nerve fibres [20]. The evolution of IVDD to spinal instability, SS, and lumbar disc herniation may also contribute to pain, which in theses stages may be mechanical or neurogenic in origin.

The very wide heterogeneity and primary objective of the studies rendered the strength of the correlation between DM and IVDD difficult to evaluate statistically. Because DM promotes generalized degeneration on connective tissue, it seems plausible that DM may have a direct harmful effect on IVDD. Clinical studies thus far have examined the association but not the causal relationship between DM and IVDD. The evidence is not consistent or concrete enough, but weakly supports a relationship between DM and IVDD. Better designed, multicenter clinical studies are necessary to establish a causal relationship between DM and IVDD.

Laboratory studies

Biochemical and molecular changes leading to IVDD

We will briefly highlight some of the most salient molecular changes contributing to IVDD before analyzing the effects of DM on IVDD.

Under the influence of improper chemical signals, nucleus pulposus (NP) cells stop producing, or even start degrading, proteoglycans (PGs) and collagen II, leading to a decline in intradiscal pressure and NP structural integrity [21]. PGs reduction and fragmentation alter extracellular matrix (ECM) hydration levels and osmotic pressure and result in fibrocartilaginous metaplasia of the NP and impaired disc biomechanical properties [22, 23]. Degradation of disc substance takes place with the accumulation of significant levels of abnormal matrix components and matrix degradation mediators such as proinflammatory cytokines and catabolic enzymes [4].

Diabetes-induced tissue damage usually refers to specific cell subtypes, which are characterized by their incapacity to retain stable levels of intracellular glucose when they are exposed to hyperglycaemia. These cell subtypes include capillary endothelial cells in the retina, mesangial cells in the renal glomerulus, and neurons and Schwann cells in peripheral nerves [24]. Evidence from the laboratory studies as detailed in Table 2 indicates that IVD cells are also unable to effectively handle intracellular hyperglycaemia implicating DM as a definitive injurious process for generating or deteriorating IVDD.

Diabetic-related pathways leading to IVDD

We analyze the pathways leading to IVD degradation according to the various responsible pathophysiological contributions in diabetic animals such as: transport of the nutrients into the IVD from compromised vertebral endplate permeability, cell senescence, cell death (apoptosis and autophagy), hyperglycaemia-induced inflammatory reactions from toxic end products of glycation (Advance glycation end products (AGEs) and Receptor for AGEs (RAGEs)), osmotic stress, polyol pathways, and adipokines.

Vertebral chondral endplate A comparative study between diabetic and non-diabetic rats demonstrated that vertebral endplate microvessels are significantly narrower in diabetic animals resulting in the decline of the blood supply and nutrition to the IVD [25]. Conjointly, the vertebral endplate may become sclerotic, further compromising its permeability to nutrients. This sclerosis is brought about by the anabolic effects of DM on osteochondral metabolism [26]. Similar to

Table 2 Thirty-four laboratory studies examining the correlation between degeneration intervertebral disc and diabetes mellitus

No.	References	Experiment	Results
1.	Robison et al. [2]	Human IVD harvested from 5 DM and 5 non-DM pts underwent discectomy	IVD harvested from DM pts exhibit PGs with lower buoyant density and a significant undersulphated GAG content, findings consistent with IVDD. The authors postulate these findings are a possible cause of BP
2.	Shemesh et al. [18]	Ligamentum flavum human harvested from 23 pts with SS (10 with DM vs. 13 without DM) and 6pts with LDH (without DM)	There is a significant positive correlation between fasting plasma glucose values and degree of elastin degradation ($r=0.36$, $p=0.043$). DM pts with SS show a significantly greater loss of elastic fibres (2.3 ± 0.9 vs. 1.5 ± 0.55, $p=0.009$), although fibrosis are similar to control group (1.44 ± 0.7 vs. 1.43 ± 0.88, $p=0.98$). There is no significant difference in the degree of calcification in the SS group between pts with and without DM (1.71 vs. 2.05%, $p=0.653$). Fibre orientation is less homogenous in the SS compared with the LDH group Pts with LDH exhibit less elastin degradation and less fibrosis as opposed to the pts with SS
3.	Chen et al. [25]	A total of 30 rats (1) DM ($n=15$) (2) Non-DM ($n=15$) Histological changes, collagen expression, microvessel density and apoptosis of the IVD were investigated by different methods	The endplate microvessel density is significantly smaller in the DM animals resulting in decline of the blood supply and nutrition to the IVD. Similarly, apoptosis in the DM group is significantly higher and it is correlated with the vessel status of the endplates. In DM rats hyperglycaemia, low oxidative stress and AGEs cause microvessel endothelial cell injury
4.	Stephan et al. [26]	Bovine NP cell cultures under standard culture conditions (with 3.15 g/L glucose and 10% FBS), or without glucose and/or 20% FBS	NP cell growth and survival are influenced both by cell density and the availability of serum or nutrients, such as glucose. In DM type 1, vertebral endplates may become sclerotic, further compromising its permeability to nutrients. These changes are brought about by anabolic effect of DM type 1 on metabolism
5.	Won et al. [27]	Lumbar IVD tissue DM ($n=20$ DM rats: 10 rats 6- and 10 rats 12-month old) versus non-DM rats ($n=20$ non-DM rats: 10 rats 6- and 10 rats 12-month old)	DM is associated with premature, excessive apoptosis of NP notochordal cells in rats accelerating transition of notochordal NP to fibrocartilaginous NP. This leads to IVDD. Activation of extrinsic pathway, expression of MMPs and TIMPs are significantly increased in the NP of DM rats
6.	Kong et al. [28]	Adult NP cells from rats isolated and placed in 10% FBS (normal control) or 10% FBS plus two different high glucose concentrations for 1 or 3 days	High glucose accelerates stress-induced senescence in adult rat NP cells in a dose- and time-dependent manner
7.	Jiang et al. [29]	IVD harvested from DM ($n=15$) and non-DM rats ($n=17$)	Cellular loss from apoptosis and senescence increases about twofold in the NP of DM rats with a shift in the metabolic status of the NP cells (decreased anabolism and increased catabolism). Hyperglycaemia promotes apoptosis by triggering both the extrinsic route, which is mediated by death cell receptors and the intrinsic route, which mobilizes mitochondria and endoplasmic pathways
8.	Park et al. [30]	AF cells were isolated from 4-week-old young rats cultured and placed in either 10% FBS (normal control) or 10% FBS plus two different high glucose concentrations for 1 and 3 days	High glucose concentration-induced oxidative stress accelerates premature stress-induced senescence in young rat AF cells rather than replicative senescence through deteriorative mitochondrial damage. Excessive generation of ROS telomerase activity declines, while expression of proteins related to SIPS (p16-pRB) increases
9.	Park et al. [31]	Notochordal cells isolated from 4-week-old rats, and treated either 10% FBS (normal control) and under two different high glucose concentrations for 1 and 3 days	High glucose-induced oxidative stress accelerates stress-induced senescence in rat notochordal cells. High glucose concentration enhances disruption of mitochondrial transmembane potential and excessive generation of ROS in notochordal cells

Table 2 (continued)

No.	References	Experiment	Results
10.	Park et al. [32]	Rat notochordal cells isolated, cultured, and placed in either 10% FBS (normal control) or 10% FBS plus three different high glucose concentrations for 1, 3, 5 and 7 days	High glucose concentration significantly decreases proliferation and increases apoptosis of notochordal cells via the intrinsic pathway. Expression of MMPs and TIMPs is increased with dose- and time-dependent effects
11.	Kong et al. [33]	NP and AF cells from adult rats cultured in either 10% FBS (normal control) or 10% FBS plus two different high glucose concentrations	Too high glucose significantly increases the expressions of autophagy markers in adult rat IVD cells. Autophagy is regulated by autophagy-related genes light chain protein 3
12.	Park et al. [34]	Rat notochordal cells cultured, and placed in either 10% FBS (normal control) or 10% FBS plus two different high glucose concentrations for 1 and 3 days	High glucose-induced oxidative stress promotes autophagy through mitochondrial damage of young rat notochordal cells in a dose- and time-dependent manner
13.	Chen et al. [35]	NP cells under oxidative stress (in vitro) and puncture-induced rat IVDD model (in vivo). Total rats 40 (no control study)	Metformin attenuates cellular apoptosis and senescence induced by tert-butyl hydroperoxide in NP cells. Autophagy is activated by metformin in NP cells Metformin protects NP cells against apoptosis and senescence via autophagy stimulation in vivo
14.	Tsai et al. [36]	NP cells from DM ($n=5$)/non-DM ($n=4$) rats and humans ($n=3$ DM, 3 non-DM)	The expression of AGEs is significantly increased in DM IVDs. In response to AGEs, increase in MMP-2, RAGE, and (extracellular signal-regulated kinases) ERK at both mRNA and protein expression levels are generated observed in DM NP cells. Hyperglycaemia in DM enhances the accumulation of AGEs in the NP and triggers IVDD
15.	Yokosuka et al. [37]	Immunohistochemical analysis of NP tissues from 15 men and 20 women, aged 32–64 years (mean: 48.6 years), pts undergoing surgery for to IVDD. Healthy tissues from pts with no IVDD were also collected from two males and three females, aged 15–21 years (mean: 17.8 years), who underwent idiopathic scoliosis surgery	AGEs and RAGE are localized in the NP of the IVD. AGEs are found to significantly suppress the expression of aggrecan at both mRNA and protein levels. Accumulation of AGEs and RAGEs results in down regulation of aggrecan production and significant surge of MMP-2 expression at both transcriptional and translational levels
16.	Fields et al. [38]	(1) DM rats ($n=6$ (UCD-T2DM)) (2) Lean, defective pancreatic beta cell islet function and insulin secretion (ZDF-lean) rats ($n=6$) (3) Obese, Sprague–Dawley, OSD rats ($n=6$)	In rat model of polygenic obese T2D, DM, and not obesity, is associated with high levels of AGEs which interferes with several features of matrix homoeostasis, by reducing the ECM GAG and hydration, increasing the expression of hypoxia-inducible genes, catabolic markers and oxidative stress, decreasing the expression of markers of matrix health (Timpl/Col2al). These degenerative changes correlate with increased vertebral endplate thickness and decreased endplate porosity. All these alterations result in disruption of IVD structure and compromise biomechanical integrity. IVDs from DM rats are stiffer and exhibit less creep when compressed
17.	Tsuru et al. [39]	Human herniated discs DM pts ($n=4$), non-DM pts ($n=4$) Human foetal tissue was obtained by therapeutic abortion as control	IVD herniation is associated with high concentration of AGEs apparently linked to increased apoptosis and RAGE located in the macrophages. These factors may contribute to IVDD. This suggests that high concentration of AGEs in DM may precipitate disc herniation
18.	Illien-Jünger et al. [40]	(1) low AGE chow ($n=12$ rats), produced without the use of heat (dMG-) (2) low AGE chow supplemented with synthetic MG-BSA-(AGE precursor) ($n=9$ rats)	dMG + mice exhibited a pre-DM phenotype, as they are insulin resistant but not hyperglycaemic. A diet rich in AGEs contents promotes IVD alterations involving GAG loss, increased cortical thickness, and ectopic calcification in vertebral endplates. These pathophysiological changes promote age-accelerated IVDD. These degenerative changes occur in parallel with insulin resistance supporting the concept that chronic dietary exposure to AGEs can contribute to spinal degeneration

Table 2 (continued)

No.	References	Experiment	Results
19.	Illien-Junger et al. [41]	Non-DM ($n=6$–8), DM ($n=6$–8) or diabetic mice treated with pentosan-polysulphate (anti-inflammatory) and pyridoxamine (AGE-inhibitor)($n=6$–8)	Accumulation of AGEs is associated with increased levels of TNFa, MMP-13, and ADAMTS-5, enhanced catabolism of NP cells, decreased GAG content, and structural alteration in DM IVD. There are important factors in the initiation of IVDD and decreased vertebral bone mass. However, treatment with anti-inflammatory and AGEs-inhibitor drugs prevents or reduces these pathological effects
20.	Song et al. [42]	NP cells were isolated from: (1) Degenerative NP tissues. 15 males and 20 females, aged 32–64 years (mean: 48.6 years), pts undergoing surgery due to IVDD. (2) Controls: Healthy tissues from pts with no IVDD from 2 males and 3 females, aged 15–21 years (mean: 17.8 years), who underwent surgery for idiopathic scoliosis	AGEs induce inflammatory response in NP cells and a degenerative phenotype in a NLRP3-inflammasome-dependent manner related to the receptor for AGEs (RAGE)/NF-jB pathway. Also triggers mitochondrial damage induced by mitochondrial reactive oxygen species (mtROS) generation, mitochondrial permeability transition pore (mPTP) activation and calcium mobilization. Both RAGE and mitochondrial damage primed NLRP3 and pro-IL-1b activation as upstream signals of NF-jB activity, whereas mitochondrial damage is critical for the assembly of inflammasome components. Accumulation of AGEs in NP tissue may initiate inflammation-related degeneration of the intervertebral disc via activation of the NLRP3 inflammasome
21.	Krishnamoorthy et al. [43]	21 female and 23 male mice receiving either a low AGE chow, or high AGE chow Caudal IVDs were used for western blot, histological assessment analysis and for biomechanical testing	High AGE diet results in AGE accumulation in IVD and increased IVD compressive stiffness, torque range and failure torque, particularly for females. These biomechanical changes are likely caused by significantly increased AGE crosslinking in the annulus fibrosus, measured by multiphoton imaging (increased collagen damage measured with collagen hybridizing peptide do not appear to influence biomechanical properties and may be a risk factor as these animals age). High AGEs diets can be a source for IVD crosslinking and collagen damage known to be important in IVDD
22.	Cheng et al. [44]	(1) DM rats ($n=8$) (2) DM + aldose reductase inhibitor ($n=8$) (3) DM rats + p38 inhibitor ($n=8$) (4) Control: non-DM rats ($n=8$)	There is a significant increase of glucose to sorbitol contents in the IVD of DM rats. The Polyol pathway mediates enhance degradation of ECM through activation of p38, aldose reducase, MMPs degradation of MMP-derived aggrecan, and type II collagen degradation related to MMPs. The TIMPs levels are decreased
23.	Segar et al. [45]	Bovine NP cells cultured under varying concentrations of leptin, alone or together with the proinflammatory cytokines TNF-a, IL-1β or IL-6. Responses in relation to production of nitric oxide, lactate, GAG and expression of anabolic and catabolic genes were analyzed	Leptin influences the cellular metabolism leading particularly to greater production of proteases and NO. Addition of leptin to an inflammatory environment demonstrates a marked deleterious synergistic effect with greater production of NO, MMPs and potentiation of proinflammatory cytokine production
24.	Ziv et al. [46]	IVD harvested from young ($n=15$), old ($n=15$), and young DM ($n=15$) rats	Disturbances of IVD PGs by DM can cause biochemical changes responsible for disruption of the collagen network and further inability to withstand osmotic and compressive forces. This processes accelerates IVDD
25.	Silberberg [47]	Vertebral column from DM rats	In DM animals, IVDD is accelerated and a decreased bone turnover was noticed, which was statistically significant only in regard to the length of the trabecular surface covered by osteoblasts In the vertebral column of the rats, the tendency to osteoporosis—age-linked or DM-related is lower due to the influence of local forces which promote osteogenesis

Table 2 (continued)

No.	References	Experiment	Results
26.	Aufdermaur et al. [48]	Histochemical changes in IVD harvested from DM pts, in a cadaveric study with limited number of subjects (4 DM vs. 2 non-DM)	NP of DM pts reveals a significant decrease in hexozamine content, a statistically significant increase of hydroxyproline, and significantly increased activities of four enzymes (β-glucuronidase, β-acetylgalactosaminidase, β-acetylglucosaminidase and uridine diphosphateglucose dehydrogenase) involved in the metabolism of carbohydrates
27.	Jeong et al. [49]	Human NP cells from pts of different ages (35, 42, 55, 66, and 76 yo)(5 subjects)	Human NPCs have a finite in vitro lifespan, which declined with host ageing. Both replicative and stress-induced senescence mechanisms determine their lifespan
28.	Miao and Zhang [50]	NP cells harvested from 30 male rats	Leptin alone upregulated the mRNA expression levels of MMP-1, MMP-13, ADAMTS-4, ADAMTS-5 and COL2A1. Synergy of leptin and IL-β is found in the increased expression levels of MMP-1, MMP-3 and ADAMTS-5. The leptin-treated NP cells exhibit decreased expression of collagen II. The mitogen-activated protein kinase (MAPK) pathway (c-Jun-N-terminal kinase, phosphorylated extracellular signal-regulated kinase and p38), phosphatidylinositol 3-kinase (PI3 K)/Akt pathway and Janus kinase (JAK)2/signal transducer and activator of transcription 3 pathway are all activated by leptin; however, inhibitors of all the pathways, with the exception of the PI3 K/Akt pathway, reversed the expression levels of MMP-1 and MMP-13. Leptin promote catabolic metabolism in the rat NP cells via the MAPK and JAK2/STAT3 pathways, which may be the mechanism mediating the association between obesity and IVDD
29.	Liu et al. [51]	Rat NP cells were activated with resistin with or without p38 mitogen-activated protein kinase (MAPK) pathway inhibition. The expression of a disintegrin and MMPs with thrombospondin motif-5 (ADAMTS-5), was examined	Resistin increased ADAMTS-5 expression in rat NP cells. The p38 MAPK signalling pathway is activated after exposure to resistin. Treatment with p38 inhibitor decreases the upregulation of ADAMTS-5 by resistin. These findings provide novel evidence supporting the causative role of obesity in IVDD, which is important to develop novel preventative or therapeutic treatment in disc degenerative disorders
30.	Kaplan et al. [52]	Human IVD harvested from 30 type II DM pts and 30 non-DM pts (control)	DM, and particular its duration, may play a role in the development of disc herniation by reducing collagen type IX level in the IVD
31.	Jiang et al. [53]	CEP cells are isolated and cultured in 10% FBS, (normal control) or high glucose medium for 1 or 3 days. In addition, CEP cells were treated with 0.2 M glucose for 3 days in the presence or absence of ALA	High glucose significantly increases apoptosis and ROS accumulation in CEP cells. Incubation in too high glucose concentration enhances the expression levels of cleaved caspase-3, cleaved caspase-9, Bax, and cytochrome c but decreases the level of the anti-apoptotic protein Bcl-2. High glucose-induced excessive reactive oxygen species promote mitochondrial damage responsible for apoptosis in rat CEP cells ALA inhibits the expression of cleaved caspase-3, cleaved caspase-9, Bax, and cytochrome c but enhances the expression of Bcl-2. ALA also prevents disruption of the mitochondrial membrane potential in CEP cells. ALA could prevent mitochondrial damage and apoptosis caused by high glucose in CEP cells. Appropriate blood glucose control may be the key to preventing IVDD in DM pts

Table 2 (continued)

No.	References	Experiment	Results
32.	Wang et al. [54]	NP cells harvested from healthy 22 rats cultured in either 10% FBS (control group) or 10% FBS with a high glucose concentration for 3 days Resveratrol or the combination of resveratrol and LY294002 is added into the culture medium of experiment group	High glucose significantly promotes NP cell apoptosis and NP cell senescence compared with the control group. Resveratrol exhibits protective effects against high glucose-induced NP cell apoptosis and senescence. Resveratrol suppress ROS generation and increases the activity of the PI3 K/Akt pathway under the high glucose condition. However, the LY294002 has no significant effects on ROS content in the resveratrol-treated high glucose group
33.	Qi et al. [55]	NP mesenchymal stem cells (NPMSCs)	High glucose significantly inhibits collagen II and aggrecan expression in NPMSCs. After MSC-CM treatment, the expression of these two extracellular matrix components is restored. Exposure to high glucose results in phosphorylation of p38 MAPK, while the levels of total p38 MAPK are not affected. When treated with MSC-CM, phosphorylated p38 MAPK levels of NPMSCs are lower than those without CM treatment. p38 MAPK inhibitor SB203580 can attenuate phosphorylation of p38 MAPK and resume the collagen II and aggrecan expression in NPMSCs. MSC-CM has the potential to alleviate high glucose-induced extracellular matrix degradation via the p38 MAPK pathway and abolish the ruinous effect of high glucose on cell senescence
34.	An et al. [56]	Lumbar IVD harvested from (1) Experimental group − DM rats + vitamin D ($n = 20$) (2) Control group − DM rats + citrate buffer ($n = 20$) (3) Normal group ($n = 15$) − non-DM rats + citrate buffer	Vitamin D improves the content of transforming growth factor b and insulin-like growth factor-1 in the rat IVD. Therefore, vitamin D may have potential therapeutic application in the prevention of IVD in DM pts

DM diabetes mellitus, *Pts* patients, *BP* back pain, *IVD* intervertebral disc, *T2D* type 2 diabetes, *IVDD* degenerative disc disease, *LDH* lumbar disc herniation, *SS* spinal stenosis, *TIMPs* tissue inhibitors of metalloproteinases, *MMPs* metalloproteinases, *NP* nucleus polposus, *AF* annulus fibrosus, *NPMSCs* nucleus polposus mesenchymal stem cells, *FBS* foetal bovine serum, *ROS* reactive oxygen species, *AGEs* advanced glycation end products, *RAGE* AGE receptors, *ERK* extracellular signal-regulated kinases, *MAPK* mitogen-activated protein kinases, *CEP* cartilage endplate cells, ALA alpha-lipoic acid, *PGs* proteoglycans, *GAG* glycosaminoglycan, *ECM* extracellular matrix

the generalized deleterious effects of DM in the connective tissue [24], in diabetic rats, hyperglycaemia, oxidative stress, and AGEs have been blamed for microvessel endothelial cell injury in the vertebral endplate [25]. This pathological occlusion of the microvessels impairs the transportation of nutrients to the IVD [57], interfering with the cell viability (senescence, apoptosis, etc.) [25]. Furthermore, it provokes the accumulation of intradiscal toxic metabolic waste [27, 58] further degrading the IVD matrix. These in turn jumpstart biochemical and molecular changes interfering with IVD matrix homoeostasis in different ways that lead to weakened structural changes and eventually to degeneration.

Cellular senescence, apoptosis, autophagy Senescence, or biological ageing, is a gradual deterioration of cell function. It is traditionally divided into replicative senescence regulated by the p53-p21-RB signalling pathway in a telomere-dependent manner, and stress-induced premature senescence (SIPS) that activates the p16INK4a-RB pathway independently of telomere length. SIPS is the main reason for senescence within degenerative IVD [28, 58]. Cell death is a terminal biological process that is necessary for tissue development and is divided into three main classes: apoptosis, autophagy, and necrosis. Deregulation of cell death is associated with the aetiology, and pathogenesis of many degenerative diseases including IVDD [59, 60].

From the studies highlighted in Table 2, it is apparent that DM can induce or accelerate cellular senescence [61] which can be increased about twofold in the NP of diabetic rats [29]. High glucose accelerates SIPS in adult rat NP cells [28]. AF cells and notochordal cells harvested from young rats exhibit mitochondrial damage (disruption of mitochondrial transmembrane potentials), provoked by hyperglycaemia and excessive generation of reactive oxidative species. Telomerase activity declines, while the expression of proteins related to SIPS by p16-pRB pathway markedly increases [30, 31].

The accumulating senescent cells reduce the ability of the disc to replace the cells lost to necrosis or apoptosis leading to a fewer number of metabolically active cells [4]. It is therefore conceivable that interfering with IVD matrix turnover may lead to its structural failure leading to disc herniation [4].

Cellular loss from apoptosis and senescence of IVD cells plays an important role in the process of IVDD [60]. Apoptosis and senescence are associated with a shift in the metabolic status of the NP cells (decreased anabolism and increased catabolism) [29] that contribute to the degradation of ECM. Similarly, nutrient deprivation and multiple stress stimuli trigger the apoptotic pathways in IVD cells. Hyperglycaemia promotes apoptosis [32] by triggering both the extrinsic route, which is mediated by death cell receptors, and the intrinsic route [29], which mobilizes mitochondria and endoplasmic pathways [29, 32].

DM is associated with premature, excessive apoptosis of NP notochordal cells in a rat model and accelerates the transition of a notochordal NP to a fibrocartilaginous NP, which in turn leads to early IVDD. The expression of the extrinsic pathway (FAS APO-1) [27] and the expression of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are significantly increased in the NP cells of diabetic rats [27]. In this vicious cycle, the presence of degraded ECM components leads to increased MMP production, which in turn generates more degraded ECM components [27].

Autophagy comprises a multi-step process which is highly regulated by autophagy-related genes (ATGs) and light chain protein 3 (LC3) [33]. Autophagy, triggered by hyperglycaemia [29], possibly acts as a protective mechanism against disc cell senescence and apoptosis. High glucose-induced oxidative stress promotes autophagy through mitochondrial damage of young rats' notochordal cells [34]. Hyperglycaemia increases significantly the expressions of autophagy markers, such as Beclin-1, Lc3-II, Atg3, 5, 7, and 12, in adult rat NP and AF [33].

Autophagy is currently considered an important protective mechanism in age-related degenerative diseases [33, 62]. Autophagy is closely associated with apoptosis and shares some of its regulators and molecular events. Autophagy guarantees the fine balance of synthesis, degradation and recycling of cellular components, and is essential for cell differentiation and organ development. In osteoarthritis, autophagy reduces the severity of cartilage degradation in mice [63]. However, studies in different tissues deliver contradictory and inconsistent information on autophagy as a regulator of ageing and degeneration [62, 63].

Cellular senescence and cell death through apoptosis or autophagy, triggered by hyperglycaemia, promote molecular degradation that results in disc degeneration. The dysfunctional microenvironment of the degenerative disc sets in a vicious cycle, characterized by poor nutrition, incapacity to adapt mechanical load, high levels of inflammatory cytokines, and mediators of oxidative stress, further promoting premature senescence and tissue damage [64].

Metformin protects against apoptosis and senescence of the rat NP cells, through activation of autophagy; its administration may have potential protective or even ameliorating effects in IVDD [35].

Biochemical and molecular pathways Other diabetic-related pathways or cellular mediators, such as hyperglycaemia, AGE/RAGE, sorbitol, adipokines, and cytokines acting independently or interactively through oxidative, osmotic, and inflammatory mechanisms, can cause tissue damage leading to IVDD [3]. AGEs are a heterogeneous group of molecules produced from the nonenzymatic reaction of reducing sugars with proteins, lipids, or nucleic acids [36].

Recently, much progress has been made in our understanding of how AGEs alter IVD composition and matrix homoeostasis in diabetes [36].

Brownlee et al. [65] maintained that when blood glucose levels are high, AGEs accumulate and lead to increased tissue damage. The return of glucose levels back to normal does not affect AGEs levels since they are irreversibly bound to collagen and other proteins [65]. Excessive accumulation of the AGEs in DM induces IVDD by causing permanent alterations in ECM components and blood vessel walls [36]. AGEs may begin inflammatory reactions (proinflammatory cytokines and oxygen radicals) and cellular degradation by binding to various cell surface receptors (RAGEs). In vitro, the presence of AGEs and RAGEs in human and rat discs, with increased expression in diabetic discs, results in the downregulation of aggrecan production and in a significant surge of MMP-2 expression at both transcriptional and translational levels [36, 37]. The interaction between AGEs and their macrophage receptor stimulates monokine secretion, which modulates MMPs production and the degradation of the matrix. Furthermore, crosslinking between AGEs and proteins leads to reduced elasticity and tissue stiffness [65].

Accumulation of AGEs is also associated with increased levels of tumour necrosis factor alpha (TNF-α), enhancing catabolism in NP cells and structural alterations in diabetic mice IVD, initiating its degeneration. In a rat model of polygenic obese of type 2 diabetes, DM, but not obesity, is associated with high levels of AGEs, compromising several features of disc structure, matrix homoeostasis, and biomechanical integrity. More specifically, they result in the reduction in ECM glycosaminoglycan (GAG) and hydration content, increased vertebral endplate thickness and decreased endplate porosity [38]. Discs from diabetic rats are stiffer and exhibit less creep when compressed. At the matrix level, DM increases the expression of hypoxia-inducible genes, catabolic markers, and oxidative stress and decreases the expression of markers of matrix health (TimpI and Col2aI) through AGE/RAGE-mediated interactions [38].

An immunohistochemical study of IVD specimens harvested during discectomy reveals the presence of AGE-producing cells in the degenerative and herniated discs. The excessive accumulation of AGEs results in unbalanced tissue homoeostasis and repairs causing tissue damage [39]. Chronic dietary exposure to AGEs promotes age-accelerated IVD alterations involving GAG loss, increased cortical thickness, and ectopic calcification in vertebral endplates [40]. Therefore, restriction of foods rich in AGEs may have preventive effects on IVD degeneration, particularly in diabetic patients.

Other DM-related pathways, such as osmotic stress, the polyol pathway, and adipokines, have been implicated in the development of IVDD [44, 45, 66, 67]. DM significantly contributes to plasma hyperosmolarity and consequently to cellular hyperosmotic state. Hyperosmotic stress is a potent inflammatory stimulus that triggers proinflammatory cytokine release. Cells have employed several adaptive response strategies to restore osmotic balance [68]; however, an increase in extracellular osmolarity results in detrimental effects on cellular function and viability. Hyperosmolarity induces intracellular dehydration, which leads to cell shrinkage and altered protein function. Hyperosmolarity also causes a concomitant expression of p53 and DNA damage-inducible gene activation, leading to cell circle arrest and apoptosis [69]. Cells of the IVD, especially NP cells, respond to environmental osmotic changes by altering their matrix production [68, 70].

DM may also contribute to enhanced IVD matrix degradation through the polyol pathway [44]. Chung et al. [71] believed that elevated oxidative stress caused by glucose metabolism through the polyol pathway, rather than osmotic stress, is the main underlying cause of diabetic disturbance in neural structure.

The polyol pathway mediates enhanced degradation of extracellular matrix. The levels of aldose reductase, p38, MMPs, degradation of MMPs-derived aggrecan, and type II collagen degradation are also increased, while TIMPs levels are decreased [44]. According to Brownlee [24], when intracellular glucose levels become too high, aldose reductase, an enzyme of the polyol pathway, increases susceptibility to intracellular oxidative stress and plays a critical role in the pathogenesis of chronic diabetic complications [24].

At the molecular level, significant changes in IVD proteoglycans have been observed in DM. In sand rats, DM provokes biochemical changes responsible for the disruption of the collagenous network, which becomes unable to withstand osmotic and compressive forces. This event accelerates degeneration of IVD [46, 47]. A cadaveric study reveals a significant decrease in hexosamine content, a significant increase in hydroxyproline, and significantly increased activities of 4 enzymes involved in the metabolism of carbohydrates [48]. Discs harvested from diabetic patients' exhibit PGs with lower buoyant density and a significantly undersulphated GAG content [2].

Obesity Increased adipose tissue mass is associated with alterations in adipokine production (e.g. overexpression of TNF-α, interleukin-6, plasminogen activator inhibitor-1, and underexpression of adiponectin in adipose tissue). These changes of the proinflammatory status support a plausible association between insulin resistance and endothelial dysfunction, the early stage in the atherosclerotic process, in obese individuals and in diabetic patients [72]. Altered adipokine levels, produced by adipose tissue, are seen in obesity in both the absence and presence of diabetes [67]. Obese people are known to have higher concentrations of serum leptin, and IVD cells expressing leptin receptors. Leptin can upregulate proteases involved in degenerative processes in IVD, an effect

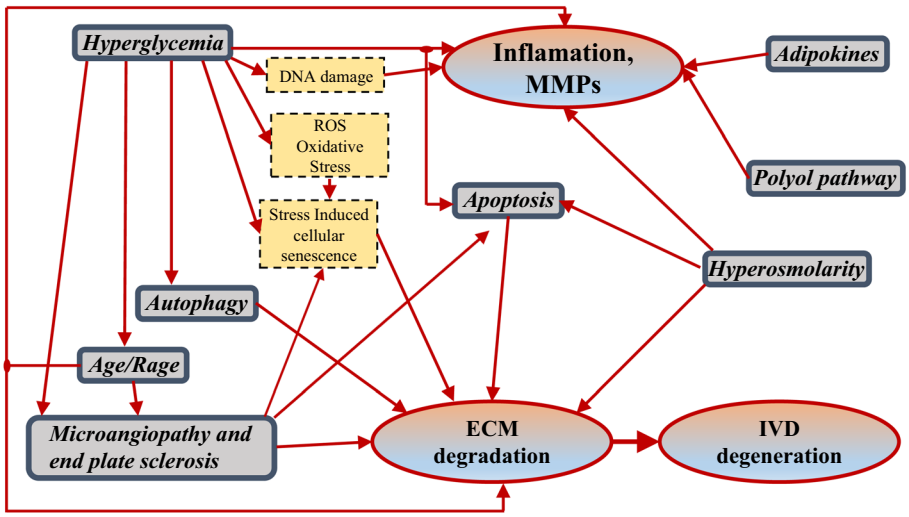

Fig. 1 Multiple aberrant molecular and biochemical pathways in the IVD matrix leading to disc degeneration

that is enhanced in the presence of proinflammatory cytokines such as TNF-α and IL-1b [45]. Because DM is often associated with obesity, it can also indirectly contribute to IVDD.

DM–induced IVD degenerative processes pursue distinct biochemical and molecular degradation matrix pathways. These include: microangiopathy of the subchondral vertebral endplate, cellular senescence/apoptosis, autophagy resulting to cellular death, intracellular hyperglycaemia, AGEs, polyol, and adipokines (particularly when associated with obesity) (Fig. 1).

Conclusion

DM–induced IVDD proceeds along different pathways than the usual pathophysiological process of genetically predisposed and traumatic IVDD, as described in laboratory studies. The laboratory science analyzed in this review is convincingly consistent with the fact that DM interferes with multipronged aberrant molecular and biochemical pathways provoking IVDD. However, the clinical studies only weakly support a relationship between DM and IVDD. Taken together, the strong laboratory evidence and weak clinical studies suggest that diabetes is a contributing factor to IVDD.

Compliance with ethical standards

Conflict of interest The authors state no conflict of interest.

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