ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: www.ijmacr.com

Volume – 2, Issue – 6, November - December - 2019, Page No. : 164 - 170

Intervertebral Disc Degeneration with Obesity and Type 2 Diabetes.

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Type of Publication: Original Research Paper

Conflicts of Interest: Nil

Abstract

Obesity (OB) and type 2 diabetes (T2D) are among the most prevalent metabolic diseases. They currently affect a substantial part of the world population and are characterized by several systemic comorbidities, including cardiovascular diseases, stroke, cancer, liver steatosis and musculoskeletal disorders, by increasing the risk of developing osteoarthritis and intervertebral disc degeneration (IVDD). IVDD is a chronic, progressive process whose main features are disc dehydration, loss of disc height and changes of load distribution across the spine, resulting in disc structure disruption and leading to low back pain onset. Given the high prevalence of these metabolic disorders and their association with IVDD, several studies have been conducted in order to investigate the causative role of biological and biomechanical characteristics proper to these conditions in the development of IVDD. This review aims to analyze the role of OB and T2D on IVDD, in order to clarify the pathophysiological drivers of the degenerative process and to delineate possible targets to which appropriate treatments may be addressed in the near future.

Keywords: obesity, type 2 diabetes, intervertebral disc degeneration, low back pain, metabolic syndrome.

Introduction

Obesity (OB) and type 2 diabetes (T2D) are pandemic conditions that are raising an alarming interest in Western countries, due to the significant impact on quality of life, social expenditure and life expectancy [1]. These diseases result from the interaction between genetic factors and, most of all, environmental factors and are associated with several systemic alterations as well as musculoskeletal disorders, including osteoarthritis and intervertebral disc degeneration (IVDD) [2] . IVDD is a chronic process that is characterized in part by progressive loss of proteoglycans and water content in nucleus pulposus (NP) the inner part of the intervertebral disc (IVD). This can clinically trigger low back pain (LBP) and progress in multiple secondary disorders, such as disc herniation degenerative spondylosis and spondylolisthesis, spinal instability and spinal stenosis. Indeed, IVDD is considered the primary cause of LBP, which represents the main cause of disability throughout the world [3]. LBP affects nearly 80% of the adult population at least once in a lifetime and is importantly associated with work absence, low quality of life, chronic pain and, as a direct consequence, an excessive socioeconomic burden [4]. Both the aetiology and the pathophysiology of IVDD have

not been fully clarified yet: the main risk factors involved include genetic background and aging, smoking, physical inactivity and overloading [5]. As IVDD results to be common in obese and diabetic individuals, causative and epidemiological correlations between OB, T2D and IVDD have been postulated. OB is a chronic condition in which the excessive accumulation of body fat exerts detrimental effects on the individual's health and it is due to an imbalance between energy intake and energy expenditure. Mechanical overload is a major causative factor that has been imputed as a driver factor for IVDD. In this regard, overweight determines the application of greater forces on motion spinal segments, especially on the lumbar spine, hence favoring IVDD even in young individuals [6]. Moreover, changes in disc microenvironment as a consequence of increased systemic inflammation that may lead to enhanced cell apoptosis, autophagy and matrix breakdown have been also considered as obesity-related factors in IVDD development [7]. Diabetes mellitus (DM) is a metabolic disease characterized by elevated glucose blood levels, due to a deficiency of insulin secretion and/or insulin resistance. DM can be classified in two main forms: type 1D, caused by pancreatic β-cell destruction on an autoimmune basis, associated with an absolute insulin deficiency; type 2D, initially characterized by insulin resistance with a consequent progressive loss of insulin secretion. DM is associated with severe systemic complications, including diabetic macroangiopathy (stroke, coronary heart disease and peripheral vascular disease) and microangiopathy (diabetic neuropathy, nephropathy and retinopathy), as well as with several alterations in connective tissues, including bone, cartilage and the intervertebral disc [8]. To date, nearly 90% of diabetic individuals are affected by T2D, whose development is part of a continuum encompassing OB, metabolic syndrome and T2D itself. Many of the environmental risk factors shared by OB and T2D can be prevented through prompt lifestyle changes. In this regard, a recent study has reported that long distance fast walking and slow running were associated with higher disc height and signal intensity in the nucleus pulposus (NP) regions at T2-weighted MRI evaluation of the lumbar spine. This clearly indicates that physical exercise may improve disc health thus ameliorating or potentially restoring physiological biomechanics in the spine [9]. Increasing evidence suggests that OB, T2D and their metabolic consequences may encourage IVDD. The purpose of this review is to investigate the connections between these metabolic diseases and IVDD for a better understanding of how these disorders may impair disc structure and function. Intervertebral disc degeneration The intervertebral disc (IVD) is a fibrocartilaginous structure located between two adjacent vertebrae and is crucial for providing loading support to the axial skeleton, while still allowing for shock absorption and force distribution across the spine during flexion, extension, bending and rotation movements. IVD consists of three specialized tissues: the annulus fibrosus (AF), the nucleus pulposus (NP) and the cartilaginous end-plate (CEP), which connects the disc with the contiguous vertebral bodies [10]. The AF is a fibro-cartilaginous ring constituting the external part of the IVD: it is divided into outer AF and inner AF. Outer AF is mainly composed of strictly organized type I collagen fibers, oriented radially and in opposite directions throughout concentric lamellae, among which an interlamellar matrix is interposed. It hosts fibroblast-like cells, which are primarily responsible for type I collagen, proteoglycans and non-collagenous proteins (such as elastin) production, thus providing the matrix with an efficient interlamellar cohesion . The NP is a less structured, gelatinous matrix rich in proteoglycans and randomly oriented type II collagen fibers, among which NP cells, a chondrocyte-like cell population,

responsible for the matrix maintenance, can be sparsely found. Proteoglycans are complex macromolecules containing a core protein with several covalently bound glycosaminoglycans (GAG), highly hydrated repeating disaccharides [11]. Aggrecan is the major non-collagenous component of the disc. It is a large proteoglycan with the ability to interact with hyaluronan and to form large aggregates, providing the disc with its own unique mechanical and chemical properties. IVDD is an aging process characterized by progressive loss of proteoglycans and free water content in the NP that is responsible of its original biomechanical properties [12]. Several studies have reported their upregulation in different conditions including mechanical overload, inflammation and genetic predisposition (many of which are present in obese and diabetic patients). The pathophysiological basis of IVDD still remains poorly understood. It usually develops in decades, and its first clinical presentation is commonly LBP; other degenerative disorders of the IVD linked with IVDD are disc herniation, degenerative spondylolisthesis, spinal stenosis and segmental instability; these conditions are often associated with neurological symptoms, including radiculopathy and myelopathy. Treatment of discogenic LBP consists of conservative and surgical procedures: both have demonstrated poor efficacy because they do not alter the pathophysiological cascade leading to IVDD, thus slowing the degenerative process instead of arresting or reversing it [13]. Obesity and Intervertebral Disc Degeneration OB is defined as an abnormal or excessive fat accumulation that presents a risk to health. According to the last WHO report, there are more than 1.9 billion adults being overweight and over 600 millions of these people being obese in the world population [14]. OB development is associated with several predisposing conditions, including genetics (mostly polygenic factors involving the regulation of energy balance, distribution and metabolism of nutrients) and their interactions with different behavioural and environmental factors, most commonly excessive food intake and a sedentary lifestyle. Elevated BMI, in particular being overweight or obese, may favour the development of IVDD through the mechanical overloading of spinal segments but, to date, this association remains largely a matter of speculation, with several studies providing conflicting evidence against such a link [15]. Okada et al. have shown that IVDD in the cervical and thoracic regions did not have significant correlation with BMI, while Samartzis et al. reported that IVDD in the lumbar region was significantly associated with overweight. In this study, the risk of developing IVDD was 1.3- fold and 1.8-fold higher in overweight and obese individuals, respectively. Similarly, a metaanalysis on the association between obesity and lumbar IVDD showed that overweight was importantly associated with degeneration of the lumbar spine, with a higher impact than age and sex. Furthermore, BMI directly correlated with the severity of IVDD and the number of levels involved. Interestingly, Liuke et al. found that having been obese at a young age (25 years old) increased the risk of IVDD more than developing OB later in middle age (40-45 years old) [16]. In contrast to aforementioned studies, a cross-sectional population analysis found that BMI, percent of fat mass and a greater accumulation of fat around the hips were only weakly associated with chronic LBP. Moreover, such influence disappeared when shared environmental and genetic background were taken into account by pairing monozygotic and dizygotic twins in the study. However, the associations between overweight or OB and the extent (i.e., the number of lumbar levels with IVDD) and the severity of IVDD of the lumbar spine remain unknown because previous studies have failed to quantitatively assess such parameters on advanced imaging. These inconsistencies can be attributed primarily to the lack of large epidemiologic studies, proper study design, insufficient statistical analyses, incongruity among

the modes of radiographic/imaging assessment used in defining the phenotype of IVDD and/or conjectures arising from limited radiographic interpretation of additional spinal findings (e.g., Schmorl's nodes and MODIC changes) that may contribute to the degenerative process . In addition, it must be stated that the different biomechanical stresses exerted on the cervical and lumbar segments in presence of a high BMI may differentially contribute to IVDD pathogenesis in such regions, suggesting that these should be independently investigated. Apart from biomechanical factors, IVDD in obese individuals may be also promoted by the effect of specific molecules released by adipose cells. Indeed, it is well known that the adipose tissue also plays an endocrine function through the secretion of proinflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), as well as hormones such as leptin, adiponectin and resistin (also known as "adipokines"). Collectively, these molecules have been reported to exert a catabolic effect on IVD tissues by directly acting on disc cells, which are provided with specific receptors both in the NP and AF [17]. Serum IL-6 levels have been reported to be associated with the onset and progression of IVDD. In a preclinical study, Miyagi et al. detected elevated levels of IL-6 in the serum of rats with IVDD. On a larger scale, a meta-analysis of clinical studies from Deng et al. have shown that IL-6 levels were consistently higher in disc bulging tissues, as compared with normal IVD tissue. Furthermore, IL-6 expression was demonstrated to increase with disease severity, thus suggesting that this cytokine may play a decisive role in IVDD progression. IL-6 levels in the peripheral blood also increase with BMI and OB in absence of other diseases [18]. Type 2 Diabetes and Intervertebral Disc Degeneration Globally, 425 million adults aged between 20 and 79 years were living with DM in 2017.

The largest numbers of diabetic people were estimated to be located in South-East Asia and Western Pacific Regions, accounting for approximately half the DM cases in the world. Worldwide, the number of people with DM has substantially increased between 1980 and 2017, rising from 108 million to current numbers that are approximately four times higher. T2D accounts for nearly 90% of total cases of DM. It is caused by an interaction among several factors, including age, race and lack of physical activity, but the most important risk factor for this condition is represented by an increased BMI: in fact, the classic phenotype of the patient with T2D is characterized by overweight or obesity and this condition causes the onset of insulin resistance. Apart from macrovascular and microvascular complications, T2D has been associated with several connective tissue alterations, including bone and cartilage. Indeed, skeletal conditions are common in diabetic individuals, such as fractures, spinal stenosis, ossification of the posterior longitudinal ligament, decreased disc height, and bone mineral density (BMD) decrease. In this regard insulin, as a major anabolic hormone also involved in bone formation, plays a fundamental role. In a rat model of T2D hyperinsulinemia, which is typical of the first stages of the disease, has been associated with increased bone mineral density (BMD) due to insulin anabolic and mitogenic effects on osteoblasts, even if neosynthesized bone quality resulted poorer [19]. A study by Chen et al. has documented that diabetic rats showed reduced size and density of microvessel cavities of the CEP when compared to the control group. The major transportation route for nutrients to the IVD passes through the bone marrow cavities inside the vertebral body and then in the capillaries of the CEP [20].

In this regard, IVDs may be particularly susceptible to the vasculopathy and neuropathy associated with DM, which may hinder the diffusion of nutrients and oxygen from capillaries that penetrate the CEP through the vertebral body towards the disc itself. Therefore, IVD nutrition might be significantly affected in DM. Hyperglycaemia can exert a direct detrimental effect on disc cell viability. Won et al. have showed that high blood glucose in diabetic rats led to increased and premature apoptosis of disc notochordal cells and transition to a fibrocartilaginous matrix with IVDD development. Similarly, a recent study concluded that exposing rat CEP cells to a high-glucose medium in vitro resulted into increased reactive oxygen species (ROS) accumulation, mitochondrial damage and subsequent cell apoptosis [21]. Conversely, the exposure of NP cells to resveratrol, a natural phytoalexin contained in peanuts and grapes, has shown to reduce high glucose-mediated cell apoptosis, senescence, oxidative stress and matrix breakdown, thus suggesting a protective effect towards IVD cells in an animal model48. Likewise, N-cadherin (N-CDH) overexpression obtained through lentiviral transfection of NP cells resulted in an attenuation of cell senescence and ROS content under high glucose conditions in vitro. N-CDH is an adhesion molecule highly expressed by healthy NP cells but downregulated in IVDD and is committed to sustain matrix synthesis and to protect against apoptosis. Increased cell autophagy has also been documented as a consequence of high glucose-induced oxidative stress. Indeed, Chen et al. showed that the administration of metformin, a first-line antidiabetic drug, reduced cell apoptosis of NP cells in vitro by activating autophagy (which might be induced as a self-defense mechanism under physiological conditions) and by slowing IVDD progression in vivo [22].

One of the major biochemical landmarks in DM is the increased production of advanced glycation end product (AGEs), a heterogeneous group of molecules derived by a nonenzymatic reaction that occurs between sugars and free amino groups of proteins, lipids and nucleic acids; the most known example of AGEs is glycated haemoglobin, which represents one of the parameters that allows to monitor blood glucose control over a 3-month period in diabetic patients. Chronically elevated blood glucose concentration and formation of AGEs in diabetic individuals have showed to yield catabolic effects on disc cells.

Discussion

DM and OB are ubiquitous conditions whose incidence in Western countries is continuously increasing, with startling repercussions on affected individuals' lifestyle and state of health. These disorders result from the interaction between genetic factors and, most of all, environmental factors including physical inactivity, sedentary life and high food intake. The latter factors, together with the metabolic alterations that characterize the aforementioned conditions, are thought to facilitate the development of IVDD. Hyperglycaemia resulting from DM impairs disc metabolism both directly and indirectly, by diminishing cell glucose uptake and via the accumulation of AGEs respectively. These products favor CEP vessel microangiopathy thus hampering nutrient diffusion to disc tissues and leading to significant changes in extracellular matrix composition. Moreover, high AGE levels activate inflammatory pathways that enhance matrix breakdown by upregulating metalloproteinase activity. Disruption of disc inherent metabolism greatly impacts on cell viability by accelerating apoptosis, autophagy and senescence. OB, which often concurs with T2D, may further boost this process due to the mechanical overload exerted on spinal segments along with the effect of specific adipose-secreted cytokines that may impair disc

cell metabolism and viability. Collectively, these alterations eventually result in IVDD. However, given the existing continuity between OB and T2D because of shared risk factors and pathophysiological background, it is difficult to clearly distinguish how the specific features of each condition discretely contribute to IVDD. Conclusion IVDD is thought to be the main cause of LBP, which is a common, disabling and expensive condition affecting nearly every individual, especially in the adult life. The incidence of LBP and IVDD seems to be higher in obese and diabetic individuals: several studies have demonstrated the existence of biomechanical and biochemical stimuli that may boost IVDD development in individuals affected by OB and T2D. While several mechanisms have been described, including excessive biomechanical stress, adipokine-mediated inflammation, vertebral microstructure alterations and toxicity of AGEs in disc tissues, it remains difficult to state whether IVDD could develop indifferently with either disorder or if it is a result of the common pathogenic background shared between OB and T2D. In this regard, additional studies are needed to further delineate the role of these conditions in favoring IVDD. IVDD is a multifactorial process, more effort is required to investigate the direct effect of OB and T2D on the disc environment as well as how inflammation, matrix breakdown, cell senescence and apoptosis specifically occur within the IVD in such conditions. On the other hand, it is necessary to design proper population studies to better understand the epidemiological associations among OB, T2D and IVDD. Nonetheless, urgent interventions are needed to antagonize the increasing impact of OB and DM on public health, in order to prevent not only discogenic back pain, but also systemic conditions.

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