

# Medical progress

## Association between intervertebral disc degeneration and disturbances of blood supply to the vertebrae

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Low back pain is a common public health problem in Western industrialized societies and the world as well. Studies indicate that the prevalence rate ranges from 12% to 35%, with around 10% of patients becoming chronically disabled. It also places an enormous economic burden on society.<sup>1</sup> Although the exact cause of low back pain has yet to be defined, intervertebral disc degeneration is considered a major source of it. Since patients with degenerative discs are often asymptomatic, the mechanisms of it are still unclear.

### NORMAL INTERVERTEBRAL DISC

#### Structure

The intervertebral disc lies between the vertebral bodies and links them together. It provides reversible resistance to compressive, rotational, and tensile loads applied to the vertebral column and it also allows the spine to bending, flexion, and torsion.<sup>2,3</sup> Three major components ensure the properties of the disc: nucleus pulposus, anulus fibrosus, and cartilaginous endplate. Nucleus pulposus represents a centrally located gelatinous homogenous mass (in juvenile discs), anulus fibrosus consists of concentrically organized layers of collagen fibrils, and endplate separates the nucleus pulposus and anulus fibrosus from the adjacent vertebral bone. Any disturbance of the integrity and interplay of one of the three structures can result in a compromised function of the intervertebral disc.<sup>4,5</sup>

The normal human intervertebral disc in adulthood consists of a large amount of extracellular matrix interspersed by a small number of cells that make up approximately 1% of the total volume.<sup>6</sup> Cells of the disc are made up of at least two phenotypically distinct populations and they are morphologically different; those in the anulus fibrosus and cartilaginous endplate are more elongated and fibroblast-like compared with those of the nucleus pulposus, which are more rounded or oval and chondrocyte-like, sometimes with a capsule around them.<sup>7</sup> These two kinds of cells behave differently, nucleus pulposus cells generally synthesize only type-II collagen in alginate beads, whereas anulus fibrosus cells produce both type-I and type-II collagen.<sup>6</sup>

The cells within the disc synthesize the matrix and maintain and repair it. The disc matrix consists of an

elaborate framework of macromolecules filled with water. The principal macromolecules are collagen and proteoglycans; the collagenous fibrils are embedded in a gel of proteoglycans and water.<sup>8,9</sup>

#### Nutrients and blood supply

In humans, the superficial layer of the anulus fibrosus of the intervertebral disc contains blood vessels for approximately three years after birth. However, the intervertebral disc becomes the largest avascular tissue without penetrating blood vessels thereafter.<sup>10</sup> But like other types of cells, the cells of the disc require nutrients, such as glucose and oxygen to remain alive.<sup>10,11</sup>

The upper and middle parts of the lumbar spine (L<sub>1</sub>–L<sub>4</sub>) receive their blood supply from four pairs of lumbar arteries, whereas the lower part of the spine is supplied by the lowest pair of lumbar arteries, the medial sacral artery and the iliolumbar arteries, of which the two lowest pairs of lumbar arteries and the middle sacral artery originate from the abdominal aorta at the aortic bifurcation. The first to fourth lumbar arteries leave the aorta in front of the corresponding vertebral body, and the middle sacral artery in the bifurcation in front of the fourth lumbar vertebra or L<sub>4</sub>–L<sub>5</sub> intervertebral space.<sup>12–14</sup> But the blood supply to the vertebrae is not constant in everyone, many variations may exist. According to a recent study, the authors collected 187 cadavers (132 men, 55 women) to figure out the accurate site of the abdominal aortic bifurcation, and found that the abdominal aorta descended and bifurcated into two common iliac arteries at the level of L<sub>4</sub> vertebra in 131 cases (70.1%), at the fourth lumbar intervertebral disc in 23 cases (12.3%), and at the level of L<sub>5</sub> vertebra in 33 cases (17.6%).<sup>15</sup> The disc is supplied by capillaries that are fed from these arteries and drain into the subchondral venous network or into the veins of the marrow spaces of the vertebral bodies. These capillaries have muscarinic receptors that regulate blood flow in response to external signals.<sup>16</sup>

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Studies show that the intervertebral disc receives nutrients through two routes: the anular route, through which the disc receives blood directly from the vascular plexus surrounding it, and the vertebral route, which supplies blood from the vertebral body through the vertebral endplate.<sup>11</sup> Different kinds of nutrients may be transported to the disc through different routes. Some evidence is provided that anions and cations are transported mainly through the anular route, whereas noncharged particles are conveyed equally through both routes.<sup>17,18</sup> While some other studies reported that the vertebral route was the main route for the transportation of noncharged particles.<sup>19</sup> Difference between these two studies may arise from differences in experimental methods and processes through which theoretic equations are deduced. The exact route remains to be clarified in the future.

## DISTURBANCES OF BLOOD SUPPLY AND INTERVERTEBRAL DISC DEGENERATION

### Intervertebral disc degeneration

Although the problem of intervertebral disc degeneration has been approached from many sides, there is no exact interpretation on what is "disc degeneration", until recently, Adams et al<sup>20</sup> proposed that the process of disc degeneration was an aberrant, cell-mediated response to progressive structural failure and a degenerated disc was one with structural failure combined with accelerated or advanced signs of aging.

One of the primary causes of disc degeneration is thought to be failure of the nutrient supply to disc cells. The activity of disc cells is very sensitive to change of extracellular oxygen and pH, with matrix synthesis rates falling steeply at acidic pH and at low oxygen concentrations,<sup>21,22</sup> and the cells do not survive prolonged exposure to low pH or glucose concentrations.<sup>23</sup> A fall in nutrient supply may lead to a lowering of oxygen tension, which results in the disc cells undergoing anaerobic metabolism with the more production of lactic acid. As removal of waste products from the large avascular mature disc is difficult, lactic acid accumulation can occur, and then cause an acidic pH environment.<sup>24</sup> The nutrient supply to the disc cells can be disturbed at several points. Factors that affect the blood supply to the vertebral body such as atherosclerosis, sickle cell anemia, Caisson disease, and Gaucher's disease all appear to lead to decrease in the nutrient supply to the disc and increase in disc degeneration.<sup>11</sup>

### Evidence of the links between interference of blood supply and intervertebral disc degeneration

Since blood supply of the intervertebral disc is mostly dependent on that of the vertebral body, reduction of blood supply to the vertebral body may indicate the similar condition of the intervertebral disc. In a recent study, the researchers recruited 25 patients and assessed two vertebral bodies (L<sub>1</sub> or L<sub>3</sub>) in each patient. After

controlling variables that might affect blood perfusion, they found that the insufficient lumbar vertebral marrow perfusion correlated well with intervertebral disk degeneration through the test of dynamic contrast-enhanced MRI and blood perfusion was 14% less in the vertebral body marrow between two degenerated disks than that between two normal disks, which meant that the insufficient vertebral blood supply might be correlated with degeneration of the intervertebral disc.<sup>25</sup>

### Atheromatous lesions

Atherosclerosis of arteries supplying the lumbar region has been suggested as a mechanism leading to intervertebral disc degeneration.<sup>26</sup> Atheromatous lesions in the wall of the abdominal aorta usually develops at the ostia of branching arteries and the bifurcation, and may obliterate orifices of lumbar and middle sacral arteries. The plaques prevent the blood supply in the lumbar arteries, resulting in ischemia and scarce blood supply to the disc area and inadequate nutrition of the discs, thus render the discs more vulnerable to mechanical stress.<sup>13,27</sup> Fifty-one Finnish patients ranging from 35 to 70 years of age (mean age, 56 years) with long-term lower back pain were tested MR aortography. The prevalence of occluded arteries was 2.5 times more than in subjects of corresponding age group in a Finnish necropsy material. More than half of the patients had significant disc degeneration. Association analysis found that disc degeneration was associated with occluded lumbar/middle sacral arteries.<sup>28</sup>

A 25-year follow-up study showed that at the baseline examination, aortic calcification, a marker for advanced atherosclerosis, was significantly associated with general disc degeneration; in longitudinal, aortic calcifications predicted disc deterioration, and calcific lesions in the upper part of the abdominal aorta predicted disc deterioration at any lumbar level, whereas calcific lesions in the lower part of the aorta, the reason of which might be that calcified plaques in the upper abdominal aorta, usually indicated more extensive atherosclerosis than lesions limited to the lower part of the aorta.<sup>29,30</sup> Furthermore, subjects whose aortic calcifications developed between the examinations had disc deterioration twice as frequently as those in whom aortic calcifications did not develop, and individuals with severe posterior aortic calcification in front of any lumbar segment were more likely than others to report back pain during adult life. So the researchers concluded that aortic calcification, a marker for advanced atherosclerosis, increased a person's risk for the development of disc degeneration and was associated with the occurrence of back pain. Posterior calcification may be a sign of atheromatous obliteration of a feeding artery or arteries of the lumbar spine, which leads to impaired nutrition of the lumbar spine.<sup>31</sup> The intervertebral disc, with its precarious nutrient supply, may be one of the first structures to suffer from insufficient nutrient supply, thus linking aortic calcification with disc degeneration.<sup>32</sup>

The results of another study proved that more than half of the patients with low back pain had atherosclerotic calcifications visible on CT scans, whereas only 21% of the age-matched patients without low back pain were found to have aortic calcifications. Nearly half of the patients with low back pain who were 50 years of age or less had aortic calcifications, whereas less than 10% of the 36 control patients had aortic calcifications. And the quantity of calcified plaques in the aorta was found to be greater in the group of patients with low back pain than in the control group, especially in the group whose patients aged less than 50 years. But they claimed no correlation between the amount of calcifications and the degree of disc degeneration assessed by CT discography,<sup>33</sup> which is not accord with the results of Kauppila et al.<sup>32</sup> Reasons may be due to the indirect assessment of the severity of arterial disease in the arteries supplying lumbar spine in this study, so the arterial flow to the disc area may thus also be different in subjects even with equal quantities of plaques. Furthermore, the degrees of disc degeneration were not comparable between the two studies.

#### Smoking

Smoking is a separate risk factor common to both low back diseases and arterial diseases.<sup>34</sup> The most widely accepted explanation for the association between smoking and disc degeneration is malnutrition of spinal disc cells by carboxy-hemoglobin-induced anoxia or vascular disease. Cigarette smokers may undergo cell apoptosis, faulty synthesis of disc macromolecules, and an imbalance between disc matrix proteinases and their inhibitors, which can induce the pathogenesis of disc degeneration. There is also some evidence that disc degeneration of cigarette smokers is of more severe degree than that of non-smokers.<sup>35,36</sup> Other studies still indicated that passive cigarette smoking caused changes in gene expression, such as the downregulation of collagen genes, which precedes the histologic changes in the intervertebral discs.<sup>37</sup> A 16-year follow-up research was carried out on 98 407 female nurses aged 30–55 years to clarify smoking as a cardiovascular risk factor for physician-diagnosed lumbar disc herniation. Besides adjusting for age, body mass index (BMI), vigorous or moderate exercise and other variables, compared with never smokers, the incidence of herniation for past smokers was significantly higher, for current smokers the incidence increased with the number of cigarettes smoked per day, and a decrease occurred after cessation of smoking.<sup>38</sup> Another 5-year follow-up longitudinal study using digital MRI on 134 male monozygotic twins (35–69 years of age) showed that smoking might predict more disc height reduction, which meant more severe progression of disc degeneration.<sup>39</sup>

An animal study provided direct evidence of the effect of smoking on the degeneration of discs. Rats subjected to passive smoking for 8 weeks exhibited great histological changes in the intervertebral discs, such as cracks, tears, misalignment of the annulus fibrosus, and increased

fibrous tissue in the nucleus pulposus. The IL-1 beta level was higher in the smoking group than that in the non-smoking one. In addition, after stopping passive smoking, progression of degeneration ceased, and the matrix of the nucleus pulposus and annulus fibrosus showed increased fibrous connective tissue and proteoglycan.<sup>40</sup> *In vitro* study showed that the chondrocytes in the disordered annulus fibrosus layer tended to grow larger and attain a rounder form than normal chondrocytes. So tobacco smoke inhalation increased decomposition of chondrocyte activity and local production release of inflammatory cytokines, which may be the indication or cause of intervertebral disc degeneration.<sup>41</sup>

Nicotine, the active ingredient of tobacco, acts pharmacologically on the cardiovascular system and results in contraction of blood vessels, tachycardia, and a rise in arterial blood pressure. Rabbits treated with nicotine for 8 weeks underwent a significant decrease in the number of vascular buds in the vicinity of the vertebral endplate, decrease in the number of red blood cells and enlargement of endothelial cells together with narrowing of the vascular lumen, which indicated that nicotine had deleterious effect on the intervertebral disc *in vivo*.<sup>42</sup> Bovine chondrocytic intervertebral disc cells were seeded in alginate with or without freebase nicotine at concentrations found in the serum of smokers (25–300 nmol/L). DNA, glycosaminoglycans (GAG), and hydroxyproline were tested as the extent of disc degeneration. At lower doses, significant increase in the above parameters was found in the early stage, while at higher doses, there was a significant dose-dependent decrease in these parameters compared with controls. Furthermore, other degenerative changes were revealed in the higher nicotine groups, such as reduced cell proliferation, disrupted cell architecture, disintegration of cells and extracellular matrix, and the presence of type I collagen in the extracellular matrix. So nicotine has an overall detrimental effect on disc cells cultured *in vitro*, and there was significant inhibition of cell proliferation and extracellular matrix synthesis.<sup>43</sup>

#### Aortic stenosis and other risk factors

According to the study of Kauppila et al,<sup>44</sup> the incidence of disc degeneration, advanced atherosclerotic manifestations, and stenosis of the ostia of the lumbar and middle sacral arteries all increased with age. After partial rank correlation analysis, keeping the effect of age constant, there was still a statistically significant association between the grade of disc degeneration and stenosis of the ostia of the arteries supplying the disc. The association was stronger at upper lumbar levels than at lower ones. They believed that stenosis of the ostia of segmental arteries played a part in lumbar disc degeneration. In a study of middle-aged Finnish males, Logistic regression analysis was used to evaluate the association between arterial stenosis in two-dimensional time-of-flight magnetic resonance angiography (2D

TOF-MRA) and low back pain. In 43% subjects, all arteries were normal, whereas 57% had at least one stenosed artery. The left L<sub>4</sub> artery was most often affected. The degree of arterial stenosis was associated with intensity, duration and frequency of low back pain.<sup>45</sup> A cross-sectional observational study was carried out on 81 (66 women and 15 men) subjects. On CT scan, a positive correlation between degree of aortic wall calcification and disc degeneration score was found.<sup>46</sup> Epidemiological studies showed that aging, high BMI, high LDLc, the risk factors of atherosclerosis correlated significantly with intervertebral disc degeneration.<sup>47</sup>

### SUMMARY

The disc is a large and avascular tissue, and disc cells depend on blood vessels at their margins to supply nutrient and remove metabolic waste. So disturbances of blood supply may play an important role in the degeneration of intervertebral disc. Many studies have shown strong association between atherosclerosis and intervertebral disc degeneration. Furthermore, cardiovascular diseases and intervertebral disc degeneration share some similar risk factors, especially smoking as a separate one.

Contradictory viewpoints also exist, however, such as in a research on 20 male volunteers underwent a lumbar spine examination showed that lumbar artery narrowing was not associated with the enhancement of the degenerative discs,<sup>48</sup> a retrospective study on the 34 patients with abdominal aortic aneurysm in whom vascular reconstruction was performed indicated that acute interruption of lumbar arteries did not induce the development or deterioration of low back pain and organic changes in lumbar discs,<sup>49</sup> and degenerative changes may be found far earlier than that of the cardiovascular diseases which disturb the blood supply to the vertebrae.<sup>11</sup> So more molecular and histological evidence should be collected besides the epidemiologic information, and attention should also be paid on that whether the medication of cardiovascular diseases has good or evil effect on the disc tissue, since some inflammatory factor may be induced after treatment, for example nitric oxide, which plays an important role in the intervertebral disc degeneration. A clear understanding of the relationship between the blood supply and the intervertebral disc degeneration may provide clues to the doctors for the prevention and treatment of disc diseases and at last be beneficial to the patients.

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