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REVIEW

Etiology for Degenerative Disc Disease

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Abstract Degenerative disc disease is a multifaceted progressive irreversible condition and an inevitable part of aging, which has been found to be a contributing factor for low back pain and might cause radiculopathy, myelopathy, spinal stenosis, degenerative spondylolisthesis, and herniations. Its etiology is complex and multifactorial. Although genetics influence more dominant, the occupational and mechanical influences still persist as a major risk factor. This review emphasizes up-to-date knowledge regarding etiology of disc degeneration with special consideration on occupational, lifestyle factors, and genetic polymorphisms.

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DEGENERATIVE intervertebral disc disease is an inevitable part of aging and found to be one of the contributing factors for low back pain.¹ Degenerative disc disease (DDD) affects the functional capability of intervertebral disc, making it unable to bear physiological loads, thus leading to damage to structural integrity, formation of disc herniation, osteophyte, and vertebral micro-fracture. Different methods have been used in the past to measure disc degeneration. The disc space height, signal intensity, and bulging are widely used to estimate degenerative changes of intervertebral disc based on computed tomography, magnetic resonance imaging (MRI), pathology, and autopsy results.²⁻³ However, lack of uniform grading system of disc degeneration impedes progress in the understanding its etiology. DDD has been attributed to various factors such as physical

loading, vehicular driving, spinal trauma, smoking, obesity, and genetic influences.⁴⁻⁹ The pathogenesis of DDD and its association with environmental and genetic factors is poorly understood. In recent years molecular mechanism of DDD has been widely studied in the various populations. This review concentrates the latest advances on the evidenced factors associated with the occurrence of DDD.

OCCUPATIONAL EFFECTS

Disc degeneration is highly linked to heavy physical loading specific to occupation. Occupational risk factors such as sustained abnormal postures, bending, vibration, twisting, sitting, heavy lifting, have been suspected to be associated with degeneration and herniation of intervertebral disc.¹⁰⁻¹² Elfering *et al*¹³ reported that lack of exercise and night shift work were significant predictors for disc degeneration and its progression. In a cross-sectional MRI study, Luoma *et al*¹ found that low back pain was more

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common among carpenters and machine workers than among office workers, but timing and signs of disc degeneration are unknown in this study. In another similar study Evans *et al*¹⁴ revealed that frequency of degenerative change in lumbar intervertebral disc of sedentary women was high, whereas degenerative change was not found in ambulatory women. However men in this study showed no significance difference in prevalence of degenerative change in lumbar intervertebral disc. Lawrence¹⁵ found that lumbar intervertebral disc degeneration was more general in miners and manual workers than in business and professional workers. Puustjarvi *et al*¹⁶ noted strenuous exercise did not exert adverse influence on the intervertebral disc of young dogs.

Kelsey and Hardy¹⁷ reported that individual who spends most of the time on driving vehicles tends to have more damage on intervertebral disc regardless of sex. This study also explained the prolonged sitting was associated with back pain or sciatica. Other studies also revealed that vehicle drivers are more prone to lumbar intervertebral disc degeneration than ones with other occupations.^{12, 18, 19} Occupational drivers often have back problem and degenerative changes of intervertebral disc due to whole body vibration that caused by driving vehicle.^{7, 20}

Although it is generally agreed occupational suspected risk factors play an important role in the pathogenesis of the degenerative process, a precise understanding of the biochemical and molecular events occurred in the disc that is exposed to prolonged sitting, heavy lifting, postural stresses and unpleasant environment remains elusive.

LIFE STYLE

Epidemiologic studies revealed smoking is a weak risk indicator but not a cause for disc generation.²¹⁻²³ Smoking has been identified to decrease blood flow to vertebral body,^{24, 25} impair fibrinolysis,²⁶ raise intra-abdominal pressure because of coughing,²⁷ and reduce bone mineral content,²⁸⁻³⁰ which might have direct or indirect effects on intervertebral disc degeneration. Kelsey *et al*³¹ found no absolute difference between smokers and nonsmokers in cervical disc changes, and smoking plays little role in severity of disease. However, An *et al*³² found smokers have higher risk for the cervical DDD than nonsmokers. Although nicotine-induced degenerative changes are irreversible, Nemoto *et al*²³ and Elmasry *et al*³³ regarded that smoking cessation is beneficial to regeneration of a degenerated disc to some extent.

Moreover, obesity or increased body mass index are closely related with disc degeneration.^{6, 34, 35} One study in

Japanese population demonstrated that degeneration among young adult men is associated with overweight and abdominal obesity.³⁴ Another study by Liuke *et al*⁶ as well supported the above conclusion. However, a study of a small sample reported by Videman *et al*³⁶ did not find obesity was interrelated with disc degeneration based on signal variation on MRI. Prevention and control of obesity are given priority to lessen the severity of intervertebral disc degeneration.^{6, 35, 37} However, more studies are needed to figure out the mechanism by which obesity and smoking increase the risk of DDD.

GENETIC FACTORS

Clearly, it is agreed that genetics, as a risk factor for DDD, has dominant influences on etiopathogenesis.^{9, 38, 39} A case-control study performed by Matsui *et al*⁴⁰ suggested a strong familial predisposition to development of DDD. They observed significant disc degeneration in patients with a positive family history of disc herniation. Videman *et al*⁴¹ examined 150 male twins who were scanned on MRI to record changes in the degenerative signs over a 5-year interval and found a prominent hereditary influences on the progression of DDD. In addition, they reported occupational factors had modest effects (from 2% to 15%) on development of DDD compared to genetic effects (from 47% to 66%). Another two studies on twins also revealed significant heritability influence on intervertebral disc degeneration.^{38, 42} Moreover, environmental factors have been revealed to impact on disc signal variation among the twins in the two studies.

Predisposing genes such as vitamin D receptor (VDR), type I collagen (COL1), type IX collagen (COL9) A2 and COL9A3, aggrecan, have been proved to have strong relationship with DDD in several ethnic population.⁴³⁻⁴⁶

VDR

VDR, a member of nuclear steroid hormone receptor, is supposed to play an important role in normal bone mineralization and remodeling. Many disorders such as osteoporosis, osteoarthritis, and DDD are associated with gene polymorphisms of VDR.⁴⁷ Videman *et al*⁴⁴ described the association of DDD with VDR in monozygotic twins from Finland. A study of 205 Japanese young adults revealed that Tt genotype of VDR gene was more highly associated with DDD than TT genotype.⁴³ A large-scale study in Chinese by Cheung *et al*⁴⁷ further supported the link between t allele of VDR gene and DDD with an odds ratio of 2.61. Videman *et al*⁴⁸ concluded that individuals with tt genotype are more prone to suffer from annular rupture.

The variant t-allele in different genetic population makes DDD phenotype more diverse.⁴⁹

COL1

COL1 is a main element of extracellular matrix and a necessary component to provide tensile strength to the intervertebral disc.⁵⁰ Polymorphisms of COL1A1 gene have been identified as likely contributors for disc degeneration in the past studies. Sarver *et al*⁵¹ found a decreased COL1 expression in mice would reduce the ability of the disc tissue to withstand mechanical forces. COL1A1 Sp1 polymorphism has been verified to be involved in osteoporosis, increased fracture risk and degenerative diseases.⁵²⁻⁵⁴ Pluijm *et al*⁵⁵ considered that individual with TT genotype of COL1A1 Sp1 polymorphism had a larger risk for disc degeneration than those with GG and GT genotypes. Similarly, Tilkerdis *et al*⁵⁶ found strong association of DDD with TT genotype polymorphism of COL1A1 in young male soldiers. Videman *et al*⁵⁷ suggested variants in the COL1A1 gene that may account for DDD, rs2075555 and rs1007086, were associated with disc signal intensity.

COL9

COL9, a tiny structural component of the cartilage and nucleus, acts as a bridge between non-collagenous and collagenous tissues and gives mechanical support to the disc.⁵⁸ As a heterotrimeric protein, COL9 consists of α chains i.e. α 1(IX), α 2(IX), and α 3(IX) that is encoded by COL9A1, COL9A2, and COL9A3 genes respectively.^{59, 60} Mutations in COL9 are associated with disc degeneration in animals and human individuals.⁶¹ The tryptophan 2 (Trp2) and Trp3 alleles may contribute to degenerative disease and symptomatic spinal stenosis.^{62, 63}

Anunnen *et al*⁴⁵ identified an allele Trp2 of COL9A2 gene to be involved in the pathogenesis of DDD. α 2 chain of COL9 was found in 6 patients among 157 cases with sciatica, but in none of 174 healthy controls. However frequency of the Trp2 allele in this study was typically low (1.9%) and this may be contributed to non-operated symptomatic patients who were not included. Jim *et al*⁶⁴ performed a case-control study in 804 Chinese volunteers, and the result revealed Trp2 allele was seen in 20% of the study population and increased risk of developing annular tears as well as intervertebral disc degeneration. Higashino *et al*⁶⁵ found that 21.4% patients carried Trp2 allele in Japanese herniated nucleus pulposus patients younger than 40 years. In contrast, Trp2 allele had no association with disc degeneration for patients older than 40 years, which is different from the result in Chinese patients. However, Trp2 alleles were not associated with DDD in the

Southern European patients.⁶⁶ Zhu *et al*⁶⁷ used immuno-histochemical analysis to compare COL9 expression in the normal adult disc with mechanical injured disc, and found COL9 expression in the degenerative adult disc but not in the normal adult disc.

Trp3 polymorphism of COL9A3 gene was considered to be a risk factor for Finnish disc degeneration patients.⁴⁶ In Southern European population, the frequency of Trp3 allele was 8.6% in intervertebral disc degeneration patients, which was significantly higher than that in the healthy controls (4.9%).⁶⁶ However, for genotyping studies in Japanese and Chinese population, Trp3 allele showed no link with DDD.^{64, 65} Solovieva *et al*⁶⁸ suggested that association of Trp3 allele with disc degeneration might be modified by interleukin 1 beta gene polymorphism. Rathod *et al*⁶⁹ found COL9A2 gene polymorphism instead of COL9A3 gene polymorphism might have correlation with DDD in a Indian population.

Aggrecan

Aggrecan, a proteoglycan in the nucleus pulposus of intervertebral disc, acts as a water binding component to make up the highly hydrated core of nucleus pulposus and to maintain the disc in its normal functional state.⁷⁰ Aggrecan can maintain structural integrity, elastic deformability and facilitate intervertebral disc and cartilage to bear compressive forces.^{71, 72} The amount of water and aggrecan decreases in the nucleus pulposus cells of degenerative disc.⁵⁰

Variable number of tandem repeat polymorphisms has been identified in human aggrecan 1 core protein gene, with repeat number ranging from 13 to 33 in exon 12.^{73, 74} Kawaguchi *et al*⁷⁵ found association of tandem repeat polymorphisms with disc degeneration in 64 Japanese female women. Kim *et al*⁷⁶ found that A21 allele was highly overrepresented among the younger population with multi-level disc degeneration. The findings of the two researches support the idea that genetic factor is more important in the pathogenesis of the degenerative process than occupational and environmental factors because young individuals enrolled in the both studies were less liable to occupational and environmental factors. In addition, studies in Turkey⁷⁷ and Iran⁷⁸ population revealed that multi-level disc degeneration and herniation associated with lower number of tandem repeats of aggrecan gene. Association was also observed in the Finnish population.⁷⁹ However, Roughly *et al*⁸⁰ did not find correlation between aggrecan gene tandem repeat polymorphisms and DDD.

In various studies of different populations, VDR, COL1A1, COL9A2, and aggrecan genes and their effects on DDD are

already apparent to us. However, various genetic criteria and small size cohort in studies make the molecular etiopathogenesis of DDD more complex. A clear phenotype definition, long-term follow-up studies with large sample size are required for genetic association to be more understandable, meaningful and successful. Also, more reliable measures would help to know DDD more precisely.

In conclusion, the definite pathogenesis of DDD is not clear yet. By now, it has become evident that disc degeneration is the result of interaction of occupational risk factors, environmental risk factors, and genetic factors. The definition of degenerative disc disease is obscure. Its occurrence and severity are found inconsistent in various studies. So, it is necessary to find the uniform interpretation of DDD. Also, better understanding of the clinical symptoms and likely causes of the pain are equally important and should be studied carefully.

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