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AN ANALYTICAL REVIEW OF CONTRIBUTORY FACTORS IN INTERVERTEBRAL DISC DEGENERATION

REVISÃO ANALÍTICA DOS FATORES CONTRIBUINTES PARA DEGENERAÇÃO DE DISCO INTERVERTEBRAL

REVISIÓN ANALÍTICA DE LOS FACTORES QUE CONTRIBUYEN A LA DEGENERACIÓN DEL DISCO INTERVERTEBRAL

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ABSTRACT

Objective: To summarize current trends in the pathogenesis and management of disc degeneration and suggest areas where more research would be of benefit. Methods: The available literature relevant to Lumbar disc degeneration (LDD) was reviewed. PubMed, MEDLINE, OVID, EMBASE, Cochrane, and Google Scholar databases were used to review the literature. Institutional Review Board approval was not applicable for this study. Results: This article summarizes trends in the pathogenesis and factors associated with disc degeneration. Conclusions: The genetic contribution to lumbar disc degeneration is a newer concept, still being researched in different populations around the world. Investigators have demonstrated a familial predisposition in the etiology of lumbar disc degeneration. The effect sizes of most genetic variants are small and, thus, individual gene-environment studies must have very large sample sizes to provide compelling evidence of any interaction. ***Level of evidence; Narrative review of available literature.***

Keywords: Epidemiology; Genetics; Aging; Environment.

RESUMO

Objetivo: Resumir as tendências atuais da patogênese e do tratamento da degeneração do disco e sugerir quais áreas de pesquisa seriam benéficas. Métodos: A literatura disponível relevante para degeneração do disco lombar foi revisada. Os bancos de dados PubMed, MEDLINE, OVID, EMBASE, Cochrane e Google Scholar foram usados para revisar a literatura. A aprovação do Comitê de Ética em Pesquisa não se aplica a este estudo. Resultados: Este artigo resume as tendências da patogênese e os fatores associados à degeneração do disco. Conclusões: A contribuição genética para a degeneração do disco lombar é um conceito mais recente, que ainda é pesquisado em diferentes populações ao redor do mundo. Os investigadores demonstraram uma predisposição familiar na etiologia da degeneração de disco lombar. Os tamanhos de efeito da maioria das variantes genéticas são pequenos e, portanto, os estudos individuais de ambiente genético devem ter tamanhos de amostra suficientemente grandes para fornecer evidências convincentes de qualquer interação. ***Nível de evidência; Revisão narrativa da literatura.***

Descritores: *Epidemiologia; Genética; Envelhecimento; Meio Ambiente.*

RESUMEN

Objetivo: Resumir las tendencias actuales de la patogénesis y del tratamiento de la degeneración discal y sugerir qué áreas de investigación serían beneficiosas. Métodos: Se revisó al literatura dispobible sobre degeneración discal. Se utilizaron las bases de datos PubMed, MEDLINE, OVID, EMBASE, Cochrane y Google Scholar para revisar la literatura. La aprobación del Comité de Ética en Investigación no se aplica a este estudio. Resultados: Este artículo resume las tendencias de la patogénesis y los factores asociados a la degeneración discal. Conclusiones: La contribución genética a la degeneración del disco lumbar es un concepto reciente, que todavía se encuentra en estudio en diferentes poblaciones de todo el mundo. Los investigadores han demostrado una predisposición familiar en la etiología de la degeneración del disco lumbar. Los tamaños de efectos de la mayoría de las variantes genéticas son pequeños y, por lo tanto, los estudios individuales del entorno genético deben disponer de tamaños de muestra lo suficientemente grandes como para proporcionar pruebas convincentes de cualquier interacción. ***Nivel de evidencia; Revisión narrativa de la literatura.***

Descriptores: *Epidemiología; Genética; Envejecimiento; Ambiente.*

INTRODUCTION

Disc degeneration is extremely common. Nonetheless, even today, a universally accepted definition of disc degeneration has proved elusive. There is disagreement in the literature regarding the definition.[1]

The process of disc degeneration is an aberrant, cell-mediated response to progressive structural failure. Structural failures along with advanced aging are the signs of disc degeneration. Early degenerative changes usually represent accelerated age-related changes in a

Study conducted at the PGIMER, Chandigarh, India.
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structurally intact disc. Degenerative disc disease is a term that should only be applied to degenerated discs that cause pain. The underlying cause of disc degeneration is the tissue weakening, which occurs because of a combination of factors, including genetic inheritance, body aging, nutritional compromise, and loading history. Intervertebral disc (IVD) degeneration is characterized by the presence of osteophytes, the narrowing of the disc space, and endplate sclerosis. Reported risk factors for IVD degeneration include age, genetic factors, cigarette smoking, work history, lumbar spine disorders, impaired metabolite transport, altered levels of enzyme activity, cell senescence and death, changes in matrix macromolecules and water content, structural failure, and neurovascular ingrowth.[1]

About 33% of lumbar disc degenerations (LDD) are seen in asymptomatic individuals. The greatest risk factor is genetic inheritance, which accounts for approximately 50–70% of the variance in disc degeneration observed in identical twins.[2,3]

The objective of this study was to summarize current trends in the pathogenesis and management of disc degeneration by conducting a narrative analysis of relevant works published between 1990 and 2021, and suggest areas where more research would be of benefit.

METHODS

An electronic search was conducted using the PubMed, MEDLINE, OVID, EMBASE, Cochrane, and Google Scholar databases. Publications written in English and published between January 1990 and January 2021 were selected for this review. The following keywords were used to retrieve the articles relevant to the topic: "risk factors" AND "association" AND "intervertebral disc degeneration" OR "lumbar disc degeneration" OR "cervical disc degeneration' OR "thoracic disc degeneration."

Articles were screened based on various inclusion and exclusion criteria. Additional manual searches were conducted based on the references contained in the selected articles. An additional reviewer was available to resolve any disagreements that arose. Studies mentioning factors associated with intervertebral disc degeneration were included. Case reports, review articles, technical reports, abstract-only publications, and thesis dissertations were excluded.

Ethical approval was not applicable for this study.

RESULTS

A total of 6,878 abstracts were found, and all abstracts were analyzed by the study group. Eleven articles met the inclusion criteria, mentioning risk factors for intervertebral disc degeneration. Demographic data, clinical data, article type, and population studied for each selected article were recorded in a spreadsheet.

Several factors, such as age, sex, environment, genetics, and lifestyle, appear to be associated with disc degeneration.

The radiological characteristics of lumbar disc degeneration (LDD) are almost universal in older adults. However, degenerative disc disease is a major cause of low back pain even in younger populations, with increasing incidence rates for both LDD and low back pain (LBP).[4]

Van Tulder et al., conducted a systematic review and found the presence of lumbar disc degeneration (LDD) to be a risk factor for back pain in adults with odds ratios ranging from 1.3 to 3.2. However, the methodological quality was low, presenting a high level of heterogenicity due to gender frequencies, age groups, radiographic grading systems, and definitions for LDD.[5]

Genetics

The IVD content is determined by specific genes, including COL1A1, COL9A2, MMP3, and VDR. Polymorphisms of these genes can result in defective discs, which can lead to IVD disease.[6]

Traditional wisdom states that an IVD becomes less hygroscopic with advancing age and that the resulting dehydration leads to disc degeneration. Contrary to earlier points of view about the etiology of this condition, current trends focus more on genetic factors and suggest that commonly indicated environmental factors have only very modest effects. Linkage analysis conducted by various investigators has demonstrated a familiar predisposition in the etiology of LDD.[7,8]

Abnormalities in the genes responsible for the structure and characteristics of extracellular matrix components, inflammatory mediators, and protein metabolism are all possible causes.[9] Genome-wide association studies have implicated several abnormal gene loci (e.g., COL1A1, COL 9A2 & 9A3, COL 11A2, IL-6, IL-1, VDR, Aggrecan, and MMP3) in pathogenesis. Population studies have also associated the COL1A1, COL9A2, MMP3, and VDR genes with LDD in various ethnic populations. The association between COL9A2 and LDD has also been noted in a recent Indian study, in which individuals with the dominant genotype for Taq1 had a significantly higher prevalence of LDD than those without it. There was no association between LDD and the Fok1 genotype.[5]

Evidence of genetic influences in disc-related disorders has also been compiled from observations of familial aggregation and heritability estimates. In classic twin studies, in which concordance rates for a phenotype of interest were compared between co-twins in monozygotic (sharing 100% of their genes) and dizygotic twin pairs (sharing 50% of their segregating genes, on average), disc degeneration and its progression were found to be substantially influenced by genetics, with high heritability estimates of nearly 75% in women in the UK and Australia, and more moderate estimates approximating 30–55% in Finnish men. Both the precise phenotype and lumbar level studied must be considered when determining heritability, however, the disc signal under MRI was not found to be heritable ($h2=0.0$) in the classic twin study reported by Sambrook et al.[8] On the other hand, in a heritability study of a similar sample size by Battie et al., the disc signal was significantly heritable ($h2=0.30–0.54$, depending on the lumbar level).

Livshits et al., studied the contributions of genetic and other risk factors to LDD among women. Their cross-sectional study, which included 2,256 women made up of 371 monozygotic and 698 dizygotic twin pairs, showed a significant ($p<0.001$) genetic correlation between LBP and LDD measurements, suggesting that approximately 11–13% of the genetic effects are shared by LDD and LBP.[9]

Twin studies have also demonstrated a genetic predisposition to disc degeneration, which has led to a search for additional genetic factors predisposing to disc degeneration. For instance, Taq1 and Fok1 of the vitamin D receptor gene have been implicated as contributors to disc degeneration in several studies. Similarly, it has been found that polymorphism occurring in the promoter region of the gene that regulates MMP3 production is a potential risk factor for the accelerated disc degeneration that occurs, particularly in the elderly. Furthermore, in humans, the AGCI gene has a coding region for the CS1 domain of chondroitin sulfate (CS) chains present in proteoglycan molecules, with polymorphism in this region being implicated in disc degeneration.[10]

In their study, Videman et al., found that genetic polymorphisms were responsible for inter-individual differences in the synthesis of disc matrix and disc degeneration. Twelve of the 99 variants show associations with disc signal intensity in lumbar discs. Genes that exhibited the strongest associations were the allelic variants AGC1, COL9A1, and COL11A2. Some variants of AGC1 and COL9A1, as well as variants of the COLL11A1 gene, were associated with disc bulging and disc-height loss. These investigators, therefore, concluded that disc degeneration is a polygenetic condition caused by a combination of several factors.[11]

Rajasekaran et al. identified specific single nucleotide polymorphism (SNP) associations between five genes — COL11A1, ADAMTS5, CALM1, IL1F5, and COX2 — and severe lumbar disc degeneration in young adults. In their study, degenerative disc disease was found to be a complex condition involving an intricate interplay between multiple genetic polymorphisms.[12] In 2013, Chen et al., analyzed gene expression profiles at different stages of disc degeneration, using bioinformatics, and found that MAP and Rho family genes - in particular, MAP2K6 and RHOBTB2 - may play important roles in the progression of grade III and IV discs, respectively.[13]

Gene-environment interactions

Twin studies in which multivariate analysis was performed have permitted the examination of shared genetic influences between phenotypes, as well as the testing of (a) hypotheses regarding potential pathways for genetic influences on clinical phenotypes, and (b) the hypothesis that environments modify the effects of genes on the trait being studied and, therefore, account for a proportion of any apparent heritability. Current statistical modeling, which allows the testing of gene-environment interactions, examines whether the magnitude of additive genetic variance, common environmental variance, and unique environmental variance change as a function of a measured environmental factor.

Such models show that physical activity moderates the heritability of obesity/bone mass index (BMI). Confirmation of the relevance of these models came a few years after the first obesity studies, when Kilpelainen et al.,[13] showed that physical activity moderates the FTO gene association with BMI in a meta-analysis incorporating over 218,000 adults. As emphasized earlier, the effect sizes of most genetic variants are small and, thus, individual gene-environment studies must have very large sample sizes to provide convincing evidence of any interaction.

Like many candidate gene studies, small interaction studies have mostly failed to be replicated. Epigenetics has recently gained more attention in complex disease genetics. Epigenetics includes features that are not in the DNA sequence itself, such as DNA methylation, histone modification, and microRNAs affecting gene expression. Epigenetic changes can be maintained as cells divide, thereby allowing early environmental effects (e.g., childhood exposure) to act later in the life of an organism. These features have been of great interest in pain research, the belief being that environmental factors could affect chronic pain through epigenetic changes.[14]

Aging

During fetal life and early childhood, the nucleus undergoes a structural change, from a translucent fluid to soft amorphous tissue, due to increased collagen content. The proteoglycan content of the disc is maximal in the young and declines thereafter. Aging causes changes in the disc matrix, which result in altered strength, matrix degradation, and impaired metabolism. Age-related reductions in endplate vascularity and disc cell density could simply reflect necessary adaptations to increased mechanical loading at the onset of ambulation and reduced metabolite transport in a growing disc. Microstructural damage occurs to discs during growth but has minimal impact to mechanical disc function. Such structural damage can progress as a person ages, ultimately leading to disc degeneration. Disc cells appear to adapt the properties of their matrix to suit prevailing mechanical demands, though low cell density and the lack of blood supply ensure that such changes are not as rapid or pronounced as in the adjacent osseous vertebrae.[1]

Injured discs show increased levels of catabolic cytokines, increased matrix metalloproteinase (MMP) activity, and scar formation, especially in the vicinity of annular tears. Collagen turnover time in articular cartilage is approximately 100 years and could be even longer in discs. Proteoglycan turnover is faster, at around 20 years, and there is the potential for regeneration, as observed in animal growth studies.[1] As a person ages, proteoglycan fragmentation increases and both proteoglycan and water content decrease. There is a corresponding increase in collagen content. Fine type II collagen fibrils in the inner annulus are replaced by type I fibers near the junction of the annulus and nucleus pulposus, with type I fibers throughout the disc being coarser than their type II counterparts. This slow process leads to the entrapment of the nucleus by the fibrous annulus and cartilage endplates of the vertebrae. As long as the proteoglycan fragments remain entrapped in the disc, they can fulfill a functional role similar to that of intact proteoglycan. There is increased cross-linking between collagen and fibrils, which results in reduced matrix turnover and repair in old disc growth.[15]

Individual specific factors

Pye et al., studied a population-based sample of men and women to identify any associations between weight, BMI, regular levels of physical activity, cigarette smoking, and the radiographic characteristics of LDD. Men and women above 50 years of age were recruited for participation in a screening survey of vertebral osteoporosis (European Vertebral Osteoporosis Study) in Aberdeen, Scotland, UK. Associations between individual radiographic features of LDD and various definitions of lumbar disc degeneration for LBP were studied. Men more often exhibited osteophytes, while women more often presented narrowing of the disc space, and both these radiographic features increased in frequency with age. Disc space narrowing appeared more strongly associated with LBP than osteophytes, especially in men. Disc space narrowing at two or more spinal levels appeared to be more strongly associated with LBP than disc space narrowing at only one level. Excluding the L5–S1 level, the strength of almost all the associations increased.[16]

It has been observed that some features of disc degeneration are not associated with age. For instance, narrowing of the IVD was previously listed among the signs of aging of the lumbar disc. However, recent post-mortem studies have revealed that lumbar discs do not narrow with age, which implies the existence of a hitherto unknown process in these changes. Similarly, though pathologists believe that annular tears are a degenerative process, further studies have shown that the prevalence of annular radial tears does not correlate with the aging process.

It has been found that the hyperglycemia of diabetes mellitus impairs disc cell metabolism directly by decreasing the cellular uptake of glucose and indirectly via the accumulation of advanced glycation end products (AGEs). Accumulating these substances enhances endplate vessel microangiopathy, thereby hampering the diffusion of nutrients to disc tissues and causing changes and alterations in extracellular matrix (ECM) composition. Moreover, high AGE levels activate inflammatory pathways that enhance matrix breakdown by upregulating metalloproteinase activity. As a result, there is a disruption in the cellular metabolism of these disc cells, which impacts cell viability by accelerating apoptosis, autophagy, and senescence, leading to disc degeneration. Obesity, which often co-exists with type 2 diabetes, might accelerate this process of disrupted metabolism because of the mechanical overload obesity exerts on spinal segments, together with the effect of specific adipose-secreted cytokines that may impair disc cell metabolism and viability. Collectively, these alterations eventually result in IVD degeneration. However, given the existing continuity between obesity and type 2 diabetes and their shared risk factors and pathophysiological background, it is difficult to clearly distinguish how the specific features of each condition discretely contribute to intervertebral disc degeneration.[17]

CONCLUSION

The most widely accepted definition of the disc degeneration process is that it is an aberrant, cell-mediated response to progressive structural failure. The pathophysiology behind disc degeneration is multifactorial. The genetic contribution to lumbar disc degeneration is a newer concept still being researched in different populations around the world. Investigators have demonstrated a familial predisposition in the etiology of LDD. The effect sizes of most genetic variants are small and, thus, individual gene-environment studies must have very large sample sizes to provide strong evidence of any interaction. Through this review article, we have attempted to describe the potential roles of factors that are likely involved in this process.

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