A new immunometabolic perspective of intervertebral disc degeneration

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Abstract

Intervertebral disc (IVD) degeneration is a common finding on spine imaging that increases in prevalence linearly with age. IVD degeneration is a frequent cause of low back pain, which is the leading cause of disability. The process of IVD degeneration consists of gradual structural change accompanied by severe alterations in metabolic homeostasis. IVD degeneration, like osteoarthritis, is a common comorbidity in patients with obesity and type 2 diabetes mellitus, two metabolic syndrome pathologies in which adipokines are important promoters of low-grade inflammation, extracellular matrix degradation and fibrosis. Impairment in white adipose tissue function, due to the abnormal fat accumulation in obesity, is characterized by an increased production of specific pro-inflammatory proteins such as adipokines by white adipose tissue and also production of cytokines such as TNF-α by immune cells of the stromal compartment Investigations into the immunometabolic alterations in obesity and type 2 diabetes mellitus (such as chronic low-grade inflammation, hyperinsulinaemia, insulin resistance, hyperglycaemia, vascular inflammation and endothelial dysfunction) and their interconnections with IVD degeneration provide insights into how adipokines might affect the pathogenesis of IVD degeneration, worsen its course and impair IVD function and repair. Toll-like receptor-mediated signalling has also been implicated as a promoter of the inflammatory response in the metabolic alterations associated with IVD and is thus thought to have a role in IVD degeneration. Pathological starvation, obesity and adipokine dysregulation can result in immunometabolic alterations, which could be targeted for the development of new therapeutics.

Introduction

Low back pain (LBP) adversely affects people of all ages and socioeconomic groups, affecting approximately 700 million individuals globally in similar proportions across all continents and cultures [1,2]. LBP interferes with quality of life and is the leading cause of disability as well as being the most common reason for consulting a health care provider worldwide [3,4]. LBP incurs great costs for society, being responsible for >30% of absences from work and causing considerable loss of productivity as well as increasing direct health care costs [4].

LBP is a complex condition with multiple contributors to pain and disability, including biological, psychological and social factors[4]. LBP can arise from many causes, but intervertebral disc (IVD) degeneration has been identified as an important cause[6,7] However, IVD degeneration is not always associated with LBP[141,142]. Spinal degenerative diseases are associated with demographic factors that are increasingly prevalent in the population, including advanced age, obesity, poor diet and occupational risk factors. With ageing, which is one of the primary risk factors for LBP, overuse of and injury to the back over a long lifetime lead to degenerative changes in the IVD, gradually causing the loss of normal spine structure and function and ultimately resulting in pain and disability [8].

IVD degeneration results from a range of molecular, biochemical, cellular and anatomical alterations that arise from external insults, such as mechanical injury and metabolic perturbations, and that change over time [9]. It is possible that IVD degeneration is an adaptive response to these external insults, rather than a disease [4,9]. Nevertheless, the clinical manifestation is a disease, either objective, when observed by a physician, or subjective, when perceived by the patient. Altered cell nutrition as a result of structural alterations to the cartilaginous

endplate (CEP), a thin layer of hyaline cartilage that lies between the vertebra and disc, is considered a main cause of IVD degeneration[10]. Bidirectional crosstalk between the IVD and the adjacent bone marrow determines the microenvironment and pathological progression [11,12].Degradation of the disc extracellular matrix (ECM), and the consequent fibrosis that occurs in the IVD and in the subchondral bone following a cascade of cellular and molecular changes, leads to biomechanical failure of the IVD and surrounding structures[13]. IVD degeneration is thought to occur when the homeostatic balance of the disc environment is lost and a predominantly catabolic and hypoxic microenvironment and a senescent cell profile develops in the IVD [143], with consequent immunometabolic alterations [14,15] (**Box 1**).

IVD degeneration and osteoarthritis (OA) have important similarities. Traditionally, IVD degeneration has been considered a result of age-related 'drying and cracking' of the disc tissues associated with loss of proteoglycan content, which can lead to decreased intravertebral height. In addition, alterations to the CEP might impair the delivery of essential nutrients to the IVD and compromises disc–vertebra crosstalk, with bone marrow oedema playing an evocative (important?) role in the conversion from silent to symptomatic joint degeneration[12]. Similarly, OA has been considered as a 'wear and tear' disease of articular cartilage, but this outdated view has been challenged in the past two decades. There is increasing evidence for the involvement of low-grade inflammation and metabolic disturbances in both OA[16–20] and in IVD degeneration[21–23], shifting the focus of research to the immunometabolic features of disease pathophysiology and the severe alterations in metabolism [24].

In OA and IVD degeneration in the context of obesity, dysfunctional adipose tissue contributes to the creation of a catabolic and detrimental systemic and local environment. Systemic low-grade inflammation is fuelled by high concentrations of pro-inflammatory cytokines and adipokines as well as by high concentrations of sugars and circulating lipids that in turn impair the metabolism of articular chondrocytes and IVD cells [17,23]. Increasing clinical evidence suggests that obesity and type 2 diabetes mellitus (T2DM) are interrelated: obesity is associated with insulin resistance (a hallmark of T2DM) and is one of the main risk factors for T2DM as well as being highly prevalent in patients with the disease [144]. The term 'diabesity' describes the coexistence of both diseases in association with a state of chronic, low-grade inflammation[25,26]. Diabesity is characterized by considerable metabolic alterations, abnormal fat accumulation, dysfunction of white adipose tissue, altered glucose and lipid metabolism and inflammation[27], all of which strongly influence the development of IVD degeneration **(Figure 1).** Indeed, IVD degeneration is more severe in patients with adiposity (overweight and obesity) than in patients with normal weight and normal fat mass accumulation [28]. Furthermore, a Mendelian randomization study determined that BMI has a causal effect on LBP and chronic back pain [29].

In this Review, we focus on the role of immunometabolic alterations that are involved in the pathogenesis of IVD degeneration, drawing on similarities between OA and IVD degeneration and summarizing the current state of knowledge about the role of adipokines in impaired metabolism in IVD cells. As evidence suggests that Toll-like receptors (TLRs) promote the inflammatory response in the metabolic alterations of IVD, their role in IVD degeneration is also

discussed. We also highlight opportunities for future research, such as the opportunity to target metabolic pathways and mediators therapeutically.

Metabolic consequences of IVD degeneration

The metabolic state of the IVD and of articular cartilage is intimately linked to the supply of oxygen and nutrients. Nutrients that support cells in the nucleus pulposus region (Box 1) are supplied by the blood vessels at the IVD margins and diffuse through the ECM of the avascular disc to the nucleus pulposus cells[30]. IVD cells are acutely sensitive to glucose deprivation and lactate accumulation[33]; within the nucleus pulposus region, however, the notochordal cells that are gradually replaced by chondrocyte-like mature nucleus pulposus cells during development are fundamentally different in terms of their nutritional requirements and responses to nutrient deprivation: mature nucleus pulposus cells are far more sensitive to nutritional deprivation[34] . Nutrient supply pathways to the nucleus pulposus can be compromised with ageing[10] and with other comorbidities [30], including atherosclerosis, sickle cell anaemia, Caisson disease and Gaucher's disease, all of which are associated with increased IVD degeneration[31] [32]. Interruption of nutritional supply pathways by systemic and vascular diseases can have with severe consequences for cell metabolism, cell survival, IVD degeneration and even IVD repair. Furthermore, changes in osmotic concentration and mechanical loading also occur in these diseases and are likely to influence IVD cell metabolism even further. Therefore, understanding the nutrition and metabolism of IVD cells is important for the development of strategies to support sustained nutrient supply through the CEP and avoid the nutritional deprivation that is believed to accelerate IVD degeneration[35].

Considering the nutritional complexities of the IVD, it is essential to consider the consequent metabolic changes that occur along with the microenvironmental alterations in IVD degeneration. In the healthy IVD, the CEP is the main route through which essential nutrients diffuse from the peripheral vasculature to the nucleus pulposus [36]. Structural alterations to the CEP are thought to impair IVD cell nutrition, thus inducing cell death while simulating the effects of ECM degradation in the IVD[30]. The strong association between bony endplate damage and LBP has been demonstrated in population-based studies in the TwinsUK cohort[37,38]. MRI can reveal signal intensity changes – so-called Modic changes in bone adjacent to the CEP, characterized by inflammation, high bone turnover and fibrosis[12]. Modic changes are specific to discogenic LBP given the lack of biomarkers to distinguish silent versus symptomatic disc degeneration. Bony endplate damage causes coupling between the disc and vertebra that affects the bi-directional transport of pro-inflammatory and pro-osteoclastic factors, which ultimately leads to the accumulation of damage and 'frustrated healing'[11]. Chronic stimulation of TLRs by ECM fragments leaking from degenerated discs facilitates the conversion of bone marrow to fat, as seen in Modic changes [12]. Therefore, understanding the metabolic changes in the IVD, especially in the CEP, should have a great influence on the development of regenerative and therapeutic strategies for the IVD.

Obesity, adipokines and IVD degeneration

Clinical evidence

Increasing evidence implicates increased body weight and elevated BMI as risk factors for the development of IVD degeneration [29,39,40]. Cross-sectional analysis directly associates high BMI with disc space narrowing and severity of lumbar IVD degeneration[41]; nevertheless, correlations with sex are somehow contradictory [42,43]. Having overweight seems to affect IVD degeneration more profoundly than age or sex[44], as young individuals with obesity have a greater risk of IVD degeneration than those who developing obesity in middle age (40-45 years old)[45]. Single nucleotide polymorphisms (SNPs) associated with obesity and fat mass, namely SNPs rs11076008 and rs1121980, correlate with the onset of IVD degeneration and have been proposed as potential diagnostic and prognostic biomarkers for IVD degeneration [46,47]. However, some studies failed to correlate BMI, fat mass percentage or fat distribution with LBP or progression of IVD degeneration[48,49].

Adipokines

Excessive body weight determines the application of cumulative and repetitive forces on spinal motion segments, in particular in the lumbar spine, that can modify IVD biomechanics and thus favour IVD degeneration. Aside from abnormal mechanical overloading, the dysregulated production of adipokines by adipose tissue in obesity is now recognized as an important contributor to the metabolic and pro-inflammatory pathophysiological pathways affecting IVD homeostasis[23]. Adipokines (**Table 1**), initially described as regulators of energy metabolism, are nowadays recognized as crucial players in the immune system and the inflammatory response[50,51]. Thus, these low-molecular-weight, biologically active peptides contribute to chronic, obesity-associated, low-grade

inflammation, and are implicated in augmented cell apoptosis, autophagy and ECM breakdown in IVD degeneration[21,40] **(Figure 2).** Most published studies have focused on the identification of adipokine receptors, activated signalling pathways and cellular proteome changes in IVD. However, this research has largely been limited to cells and/or tissues from animal models or patients undergoing surgery, and data on clinical aspects, such as IVD degeneration in MRI, is scarce [23]. Also, as far as we are aware, no studies have analysed the correlation between circulating concentrations of adipokines and their local levels in the spines of patients with IVD degeneration. However, several lines of evidence showed that annulus fibrosus and nucleus pulposus cells, cultured *in vitro,* secrete considerable levels of adipokines. Thus, IVD tissues produce adipokines that might affect cell function [22,23]. Further characterization of adipokine molecular signalling pathways and their multifaceted effects on the aetiology and development of IVD degeneration will lead to a more thorough understanding of the disease pathogenesis, supporting the development of much needed new therapeutic approaches for IVD degeneration.

The current understanding of the mechanisms by which adipokines contribute to inflammatory and metabolic processes in IVD degeneration are summarized in the following sections and in Table 2.

Leptin

Owing to the broad expression of leptin receptor (LEP-R; also known as obesity receptor (Ob-R)) in peripheral tissues, leptin, encoded by *LEP* (also known as *ob*), has pleiotropic activity in physiological and pathological states and has been identified as a cornerstone molecule in the interplay between

metabolism and the immune system[50]. Initially described as a metabolic sensor that controls appetite and body weight homeostasis, leptin also regulates inflammation, infection, bone and cartilage homeostasis, insulin secretion, thermogenesis, lipid homeostasis, angiogenesis and reproductive functions[50]. Both leptin and its receptor have been identified in IVD tissues, with increased expression in degenerated discs [52–54]. Local expression of leptin is increased in the posterior compared with the anterior annulus fibrosus, and it is produced by 3D cultured annulus fibrosus cells, highlighting the presence of a local autocrine or paracrine regulatory system in IVD[52,55]. Since its discovery in the IVD, leptin has been implicated in disc cell proliferation, cytoskeletal remodelling and proteome alterations, namely augmenting catabolic and pro-inflammatory mediators of ECM degradation. CEP calcification and degenerative mechanisms in adjacent connective tissues associated with IVD are also influenced by leptin[23].

Leptin augments annulus fibrosus and nucleus pulposus cell proliferation via induction of cyclin D1 and activation of PI3K–Akt, JAK–STAT3 and MEK–ERK signalling transduction pathways[54]. These proliferating cells demonstrate deficient ECM synthesis owing to increased ECM expression of proteolytic enzymes, which contributes in part to the disc cell senescence that underlies IVD degeneration[53,54]. The observation that leptin also induces the expression and organization of cytoskeletal proteins, namely β-actin and F-actin stress fibres, in nucleus pulposus cells through Rho–ROCK–LIMK–cofilin signalling also provides novel insights into the role of leptin in IVD degeneration [56,57].

In bovine and rat disc cells (annulus fibrosus and nucleus pulposus cells), leptin, alone or in synergy with IL-1β, IL-6 or TNF-α, increases the production of nitric oxide and the expression of both pro-inflammatory cytokines (IL-6 and TNF-

α) and ECM-degrading enzymes (namely the matrix metalloproteinases MMP-1, MMP-3, MMP-7, MMP-9, MMP-11 and MMP-13, ADAMTS-4 and ADAMTS-5)[58,59]. The activation of JAK2–STAT3, ERK, JNK, and p38 MAPK signalling pathways is involved in leptin-induced expression of MMP-1 and MMP-13 expression[59]. Furthermore, in nucleus pulposus cells, leptin down-regulates aggrecan levels (at both the mRNA and protein levels) through the p38 MAPK–ADAMTS pathway[60]. Thus, leptin leads to an imbalance favouring catabolic degradative processes, together with a decrease in hydrostatic pressure and increase in shear forces owing to decreased proteoglycan synthesis, all of which contribute to progressive IVD degeneration.

In a rat model of lumbar disc degeneration, leptin is co-expressed in the CEP with markers of CEP calcification and chondrocyte hypertrophy. In particular, leptin increases expression of the osteogenic factors RUNX2 and osteocalcin in a dose-dependent and time-dependent manner, and promotes the mineralization of CEP cells via activation of STAT3 and ERK1–ERK2 signalling pathways [61]. Calcification of the CEP limits nutrient supply and can thus impair disc cell activity and viability. Leptin also induces terminal differentiation of annulus fibrosus cells, as assessed by expression of collagen X and MMP13, through p38 MAPK and ERK1–ERK2 signalling but not through JNK1–JNK2 pathways [62]. In IVD-adjacent tissues, leptin expression is increased in ligamentum flavum tissue of patients with lumbar spinal stenosis, and promotes expression of IL-6 (one of the key mediators of low-grade inflammation) and type I and III collagens in the ligamentum flavum, being positively correlated with its hypertrophy and fibrosis [63].

Adiponectin

Patients with morbid obesity and those with obesity-associated metabolic disease tend to have diminished circulating concentrations of adiponectin, which are restored following weight loss or treatment with the peroxisome proliferator-activated receptor-γ (PPARγ) agonists thiazolidinediones[64]. Specific binding of adiponectin to its receptors AdipoR1 and AdipoR2 enhances insulin sensitivity via AMP-activated protein kinase (AMPK) and modulates fatty acid and glucose metabolism through AMPK, calcium ion, and PPAR-α[65]. Thus, adiponectin has recognized activity in metabolic syndrome and T2DM as well as in the function of immune cells and in cartilage and bone metabolism[66].

Although adiponectin is associated with IVD degeneration, conflicting results in the published literature call into question whether it has a protective or degenerative influence. Circulating concentrations of adiponectin were reported to be increased in patients with lumbar IVD degeneration[67], but a subsequent study indicated that adiponectin is downregulated in nucleus pulposus cells from degenerated human IVD compared with healthy tissue, and adiponectin concentrations in IVD tissue negatively correlated with the severity of IVD degeneration[68]. Differences in adiponectin sources and tissue samples could contribute to such discrepancies. Because IVD tissue is mainly avascular, the serum concentration of adiponectin is likely to be poorly related to its local levels in the IVD. Adiponectin downregulation in the IVD could be related to decreased viability of nucleus pulposus cells or impaired protein synthesis in senescent cells, and could lead to an IVD degeneration-associated inflammatory response[69]. The secretion of adiponectin by both healthy and degenerated

nucleus pulposus cells points to the presence of a local paracrine regulatory system[69]. Published data on adiponectin receptors is also contradictory. Whereas one study reported a gradual reduction of AdipoR1 and AdipoR2 expression with increased severity of IVD degeneration[70], another found their expression increased in degenerated IVD tissues and nucleus pulposus cells, probably attributable to a compensatory mechanism to enhance tissue sensitivity to adiponectin in response to low levels of adiponectin expression [69].

Adiponectin decreased TNF-α production and secretion in a time-dependent and dose-dependent manner, both in human degenerated nucleus pulposus cells and IL-1β–stimulated nucleus pulposus and annulus fibrosus cells from rats, with no effect on IL-1 β-induced IL-6 expression. By repressing the production and release of pro-inflammatory cytokines, adiponectin might contribute to the re-establishment of disc homeostasis and protect the IVD from degeneration [69,70].

Resistin

The dimeric cysteine-rich adipokine resistin promotes insulin resistance and expression of pro-inflammatory mediators via TLR4 binding[71–73]. Resistin concentrations are low in healthy discs and increase during IVD degeneration in a dose-response relationship with the severity of IVD degeneration[74]. Resistin acts in a dose-dependent and time-dependent manner to enhance ADAMTS-5 expression in rat nucleus pulposus cells through activation of the p38 MAPK pathway[75], and in degenerated human nucleus pulposus tissue resistin promotes the expression of CCL4 (also known as macrophage inflammatory protein-1β) by binding to TLR4 [74]. Resistin-induced CCL4 expression occurs via stimulation of

p38 MAPK (but not JNK or ERK) and p65 phosphorylation with consequent NF-κB activation and promotion of CCL4 gene expression, which is required for resistin-induced macrophage attraction by rat nucleus pulposus cells[74]. Thus, the promotion of expression of metalloproteinases and pro-inflammatory mediators, together with macrophage infiltration, could lead to resistin-mediated IVD degeneration.

Visfatin

The homodimeric cytokine-like enzyme visfatin (nicotinamide phosphoribosyltransferase), which limits the biosynthesis of nicotinamide adenine dinucleotide (NAD) from nicotinamide and is likely to be involved in cell differentiation, stress response and apoptosis, is present at increased concentrations in metabolic diseases and inflammation [73]. Visfatin concentrations in nucleus pulposus tissues from IVDs with moderate-to-severe degeneration are higher than in IVDs with less extensive degeneration, strongly indicating a correlation between visfatin concentration and disease severity[76]. Visfatin expression is dose- and time-dependently increased by IL-1β in nucleus pulposus cells. Administration of the visfatin inhibitor APO0866 and knockdown of visfatin expression with short hairpin RNA reveals that visfatin is involved in the IL-1β-induced upregulation of the ECM-degrading enzymes ADAMTS 4. ADAMST-5 and MMP13, and downregulation of the ECM proteins aggrecan and collagen II[76]. Visfatin inhibition also induces nucleus pulposus cell autophagy by increasing the conversion of MAP1A/MAP1B LC3 B (LC3-I) to MAP1A/MAP1B LC3 A (LC3-II) and the expression of beclin-1. Interestingly, inhibition of autophagy blocks the effects of visfatin inhibition on ECM protein expression. Hence, visfatin inhibition

has been proposed as a potential therapeutic approach to protect nucleus pulposus cells from ECM degradation and apoptosis, via autophagy[76].

Lipocalin-2

Through binding to the Gram-negative bacteria siderophore enterobactin, lipocalin-2 (also known as neutrophil gelatinase-associated lipocalin) depletes iron stores and exerts bacteriostatic effects. This glycoprotein has also been implicated in apoptosis of haematopoietic cells, metabolic homeostasis and inflammatory and immune system disorders[77]. Even though it has potential as a biomarker of rheumatic disease, the role of lipocalin-2 in IVD degeneration has been underexplored. In rat annulus fibrosus cells, nerve growth factor (NGF) augments expression of lipocalin-2, which blocks MMP-9 auto-degradation via the formation of stable covalent complexes. Accordingly, NGF stimulation increases MMP-9 protein expression but not *Mmp9* gene expression in annulus fibrosus cells[78,79], suggesting that NGF acts by activating pre-existing MMP-9 and increases the stability of the protein.

Progranulin

Intact progranulin has well-recognized anti-inflammatory activity via its binding to TNF-α receptors, whereas the products of its enzymatic proteolysis, namely granulins, have pro-inflammatory properties[80]. Because progranulin binds to TNF receptor 1 (TNFR1) (linked with pro-inflammatory effects) with an affinity similar to that of TNF-α, and has a higher affinity than TNF for TNFR2 (associated with immunosuppressive action), this cysteine-rich glycoprotein antagonizes the deleterious activities of TNF-α. Thus, the synthesis of the

engineered progranulin-derived protein atsttrin could provide a new therapeutic strategy in the management of rheumatic diseases[80,81].

Progranulin concentrations are elevated in peripheral blood sera and disc tissues of patients with IVD degeneration, and correlate with clinical symptoms[82]. In addition, progranulin co-localizes with activated macrophages and microglia in spinal cord contusions[83]. Progranulin expression is also upregulated in the disc tissue of mice during the ageing process [84]. The mechanisms of action of progranulin in IVD degeneration pathophysiology were nicely revealed in progranulin knockout mice, with effects such as disordered bone metabolism, aggrecan degradation and increased concentrations of MMP-13 and ADAMTS-5, proteoglycan loss in annulus fibrosus and CEP tissues, increased gene and protein expression of inducible nitric oxide synthase (iNOS), and increased activation of NF-κB and Wnt–β-catenin signalling. . Enhanced catabolism in *Pgrn*$^{-/-}$ mice leads to dysfunction in annulus fibrosus and CEP tissues, which substantially affects nutrient diffusion to the nucleus pulposus and accelerates IVD degeneration[84]. Progranulin could also reduce TNFR1-induced production of IL-17 with a consequent decrease in recruitment of type 17 T helper cells, and could increase IL-10 production and anti-inflammatory activity via TNFR2 activation[85]. The protective role of progranulin in IVD degeneration is strengthened by evidence that TNF-induced expression of iNOS, cyclooxygenase-2, IL-6, IL-17 and MMP-13 in human nucleus pulposus cells is inhibited by atsttrin, which has been proposed as a new candidate drug for disc degeneration[86].

Ghrelin

Ghrelin is produced mainly in the oxyntic glands of the stomach. Acting via growth hormone secretagogue receptor type 1 (GHS-R), ghrelin induces the secretion of growth hormone and regulates food intake, gastrointestinal tract motility, adiposity, glucose metabolism, the reproductive axis and anti-inflammatory processes[87–89]. Ghrelin is expressed in tissues and cells harvested from living tissues (primary cells) of human nucleus pulposus and its expression in these cells is down-regulated by IL-1β[90]. Ghrelin counteracts IL-1β-induced catabolism, inflammation (namely expression of ADAMTS-5, MMP-13, iNOS and TNF-α), apoptosis and disorganized proliferation in human primary nucleus pulposus cells and attenuates the expression of MMP-13, ADAMTS-4 and ADAMTS-5 in a rabbit model of IVD degeneration[90]. Ghrelin-mediated protection against IVD degeneration is also supported by the induction of aggrecan, collagen-II and Sox-9 proteins via GHS-R in the rabbit model. Ghrelin also acts via inhibition of the NF-κB signalling pathway by reducing IκB phosphorylation and p65 nuclear translocation and by inducing Akt signalling, which is involved in the anabolic activity of ghrelin in nucleus pulposus cells [90].

T2DM and IVD degeneration

Clinical evidence

The results of several cross-sectional and retrospective studies implicate T2DM as a risk factor for IVD degeneration that correlates with the severity of degeneration[39,40]. In particular, in the Wakayama Spine study, which involved a large, longitudinal population-based cohort, T2DM was associated with IVD degeneration in the upper lumbar spine[91]. Long-standing and poorly controlled

T2DM is also associated with the severity of IVD degeneration [92]. T2DM has also been associated with spinal stenosis, osteoporotic vertebral fractures and IVD herniation[39]. Nevertheless, some researchers correlate IVD degeneration only with T2DM-associated risk factors, such as BMI, age or high levels of LDL cholesterol, but not with T2DM itself[93–95]. Given the vast heterogeneity and differences in the primary objectives of published studies, the causal relationships between T2DM and IVD degeneration are sometimes inconsistent or elusive; therefore, well-designed multicentre clinical studies are needed[39].

Pathophysiological mechanisms

Obesity is the main risk factor for the development of T2DM; therefore, both chronic inflammation and deregulation of adipokine concentrations could contribute to IVD degeneration in patients with T2DM. Nevertheless, preclinical evidence from studies in a rat model of polygenic obesity and T2DM suggests that T2DM, but not obesity, compromises IVD composition, ECM homeostasis and biomechanical behaviour [96], indicating the involvement of obesity-independent mechanisms in T2DM-induced IVD degeneration. T2DM is a highly prevalent metabolic disease characterized by insulin resistance, hyperinsulinaemia, and irreversible formation and accumulation of advanced glycation end-products (AGEs) as an outcome of hyperglycaemia (see **Figure 1**). These biochemical alterations follow pathophysiological changes in the bony endplate and CEP) and contribute to undermining the nutrient supply, cell viability, matrix homeostasis and biomechanical properties of the IVD, leading to structural weakening and, ultimately, IVD degeneration (Box 2) [39].

Bony endplate changes

As the intermediary bed between the vertebra and disc, the bony endplate and CEP provide a passageway for blood, nutrients and metabolic wastes moving to and from the avascular disc's nucleus pulposus and inner annulus fibrosus tissues[97]. Reduced CEP permeability and microvascular density compromises IVD nutrition and hampers cell metabolism and biosynthetic function, thus causing or accelerating IVD degeneration [97].

Given the anabolic activity of insulin on bone [145], T2DM-associated hyperinsulinaemia induces an increase in bone mineral density and osteoblast activity that contributes to bony endplate sclerosis. Concurrently, increased oxidative stress and AGEs derived from T2DM-related hyperglycaemia cause narrowing of the bony endplate microvessels and result in a reduction of microvasculature density[98]. Both endplate sclerosis and vascular injury limit blood flow as well as the passage of nutrients to IVD cells, thereby compromising disc nutrition and the removal of metabolic waste, inflammatory mediators and toxins, with adverse effects on the activity and viability of IVD cells [39,96,99,100].

Cellular apoptosis, senescence and autophagy

The IVD nutrient deprivation and hyperglycaemia observed in T2DM represent cellular stress stimuli that trigger death receptors, as well as endoplasmic and mitochondrial apoptosis pathways, in IVD cells[100–102]. Elevated concentrations of glucose also trigger production of reactive oxygen species, mitochondrial damage and stress-induced premature senescence in annulus fibrosus, nucleus pulposus and notochordal cells[103–105]. Cell senescence diminishes the potential to replace necrotic and apoptotic IVD cells, leading to a

net reduction in metabolically active cells and ECM turnover, which implies a shift towards catabolic ECM degradation, structural failure and the probable development of IVD degeneration[39,106]. Counteracting T2DMs-induced IVD cell senescence and death, hyperglycaemia augments cell autophagy markers, probably as a protective mechanism[100]. Nevertheless, autophagy is closely associated with apoptosis, and a pro-inflammatory and/or catabolic disc microenvironment could set in motion a vicious cycle that leads to IVD degeneration.

Advanced glycation end-products

Produced by non-enzymatic reactions between reducing sugars and amino acid groups in proteins, lipids and nucleic acids, AGEs accumulate and cause tissue damage in patients with T2DM via irreversible changes to ECM components and blood vessel walls [39]. AGEs decrease the hydrophilic charge of ECM glycosaminoglycans, correlated with reduced disc hydration and endplate sclerosis (with endplate thickening and reduced porosity) [96]. AGE-induced changes in the CEP microarchitecture affect the biomechanical behaviour of the IVD; that is, they diminish IVD creep deformation and increase disc stiffness. Concomitantly, the interaction of AGEs with their receptors (RAGEs) is associated with increased production of ROS, expression of pro-inflammatory cytokines as well as genes associated with hypoxia and catabolism, and decreased markers of ECM health (metalloproteinase inhibitor 1 and type II collagen)[96,99]. Moreover, the elasticity of IVD tissue is reduced by protein crosslinking with AGEs[39]. As chronic dietary intake of AGEs contributes to ageing-accelerated alterations to the IVD, including loss of glycosaminoglycans,

increased vertebral cortical thickness and ectopic calcification of bony endplates, restricting intake AGE-rich foods might prevent IVD degeneration in patients with T2DM [107].

Adipokines

Supporting a strict correlation between adipokines, T2DM and the aetiology and development of IVD degeneration, in LEP-R-deficient (db/db) mouse, a well-established model of T2DM, a diminished vertebral bone mass and increased risk of IVD failure were associated with altered mechanical properties, increased intradiscal notochordal band area and increased expression of MMP13 and apoptosis in IVD[108,109]. Patients with T2DM have hyperleptinaemia and down-regulation of adiponectin, which are restored by treatment with anti-diabetic drugs. In particular, sitagliptin, metformin, pioglitazone, liraglutide, and empagliflozin reduce leptin levels[110], whereas the PPARγ agonists thiazolidinediones, such as pioglitazone and rosiglitazone, increase circulating concentrations of adiponectin in both animals and humans[111]. Mounting evidence from preclinical research correlates the pathological expansion of adipose tissue and the associated dysregulated adipokine production with an increase in the risk of developing T2DM mediated by modulation of the underlying pathophysiologic mechanisms, including insulin resistance, vascular inflammation and endothelial dysfunction [112]. Nevertheless, the clinical implications of these associations, in particular their potential implications for diagnosis, prognosis and therapy, have not been fully established.

Leptin and adiponectin can modulate insulin sensitivity by reducing the production of glucose by the liver, increasing fatty acid oxidation and decreasing

triglyceride levels in skeletal muscle [113]. Moreover, converging pathways of insulin and adipokine signalling are responsible for sensing insulin inputs in insulin-responsive tissues[111,113]. Because AdipoR1 and AdipoR2 activate insulin receptor substrate 1 (IRS-1), IRS-2, AMPK, PPARα and p38MAPK, with concomitant translocation of the glucose transporter GLUT4, glucose uptake and fatty acid oxidation, adiponectin replacement therapy or dietary interventions that aim to restore adiponectin secretion by adipose tissue have been suggested as therapeutic strategies for T2DM[111]. Glucose uptake is also increased by omentin and visfatin, which agonistically bind insulin receptor but not insulin-like growth factor 1 receptor, and insulin sensitivity is increased by vaspin, apelin, and omentin (**Table 1**)[113]. Activation of LEP-R induces inhibition of ATP-sensitive potassium channels, phosphodiesterase 3B activation, decrease in cAMP levels and inhibition of phospholipase C-protein c, overall leading to the inhibition of insulin secretion[113]. Ghrelin can modulate insulin receptor signalling as well as inhibit insulin secretion[113]. By contrast, resistin induces insulin resistance, suppresses insulin-stimulated glucose uptake and increases plasma concentrations of glucose, effects that are reversed by administration of anti-resistin antibody [113].

Vascular function is affected by T2DM-associated dysregulation of adipokine concentrations, thus increasing the risk of cardiovascular complications. Leptin, chemerin and resistin have deleterious vascular effects by causing vasoconstriction, promoting the proliferation and migration of smooth muscle cells or inducing expression of prothrombotic and pro-inflammatory factors as well as adhesion molecules [114]. Conversely, adiponectin and omentin have anti-inflammatory as well as endothelium-protective effects through the

inhibition of smooth muscle cell proliferation and migration, enhancement of endothelial nitric oxide-mediated vasodilation or reduction in the expression of adhesion molecules and, thus, leukocyte–endothelium interactions, a critical step in the development of macrovascular and microvascular complications[114].

By governing T2DM-associated insulin resistance and vascular complications, adipokines are evidently critical contributors to T2DM progression, especially in the maintenance of hyperinsulinaemia, hyperglycaemia and microvessel injury, thus contributing to pathophysiologic mechanisms associated with IVD degeneration.

Bacterial infections and TLRs in the metabolic microenvironment of IVD

Toll-like receptors (TLRs) initiate immune responses to bacterial pathogens and are thus crucial to the innate immune systems. TLRs are also activated by TLR ligands that originate from the degradation of host tissue. Emerging evidence suggests that bacterial TLR ligands and ECM degradation products mediate ligand-mediated TLR signalling in the process of IVD degeneration, in response to internal (host-derived) and external (pathogen-derived) signals. Research has shown that anaerobic bacteria are present in a large percentage of painful, herniated discs[115,116] and that discs infected with anaerobic bacteria are more likely to develop Modic changes in the adjacent vertebrae than sterile discs or those with aerobic infections [116]. These observations have led to the development of novel hypotheses about the importance of bacteria in the pathogenesis of LBP[117]. These new hypotheses are contributing to new research to determine whether low-grade bacterial infection, particularly with anaerobic bacteria, can contribute to IVD degeneration and LBP and whether antibiotics

might be used to treat these conditions. Indeed, the first randomized controlled trial, published in 2013, showed that antibiotic intervention was more effective than placebo in patients with LBP and type 1 Modic changes [118, 146].

A systematic review concluded that bacteria are common in the IVD of people undergoing spinal surgery[119]. The analysis found moderate evidence for an association between the presence of bacteria and LBP with disc herniation, and between bacterial infection and Modic changes with disc herniation, and there was modest evidence of a causal relationship between the presence of bacteria and LBP. Whether these microorganisms are found in IVDs as a result of actual infection or because of contamination remains a matter of debate [119]. Among the bacteria implicated in degenerative disc disease and the development of Modic changes are *Cutibacterium acnes*, which are bacteria commonly found in the skin, hair follicles and sebaceous glands [120]. This observation has led to suggestions that long-term treatment with antibiotics that are used for the treatment of acne could be used, albeit cautiously, to resolve symptoms associated with chronic LBP[120]. However, a 2019 randomized controlled trial by Norwegian researchers could not replicate the results of the only previous randomized trial to assess the efficacy of antibiotic treatment in patients with LBP, as treatment with amoxicillin for 3 months did not produce clinically relevant benefits compared with placebo[121].

Anaerobic bacteria in the IVD might stimulate inflammatory pathways through TLRs to further exacerbate disc degeneration. However, it has also been proposed that the altered immunometabolism associated with T2DM and metabolic syndrome can lead to the formation of ECM degradation products that equally have the ability to engage TLRs and activate many of the same

inflammatory pathways as seen during microbial infection[122]. This idea fits perfectly well with evidence emerging from research in OA, suggesting that TLRs are activated in both OA and IVD degeneration, linking mechanical stress, pro-inflammatory cytokines, IVD and cartilage degeneration to pain via increased neurotrophic, angiogenic and nociceptive factors[123–126]. Therefore, TLRs are important players in catabolic cell signalling in the context of IVD degeneration, but their activation need not necessarily occur through bacterial infections. Endogenous TLR ligands, including ECM degradation products, are likely to mediate ligand-mediated TLR signalling in the process of IVD degeneration[127–129].

Conclusions

The classic literature on the physiology of the IVD has established that the acidic milieu of this structure leads to the development of a highly catabolic microenvironment, which has adverse effects on metabolism. Studies from the past 20 years suggest that fibrosis is a feature of IVD degeneration and fibrotic events could be linked to immunometabolic changes, especially in patients with insulin resistance and diabetes mellitus. Having overweight also profoundly affects IVD degeneration. Therefore, the combination of declining oxygen and nutrient supply to the IVD and increasing levels of the pro-inflammatory adipokines reviewed herein alter the phenotype of IVD cells, negatively affecting their metabolic rate. Metabolism is known to be drastically altered in chondrocytes in OA, and aberrant immunometabolism of cells could be a key feature of ECM degradation in many phenotypes of OA[130]. Similar mechanisms may operate in IVD degeneration; the combined effects of pathological starvation

and elevation of adipokines are likely to lead to immunometabolic alterations and these must be studied in greater detail to identify new therapeutic targets which may benefit research on spine and cartilage. Emphasizing the similarities and substantial overlaps between OA and IVD degeneration, rather than their differences, will raise awareness of the many basic, translational and clinical research opportunities at the intersection of OA and IVD degeneration research. Collaboration between clinicians and scientists involved in both fields can provide cross-fertilization of research in order to improve treatments and diagnostics for both conditions [24]. At present, there are no drugs that specifically target immunometabolic alterations in OA and IVD degeneration. However, we know that implementing behavioural changes, increasing physical activity and avoiding obesity and diabesity are the only preventive measures for OA and IVD degeneration. Nonetheless, as far as we are aware, no clinical studies have been performed to assess the targeting of obesity and T2DM. Exploratory analysis of data from the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial suggest that inhibition of IL-1β with a biologic drug originally designed for the treatment of atherosclerosis and thrombosis benefitted patients with OA, suggesting that this therapy could delay total knee replacement[131]. The findings of this analysis support further and more detailed investigation of IL-1β inhibition for the treatment of OA in large and load-bearing joints and of IVD degeneration in the spine. Biologic drugs that inhibit the function of the key adipokines involved in IVD degeneration should be trialled in clinical studies of LBP in the future.

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Author contributions

O.G., V.F., J.P., M.A.G.G., F.L., O.T., J.K. and A.M. researched data for the article. O.G., V.F., J.P., M.A.G.G., F.L., J.K., O.T. and A.M. made substantial contributions to discussions of the content. All authors contributed to writing, reviewing and/or editing the manuscript before submission. [

Competing interests

The authors declare no competing interests.

Key points

- Intervertebral disc (IVD) degeneration is a common comorbidity in patients with obesity and those with type 2 diabetes mellitus.
- Dysregulation of obesity-associated pro-inflammatory adipokines and high concentrations of circulating lipids promote a chronic state of low-grade inflammation and promote extracellular matrix degradation in the IVD.
- Insulin resistance, hyperglycaemia, adipokines, advanced glycation end-products and microvascular alterations negatively affect the IVD metabolic environment in type 2 diabetes mellitus.
- Premature senescence, increased cellular apoptosis and altered autophagic mechanisms perpetuate a catabolic environment in the IVD.
- Therapeutic strategies aimed at counteracting dysregulated pro-inflammatory adipokine production could be effective for the treatment of IVD degeneration.

Box 1: IVD anatomy and physiology in health and disease.

The intervertebral disc (IVD) is a shock-absorbing structure of the spine that has three main components: the inner nucleus pulposus, the outer annulus fibrosus and the cartilaginous endplates (CEPs), which anchor the disc to the adjacent vertebrae (see figure)**.**

The nucleus pulposus is a gel-like, highly hydrated, proteoglycan-rich tissue. The healthy nucleus pulposus generates an intradiscal pressure that separates the two vertebrae, distributing pressure evenly over the two adjacent CEPs. The degenerated nucleus pulposus is an unorganized fibrous tissue that has largely lost its capacity to bind water under compression, resulting in a disc with greatly reduced height. Overall, the nucleus pulposus undergoes the most extensive structural alterations during IVD degeneration.

The healthy annulus fibrosus is a highly organized fibrous structure composed of concentric lamellae of tilted collagen fibres with scattered proteoglycans. In the degenerated IVD, the annulus fibrosus is severely deformed and accumulates structural defects such as axial fractures and edge lesions.

Healthy CEPs are hyaline cartilage structures of uniform thickness that do not protrude into the vertebrae. By contrast, in IVD degeneration, there is an enhancement in microscopic and macroscopic impairment to the CEP. Furthermore, there is a marked increase in the sclerosis of the subchondral bone, similar to degenerated cartilage in OA. These alterations to the CEP, as well as to the vertebral subchondral bone morphology, seem to precede IVD degeneration itself). Overall, the CEP can be regarded as a relevant structure of the disc because damage to the endplate is strongly related to both IVD degeneration and LBP.

Globally, the degenerated IVD differs from its healthy counterpart in that disc height is substantially decreased or depleted owing to ECM depletion, a fibrous and dehydrated nucleus pulposus, severe structural modifications of annulus fibrosus collagen fibres, extensive CEP damage and sclerosis of the subchondral bone. Loss of disc height is a common finding on spine radiographs, and is an indicator of IVD degeneration, which is then followed up with more advanced MRI.

Box 2: T2DM and IVD degeneration

- Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, hyperglycaemia, hyperinsulinemia and accumulation of advanced glycation end products (AGEs). These alterations induce pathophysiological changes to the intervertebral disc (IVD) including decreased nutrient supply, decreased disc cell viability and extracellular matrix degradation.
- T2DM-associated hyperinsulinaemia induces an increase in bone mineral density, leading to endplate sclerosis.
- T2DM-associated increase in AGEs causes microvessel injury, limiting blood flow and nutrient supply to IVD cells as well as reducing the clearance of local inflammatory mediators and toxins.
- High glucose levels induce production of reactive oxygen species, mitochondrial stress and premature senescence in annulus fibrosus and nucleus pulposus cells.
- Hyperglycaemia increases apoptotic mechanisms, decreases autophagic mechanisms and contributes to an inflammatory catabolic microenvironment in IVD degeneration.

Table 1. Overview of adipokines.

Adipokine name	Description	Signalling	Function(s)	Ref.
Leptin	Non-glycosylated cytokine-like hormone of 16 kDa encoded by *LEP* (also known as the obese gene (*ob*). Mainly produced by white adipose tissue, but also by the brain, placenta, skeletal muscle, intestines, bone, and joint tissues.	LEP-R, encoded by *LEPR* (also known as the diabetes gene (*db*)), exists in at least six isoforms (one soluble, four short and one long), which differ in the length of their cytoplasmatic domain. Canonical activation of the LEP-R long isoform by leptin is mediated through JAK–STAT signalling; alternative pathways include ERK1/2, JNK, p38 MAPK, PKC, or PI3K/Akt signalling.	Crucial in appetite and body weight homeostasis, via central signalling at the hypothalamus. Has also been implicated in insulin secretion, lipid homeostasis, thermogenesis, reproductive functions, angiogenesis, infection, inflammation and homeostasis of bone and cartilage.	50
Adiponectin (also known as ACRP30)	244-aa adipokine encoded by *ADIPOQ*. Structurally homologous to complement factor C1q, collagen VIII and collagen X. Produced mainly by adipose tissue but also by skeletal muscle, bone marrow and cardiac tissue. Found in several molecular configurations (trimers, hexamers, and 12-18-monomers forms).	Specific receptors AdipoR1 (prevalent in skeletal muscle) and AdipoR2 (mainly present in the liver). Signal transduction involves AMPK, PPAR-α or PPAR-γ pathways.	Increases fatty acid oxidation and glucose uptake in the muscle and reduces the synthesis of glucose in the liver, and is implicated in metabolic syndrome, cardiovascular complications, osteoarthritis and rheumatoid arthritis.	64
Resistin (also known as ADSF or cysteine-rich secreted protein (FIZZ3))	Cysteine-rich 12.5 kDa protein found as dimers in human blood. It is highly expressed in mononuclear leukocytes, macrophages, spleen, and bone marrow cells.	No specific receptor has been described, but TLR4 was shown to mediate the resistin-induced secretion of pro-inflammatory cytokines (IL-12, IL-6 and TNF-α), probably via CCAAT/enhancer-binding protein (C/EBP)β and NF-κB.	Has been described as a link between obesity and diabetes by promoting insulin resistance. Seems to be involved in musculoskeletal diseases pathology by modulating angiogenesis and	71, 72, 132

			inflammatory environment within the joint.	
Visfatin (also known as NAMPT or PBEF)	Homodimeric 52 kDa cytokine-like peptide that has both extracellular (eNAMPT) and intracellular (iNAMPT) forms	Acts as the rate-limiting enzyme in the biosynthesis of NAD from nicotinamide. No specific receptor has been described.	Likely to be involved in cell differentiation, stress response and apoptosis. Function is still ill-defined, but evidence suggests it has activity in metabolic pathologies, inflammation and musculoskeletal diseases.	133
Lipocalin-2 (also known as neutrophil gelatinase-associated lipocalin)	Multifunctional 25 kDa glycoprotein expressed in white adipose tissue as well as in kidney, human neutrophil granules, immune cells, spleen, liver and chondrocytes	Mouse lipocalin-2 binds to the transporter protein SLC22A17 (24p3R), whereas human lipocalcin-2 binds to megalin/glycoprotein GP330, an LDL receptor.	Has regulatory roles in haematopoietic cells apoptosis, immune system response and metabolic homeostasis. Also described as a sensor of mechanical load and inflammatory status of the joint.	77
Progranulin (also known as proepithelin, PC-cell-derived growth factor, granulin-epithelin precursor or acrogranin)	68-88 kDa cysteine-rich secreted glycoprotein that can be proteolytically cleaved into homologous subunits, in particular granulins and epithelins. Lately recognized as an adipokine, progranulin is also produced by macrophages, epithelial cells and chondrocytes.	Directly interacts with TNF receptors, with greater affinity than TNF-α for TNFR2 (linked to immunosuppressive effects), but comparable to TNF-α in binding affinity for TNFR1 (associated with pro-inflammatory activity).	Implicated in inflammation, wound healing, obesity, and rheumatic diseases.	134
Ghrelin	28-residue peptide hormone mainly secreted by the stomach's oxyntic glands, but also expressed in lung, hypothalamus, ovary, testis and pancreatic islets	Signals via GHS-R	Stimulates food intake and adiposity and regulates glucose metabolism, gut motility, reward behaviour and the immune system, as well as bone and	88, 135, 136

			cartilage metabolism, proliferation and differentiation. Plasma concentrations of ghrelin and LEAP2 (a recently discovered endogenous antagonist of GHS-R) correlate with rheumatoid arthritis pathology.	
Omentin (also known as intelectin-1)	40 kDa protein secreted by omental adipose tissue and highly abundant in human plasma. Newly identified type of calcium-dependent lectin.	Has affinity for galactofuranosyl residues (constituents of pathogens and dominant immunogens).	Suggested to have an important role in the innate immune response to parasite infection, through specific recognition of pathogens and bacterial components. Also implicated in obesity, asthma and Crohn's disease.	137, 138
Vaspin (also known as serpin A12 or visceral adipose-specific serpin)	45 kDa single peptide with a hydrophobic N-terminus belonging to the serine protease inhibitor family. Newly identified adipokine.	Has insulin-sensitizing effects.	Might provide a compensatory response to obesity and its inflammatory complications. Also associated with glycolipid metabolism, blood pressure, apoptosis, diabetes mellitus and atherosclerosis.	138
Apelin	Endogenous peptide encoded by *APLN* and expressed as a 77-amino acid prepropeptide, which is then cleaved into mature a apelin peptide (apelin-36) or a family of shorter peptides (apelin-17, apelin−12 and	Ligand for the orphan G protein-coupled receptor APJ (also known as the apelin receptor), which is closely related to the angiotensin receptor.	Expression of apelin in adipose tissue is increased by TNF-α, and it might act as a pro-inflammatory adipokine that contributes to	139

	apelin−13), which have more potent functionality than apelin-36; a pyroglutamyl form of apelin-13 also showed high activity. **[Au: Please remove this information from here since it is also mentioned in "Function(s)" column]**		vascular wall inflammation.	
Chemerin (also known as retinoic acid receptor responder protein 2 (RARRES2) or TIG2)	Secreted as an inactive precursor, prochemerin, which is activated by proteolytic C- terminal cleavage by neutrophil-derived proteases (elastase and cathepsin G), mast cell products (tryptase), proteases of the coagulation cascade, and certain bacterial proteases at the inflammatory site.	Strong chemotactic adipokine that binds to chemokine-like receptor 1 (also known as G protein-coupled receptor ChemR23). Two other receptors for this adipokine have been described, CCRL2 and GPR1, but their functional relevance is largely unknown.	The chemerin–ChemR23 signalling pathway could serve as a bridge between innate and adaptive immunity, as ChemR23 is expressed primarily by antigen-presenting cells (e.g. dendritic cells), natural killer cells and macrophages	140

ADSF, adipose tissue-specific secretory factor; AMPK, AMP-activated protein kinase; GHS-R, growth hormone secretagogue receptor type 1; LEAP-2, liver-enriched antimicrobial peptide-2; LEP-R, leptin receptor; NAD, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; PBEF, pre-B cell colony-enhancing factor 1; PPAR, peroxisome proliferator-activated receptor; TLR4, Toll-like receptor 4.

Table 2. Adipokines involved in low-grade inflammation and metabolic responses in IVD degeneration

Adipokine	Effects on NP cells	Effects on AF cells	Effects on CEP cells
Leptin	Expression of functional LEP-R ↑ cell proliferation ↑ proteolytic enzyme synthesis ↑ NO production ↓aggrecan levels	Expression of functional LEP-R ↑ cell proliferation ↑ NO production Induces terminal differentiation of AF cells	↑ RUNX2 and osteocalcin Regulates CEP degeneration and ossification through activation of MAPK-ERK signalling
Progranulin	Engineered analogue (atsttrin) inhibits TNF-α-induced expression of iNOS, COX2, IL-6, IL-17 and MMP13	↑ concentrations of MMP13 and ADAMTS-5 ↑ iNOS expression ↑ activation of NF-κB and Wnt-β-catenin signalling	↑ concentrations of MMP13 and ADAMTS-5 ↑ iNOS expression ↑ activation of NF-κB and Wnt-β-catenin signalling
Adiponectin	Conflicting evidence of functional AdipoR1 and AdipoR2 expression ↓ expression in degenerated NP cells ↓ secretion of TNF-α	↓ TNF-α secretion	NR
Visfatin	High concentrations in NP cells with severe degeneration Expression increased by IL-1β Regulates autophagy via LC3-I, LC3-II and Beclin-1	NR	NR
Resistin	↑ concentration with IVD degeneration ↑ expression of ADAMTS-5 and CCL4, thereby increasing macrophage attraction	Low levels in healthy discs increasing with degeneration	NR
Lipocalin-2	NR	Concentration increased by nerve growth factor (in rat AF cells), which blocks MMP9 autodegradation	NR
Ghrelin	Counteracts the catabolic effects of IL-1	NR	NR

AF, annulus fibrosus; CEP, cartilaginous endplate; COX2, cyclooxygenase 2; iNOS, inducible nitric oxide synthase; IVD, intervertebral disc; NP, nucleus pulposus; NR, not reported.

Figure 1. Diabesity, low-grade inflammation and IVD degeneration. Diabesity, which describes the co-occurrence of type 2 diabetes mellitus and obesity, results in a pro-inflammatory systemic environment that promotes insulin resistance, hyperglycaemia and increased production of adipokines, which, in turn, sustain the low-grade inflammation required for activation of Toll-like receptors (TLRs) and the interaction of advanced glycation end products (AGEs) with receptor for advanced glycation end products (RAGE). These events activate multiple catabolic pathways that result in extracellular matrix degradation, decreased cell viability and metabolic dysfunction at the cellular level, thus promoting intervertebral disc (IVD) degeneration.

Figure 2. Adipokines involved in low-grade inflammation and metabolic responses in IVD degeneration. Increased white adipose tissue mass in diabesity results in adipocyte dysfunction, in the form of immunometabolic alterations that increase the production and secretion of leptin. Leptin, as prototypical adipokine, contributes to catabolic effects on the cells within the nucleus pulposus, annulus fibrosus and cartilaginous endplate (CEP), promoting the production and secretion of more leptin and the pro-inflammatory cytokines IL-1β, TNF-α and IL-6 by these cells. Consequently, concentrations of the matrix metalloproteinases MMP-1, MMP-3, MMP-7, MMP-9, MMP-11, MMP13 and ADAMTS-4 and ADAMTS-5 genes are increased, resulting in extracellular matrix degradation, apoptotic cell death and loss of differentiated disc cell function, all of which contribute to disc degeneration.

Glossary

Adipokines: Cytokines derived from adipose tissue that have pleiotropic functions in energy metabolism, immunity and inflammation; most adipokines are augmented in obesity and contribute to the associated low-grade inflammatory state.

Adiposity: The quality or state to accumulate abnormal amounts of fat in the body, especially in the visceral compartment. Adiposity is associated with several secondary diseases, such as type 2 diabetes mellitus, hypertension, cardiovascular diseases, fatty liver and musculoskeletal diseases such as osteoarthritis and intervertebral disc degeneration.

Bony endplate: thin layer of porous bone, containing vessels, that is localized between the vertebral bone and cartilaginous endplate.

Cyclin D1: A protein that regulates cell-cycle progression through the G1 to S phase transition.

Ligamentum flavum: One of a series of ligaments of yellow elastic tissue connecting the laminae of adjoining vertebrae from the axis to the sacrum, forming the posterior wall of the spinal canal.

Metabolic syndrome: A condition characterized by three or more metabolic risk factors (including abdominal obesity, hypertension, dyslipidemia and insulin resistance) and that is linked to increased risk for development of type 2 diabetes mellitus and cardiovascular disease.

Modic changes: Degenerative bone marrow changes seen in the vertebrae on MRI, with type 1 changes appearing as fibrovascular changes (mainly oedema and inflammation) in subchondral bone marrow, type 2 changes representing the conversion of yellow bone marrow to fat and type 3 changes appearing as highly

mineralized, sclerotic bone.

Notochordal cells: Cells of mesodermal origin that form the notochord, a rodlike structure that is the principal longitudinal structural element of chordates and of the early embryo of vertebrates.

Spinal motion segments: A functional spinal unit that represents the focus of biomechanical functioning of the spine, consisting of two adjacent vertebrae, the intervertebral disc and all adjoining ligaments.

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Fig 1

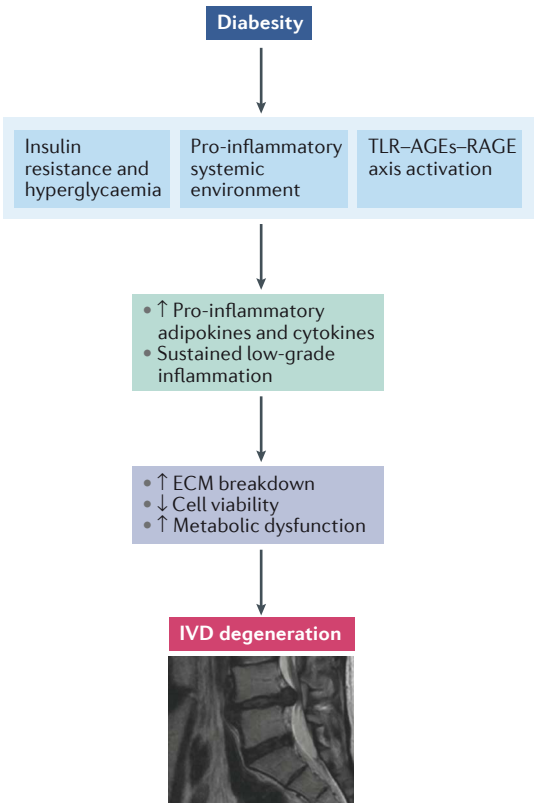
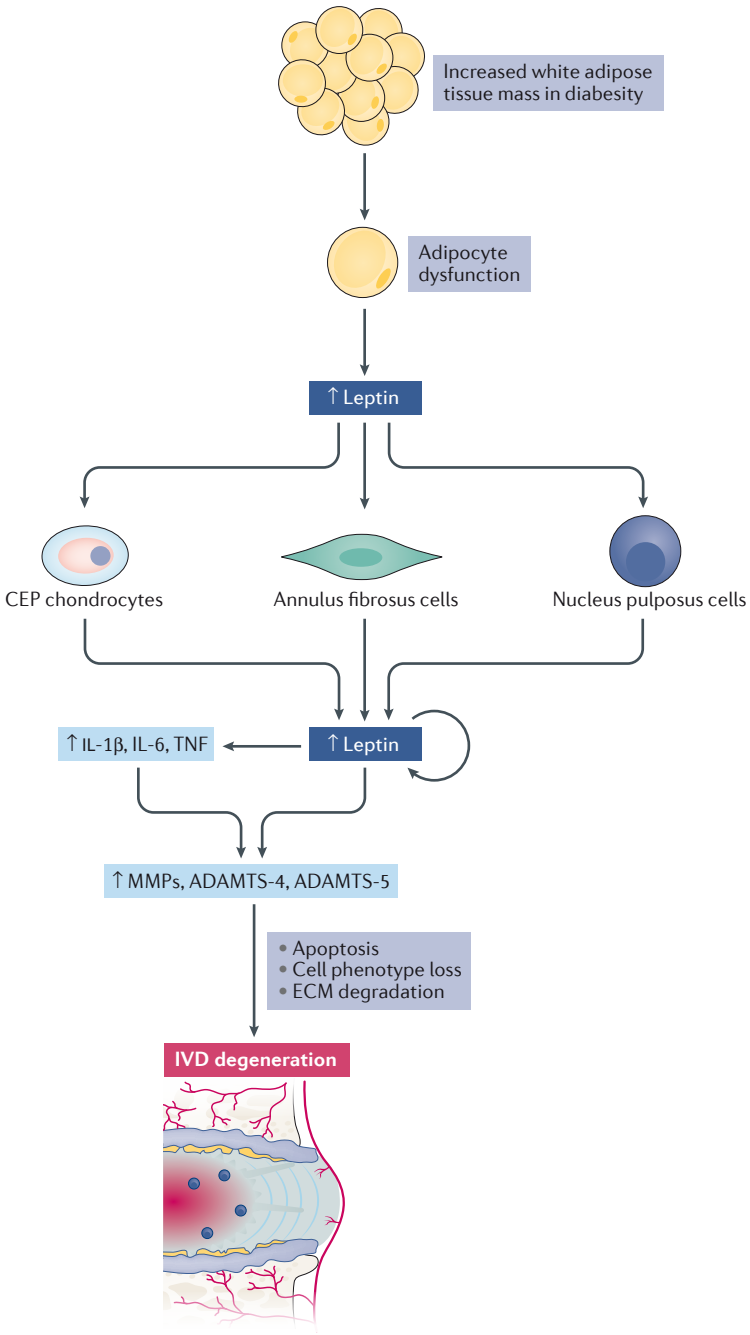
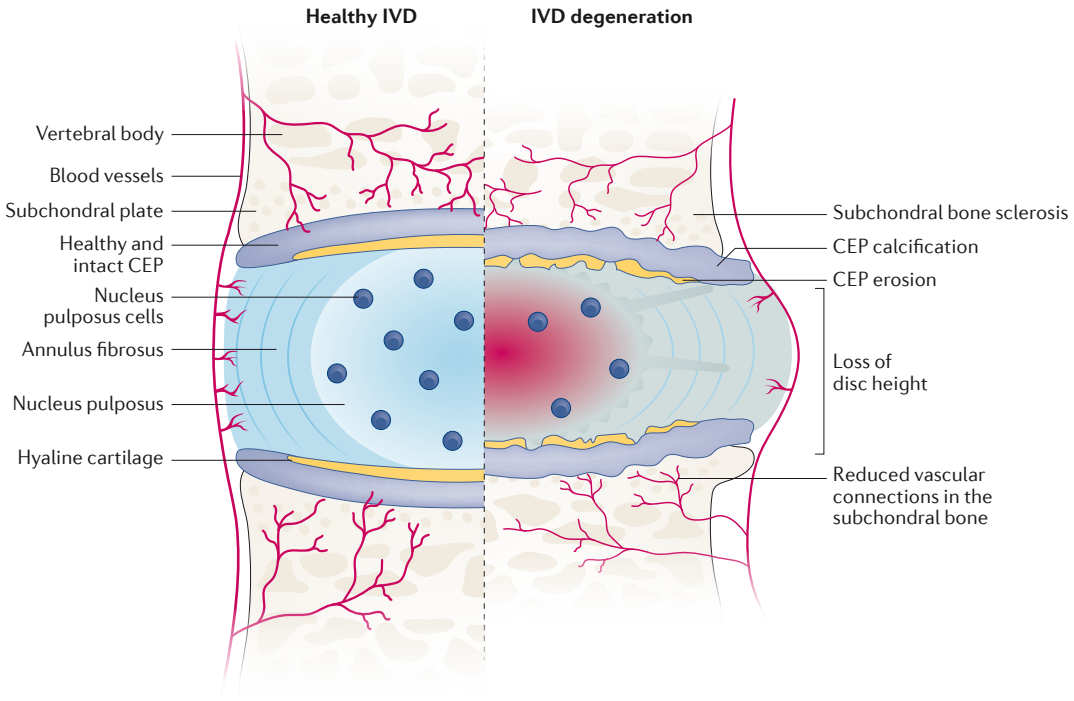

Diabesity
Insulin resistance and hyperglycaemia
Pro-inflammatory systemic environment
TLR–AGEs–RAGE axis activation
• ↑ Pro-inflammatory adipokines and cytokines
• Sustained low-grade inflammation
• ↑ ECM breakdown
• ↓ Cell viability
• ↑ Metabolic dysfunction
IVD degeneration

Fig 2


Increased white adipose tissue mass in diabesity
Adipocyte dysfunction
↑ Leptin
CEP chondrocytes
Annulus fibrosus cells
Nucleus pulposus cells
↑ IL-1β, IL-6, TNF
↑ Leptin
↑ MMPs, ADAMTS-4, ADAMTS-5
• Apoptosis
• Cell phenotype loss
• ECM degradation
IVD degeneration

Box 1 fig


Healthy IVD
IVD degeneration
Vertebral body
Blood vessels
Subchondral plate
Healthy and intact CEP
Nucleus pulposus cells
Annulus fibrosus
Nucleus pulposus
Hyaline cartilage
Subchondral bone sclerosis
CEP calcification
CEP erosion
Loss of disc height
Reduced vascular connections in the subchondral bone