Intervertebral Disk Nutrients and Transport Mechanisms in Relation to Disk Degeneration: A Narrative Literature Review

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Abstract

Objective: The purpose of this paper was to review the literature regarding the mechanisms leading to degeneration in intervertebral disks and to discuss contributing mechanical and biological factors.

Methods: The inclusion criteria for the literature review were research studies conducted in the last 3 decades with free full-text available in English. Review articles and articles pertaining to temporomandibular joints and joints of the body other than the intervertebral disk were excluded. The following databases were searched: PubMed, EBSCOhost, and Google Scholar through September 9, 2016.

Results: A total of 57 articles were used in this review. Intervertebral disk cells require glucose for sustainability and oxygen to synthesize matrix components. Nutrients enter the disk via 2 vascular supply routes: capillary beds of end plates and the peripheral annulus fibrosus. Solute size, shape and charge, compression, and metabolic demand all influence the efficiency of nutrient transport, and alterations of any of these factors may have effects on nutrient transport and, potentially, disk degeneration.

Conclusions: Progressive nutrient transport disruptions may actively contribute in advancing the phases of degenerative disk disease. Such disruptions include dysfunctional loading and spinal position, lack of motion, high frequency loading, disk injury, aging, smoking, an acidic environment, and a lack of nutrient bioavailability. (J Chiropr Med 2018;17:97-105)

Key Indexing Terms: *Intervertebral Disk Disease; Diet, Food, and Nutrition; Intervertebral Disk Degeneration*

Introduction

Mechanisms behind nutrient delivery that may lead to intervertebral disk (IVD) degeneration are complex.[1-5] Understanding how nutrients play a role in degeneration may help in treatment and prevention of spinal disease. This study reviews the literature on biomechanical and biological factors in nutrient transport mechanisms and the role these processes have in IVD degeneration.

Methods

PubMed, Google Scholar, and EBSCOhost were searched from January 1977 to September 9, 2016. The search included the following terms: intervertebral disk, disk nutrition, and degeneration. Inclusion criteria were use of human participants or animal subjects and English language. Studies pertaining to temporomandibular joints and joints of the body other than the IVD and any articles that were not available in full text were excluded. Fifty-seven articles were included in this review.

Results

Overview

The IVD cells require energy supplied through vital nutrients. Glucose is a major nutrient necessary for cell survival in the disk. Glycolysis is the energy pathway of choice and consists of breaking down glucose to produce adenosine triphosphate (ATP), with lactate as a byproduct. Oxygen is needed to produce glycosaminoglycans (GAGs),[1] which provide mechanical strength and integrity for the disk's extracellular matrix (ECM).[2] There are 2 blood delivery routes to supply nutrients to the avascular disk. The predominant route is via the capillary beds of the cartilaginous end plate, and the other is via the peripheral annulus. Impeding any of these paths deprives the disk of

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vital nutrients. Transport of these nutrients mainly depend on the size of nutrient solutes; the larger solutes (ie, GAGs, growth factors, proteins, enzymes, and hormones)[2-5] rely on convection as a transport mechanism whereas smaller ones (ie, glucose, oxygen, and lactate) rely on diffusion. Convection is powered by hydraulic pressure gradients influenced by mechanical loading, and diffusion is mainly influenced by solute concentration gradients.

Disk Nutrients

Glucose. Glucose may serve as the disk's main energy supply.[3,6,7] It is essential for cell survival.[6,8,9] If its concentration falls below 0.5 mmol/L for more than a few days, cell death may result.[3] A combination of low pH and no glucose causes greater cell death than either variable acting alone.[8] Cell death may begin as glucose concentration reaches 0.5 mM and as pH reaches 6.8.[10] As these numbers progressively diminish to 0.2 mM and pH 6.4, all cells are likely considered dead.

Oxygen. Although disk cells may remain alive for several days without oxygen supply,[6,7] this nutrient is required for proper cell function. It plays a vital role in the rate of sulfated GAG and protein synthesis.[1,7] At 5% oxygen content, matrix synthesis rates are maximized.[7] Levels dropping below 5% limit matrix production drastically.[3] Complete oxygen deprivation, as well as acidic pH, decrease proteoglycan production, which is a property seen in disk degeneration.[6]

Oxygen levels do not seem likely to affect mitochondrial function until they fall to extreme levels (0.1-0.3 kPa).[8] In the disk's nucleus, the central area has the lowest level of oxygen concentration and, in turn, produces more lactic acid via glycolysis. Hypoxia often coincides with low pH and low glucose concentrations.[8,11] Such oxygen-deprived conditions predictably shift the main energy source from glucose to amino acids.[8]

Lactate. In anaerobic glycolytic metabolism, cells consume glucose to create ATP and produce lactic acid as a metabolite at fairly high rates.[3,10,11] Any buildup of lactic acid and carbon dioxide can lower the disk's pH and activate certain pH-dependent proteolytic enzymes that degrade the matrix.[1,3]

Nutrient Transport Mechanisms

There are 2 mechanisms for solute transport into disk tissue: passive molecular diffusion and convection (or fluid flow).[1] Figure 1 provides an overview. Overall, diffusion is more effective than fluid flow in supplying nutrients to the disk.[12] Diffusion efficiency depends highly on concentration gradients, the absolute concentration, solute properties, and tissue integrity.[1,13,14] Conversely, fluid convection is dependent upon hydraulic (or osmotic) pressure gradients and mechanical loading of the matrix to deliver nutrients.[1,14] Small

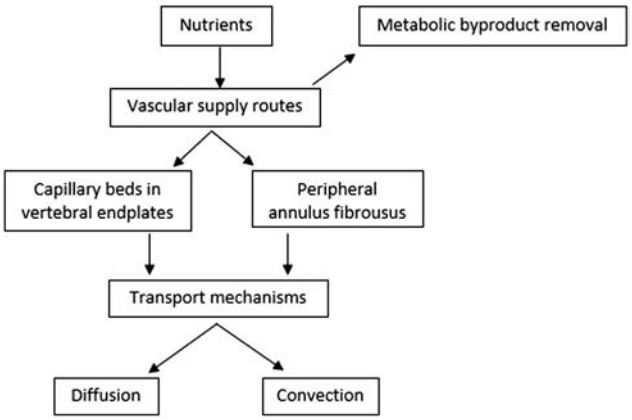

Fig 1. *Nutrient delivery mechanisms to the intervertebral disk.*

solutes, such as glucose, oxygen, sulfate, and lactate, almost exclusively rely on diffusion for transport.[1,3,15-17] In contrast, the pumping action of convection (mechanical loading) plays a greater role with large-solute transport.[3-5,15-18]

Nutrient Delivery Routes/Channels. The disk is largely avascular, but there are many arterioles and capillaries in the outer annulus, limited to the marrow space of vertebrae on the end plate side.[19] The cartilaginous end plate absorbs nutrients rapidly and delivers them into the disk.[20] A greater amount reaches this destination via the annulus, with a greater nutrient concentration found toward the periphery of the disk and decreasing amounts toward the nucleus pulposus (NP). The dorsal aspect is also more saturated with nutrients.

Nearly the entire disk receives its nutrients from its end plate's blood supply.[3,4,8,11,12,21-24] From there, it diffuses across 7 to 8 mm of end plate and matrix into the cells of the disk. Metabolic waste is removed via this system in a reverse route.[3] Only the outer annulus depends on peripheral vasculature, whereas the inner annulus receives its nutrients from the end plates.[3,4,12]

Uncharged solutes, such as oxygen and glucose, enter the disk via the end plate and annulus; anions such as sulfate ions diffuse mostly via the annulus and cations such as Ca^{2+} via the end plate.[1,16,22]

Potential Factors Responsible for Disk Degeneration From a Disk Nutrition Perspective

Disk degeneration has 2 main contributing pathways: decreased nutrition and structural failure (by its subsequent damage to the NP framework).[24] Macro damage can lead to such structural failure, whereas minor ones are able to heal.

Acidic Environment. In the glycolytic pathway, glucose is broken down to lactate, accounting for the acidic pH in the center of the disk.[11] Oxygen concentration is inversely related to pH and oxygen consumption.[25] Oxygen

concentration and pH play strong roles in a disk's cellular activity and gene expression and matrix synthesis rates.[11] A pH between 7.0 and 7.3 is ideal for protein and proteoglycan synthesis.[25] Low pH slows glycolysis and oxygen uptake, thus inhibiting matrix synthesis and possibly promoting matrix breakdown.[3,11] Acidic pH levels increase cell death rates, even at a reduction to pH 6.0 when adequate glucose is available.[6,11]

Proteoglycan Loss. As we age, proteoglycan content decreases, which opens channels that allow for substances that are normally excluded (ie, cytokines and enzymes) to enter the disk as more proteoglycans may exit the disk, creating a degenerative cycle.[26] Glycosaminoglycans protect the disk from excessive fluid loss during weight bearing. With low amounts of these compounds, one will see that greater water loss occurs during loading phases, which will increase tissue stresses and may cause surface damage, potentially wear down more GAGs, and develop a degenerative cycle.[2,27,28]

Differences in NP and AF Cells. The annulus contains twice the number of cells of the nucleus, contributing to greater cell density, and the end plate contains 4 times the amount.[16,19,29] The annulus prefers glycolysis as its main metabolic pathway to create ATP for energy. Conversely, NP cells prefer aerobic mitochondrial respiration (tricarboxylic acid cycle or Krebs cycle)[30] and electron transport chain pathways.[31] Thus, cells in the nucleus use less glucose and produce more ATP than cells in the annulus.[31] Cells in the nucleus are also more metabolically active[31,32] and rely on an adequate supply of nutrients to perform their normal function.[9,31,32]

Transition From Notochordal Cells to Mesenchymal Cells. Disk degeneration may begin in childhood as one loses notochordal cells and the nucleus decreases in vascular density.[6] The nucleus develops from the notochord (whereas annulus fibrosus cells develop from the mesenchyme) but is replaced before maturity by chondrocyte-like mature cells in humans. Unlike other species that retain their notochordal cells, in humans this replacement is accompanied by decreased nutrient supply to the disk, increased oxygen and glucose consumption, and higher rates of disk degeneration. Such nutrient deprival ages the nucleus, and increased metabolism produces more lactate.[33] These mature NP cells produce a more collagenous and less hydrated matrix, which is suggested to play a role in the development of degeneration as well.

Fixed Negative Charge. The fixed negative charge from proteoglycans, notably aggrecan, attracts cations and repels anions.[26] High aggrecan levels have the potential to limit the transport of even small, uncharged molecules, as shown in the instance with glucose partially excluded from the nucleus, which has high aggrecan concentration. Cations such as Na^+ and Ca^{2+} and positively charged antibiotics such as gentamycin and aminoglycosides are more readily transported, whereas anions such as the negatively charged antibiotics penicillin and cefuroxime are repelled to a greater extent.[2,3,5]

Sulfate ion incorporation into the disk matrix precedes GAG synthesis.[1] The sulfate incorporation mechanism is of note: Because of a sulfate ion's negative charge, it is partially repelled from the negatively charged matrix, making its uptake a slow process (160-600 days). Uncharged methyl glucose (similar chemical nature and size of glucose), on the other hand, is more easily incorporated. Glycosaminoglycan content is highest in the nucleus.

Water Content and Porosity and Pore Size. Diffusion relies on a certain level of porosity.[13] Greater water content corresponds with greater pore size.[34,35] A 10% decrease in porosity may be enough to completely remove glucose from the nucleus and inner annulus.[13] Pores affect the solute transport in the matrix. Smaller molecules, such as oxygen, sulfate, and glucose, experience less resistance diffusing, whereas larger ones face greater friction.[2,36]

Low hydration inhibits the movement of molecules into tissue.[3,26] Conversely, a hydrated matrix demonstrates greater diffusion.[36] Because of the higher water content in the nucleus, this region shows greater diffusion coefficients, especially for smaller solutes. There is also greater diffusion in the inner annulus compared with the outer annulus, consistent with the higher water content found in the inner annulus.[34] Lower water content reduces tissues' convective transport due to lower hydraulic permeability and reduces solute diffusivity, which ultimately decreases solute concentration.[37]

Density. Some authors have used cell density as a measure of viability.[32] The degenerated disk shows an 11% loss of cell density. Such density reductions from poor nutritional supply do not occur rapidly but rather result from continuous shortages.[28] In a disk of low cell density, intercellular signaling is limited; thus, 1 cell may not detect the stress of surrounding cells.[27] Cells are most concentrated in the outer annulus and end plates and decline toward the nucleus.[19]

Metabolic Demand. Greater cell density accompanies greater metabolic demand.[10] The more packed the disk is with cells, the less distance is covered by nutrient supply.[6,11] If cellular demand increases to a certain extent, then nutrient supply may not be enough to support cells, especially in the disk's center, which relies heavily on glucose.[6] The presence of growth factors and cytokines upregulate lactate production, which relies on glucose usage. Mechanical load also stresses cellular demand by increasing sodium pump activity, which uses 50% to 70% of the disk's ATP. If the demand for glycolysis increases, which has been suggested via the presence of cytokines or growth factor stimulation, pH and glucose levels could both decrease to damaging levels, regardless of end plate permeability.[38]

Cartilaginous End plate Permeability. The nucleus receives nutrients and excretes toxic metabolites via the end plate, which depends on contact with blood vessels.[19,21,22,24,26] Blocking the end plate may compromise nutrient delivery and toxin removal and may lead to disk degeneration.[19,21,22,26]

Fractures, such as Schmorl's nodes, and disruptions in the end plate exchange area may also affect the transport of nutrients in and out of the disk.[3,8,26,28,39,40] Post contrast magnetic resonance imaging studies can help identify end plate damage.[24] Mineralization and sclerosis associated with aging may also affect end plate permeability.[41] The end plate's central portion is shown to be the most permeable and is a major route for nutrient flow. Blocking the end plate impairs diffusion of small solutes into the NP, reducing cell viability and possibly contributing to disk degeneration and, ultimately, cell death.[10,18,22,23] Even with slight changes in porosity, the cell density and diffusion area may deplete glucose from various regions of the disk.[42] A completely impermeable end plate may deplete oxygen concentration while increasing lactate concentration, thus creating an acidic disk environment and accelerating degeneration.[38,39,43] End plate permeability <40% seems to initiate cell destruction.[10] As the end plate exchange area becomes smaller, cells continue to completely die off.[10] Scoliotic disks limit nutrition delivery as well, especially on the side of convexity and at the curve apex. Theoretically, this decrease stems from end plate calcification.[3]

Solute Size, Shape, and Charge. Solute size, shape, and charge, as well as matrix composition, dictate solute movement.[26,36] Because of the cross-linked collagen framework and negatively charged proteoglycan gel, small molecules and cations enter the matrix more readily.[1-3,14,26] The higher proteoglycan concentration in the nucleus also allows easier entrance of large solutes and anions into the annulus. In terms of shape, globular molecules enter more readily than long, chained molecules.[26]

Smoking. The capillaries that supply the disk arise from the arteries that supply the vertebral bodies.[11] External signals determine the architecture of these capillaries, bringing attention to the effect smoking and vibration has on nutrient transport.[11] Smoking and atherosclerosis both affect blood supply, suggesting links to disk degeneration.[3,8] Smoking depletes oxygen levels, and its vasoconstrictive property also blocks the escape of lactic acid.[3] Low oxygen concentration and acidic pH limit matrix synthesis.[8] Capillary density also reduces with aging, as does the permeability of the end plate with sclerosis of this area.[7]

Disk Geometry. Although disks with greater height require larger diffusion distances, they provide more leverage for deformability, an advantage for mechano-transport coupling.[44] The greater the distance from the blood supply (peripheral annulus or disk–blood vessel interface), the lower the levels of glucose and oxygen. Thus, at the disk center, these numbers are the lowest, whereas the opposite is the case for lactate concentration.[38] Compared with a healthy disk, a degenerated disk model exhibits an exaggerated trend of decreasing viability in cells farthest from their nutrient source.[28] More blood vessels occupy the anterior margin of the disk than the posterior, resulting in greater flux from the anterior and a better supply of nutrients. About 70% of the distance into the disk from the anterior holds the highest content of nutrients, suggesting the posterior portion to be at greatest risk for degeneration.[1]

Altered Blood Supply and Decreased Nutrients. As decreased nutrition most likely causes disk degeneration, we know that inhibited blood supply lowers the amount of nutrition a disk receives.[3] Without a healthy cycle of nutrient delivery and waste removal, the disk matrix is at risk for collapse and degeneration.[7] Although a decreased supply of certain nutrients may not directly cause cell death, it can limit the production of matrix, which may lead to disk degeneration. Either a decrease in nutrient supply or increased cellular demand can lead to cell death.[6]

As nutrients deplete beyond 60% of their normal values, cell death is first seen in the midplane of the nucleus-annulus border, progressively moving medially into the nucleus.[45] If the nutrient supply drops below 30%, nearly all cells will die within the nucleus. Degenerated disks show more sensitivity to nutrient deprivation, thus exhibiting greater magnitudes of cell death in these conditions. These degenerated disks have lower water content, causing reduced diffusivity and permeability of the end plate, which slows nutrient transport to the nucleus and its surrounding cells.

Beginning in the second decade of life (especially at 10-16 years old), one begins to lose blood supply to the end plate and experiences greater cartilage disorganization and cracking and less end plate cell density, all while the disk is growing.[24,46] This may be the first sign of disk degeneration. Nutrient canals spaced throughout the end plate disappear in childhood, leaving weak spots vulnerable to Schmorl's nodes that may lead to sclerosis of the subchondral plate later in life.[3] With a decreased blood supply at the end plate, the disk is left to rely on radial diffusion from the annulus, which is slower and may further impair nutrient delivery to the disk.[35] With certain diseases and aging, end plates calcify and occlude marrow contact channels, which decreases permeability. Closure of these channels results in impaired transport of nutrients in and metabolic wastes out, which lowers oxygen and glucose concentration while raising lactate levels within the disk. These factors impair matrix synthesis, which may result in disk degeneration. Consistent findings correlate disk degeneration with disk dehydration and decreased proteoglycan content.[46]

Specific conditions, such as atherosclerosis and abdominal aortic aneurisms, have a negative effect on the blood supply to vertebral bodies, presumably leading to disk degeneration and back pain.[3] Thrombophilic and hypofibrinolytic disorders (ie, sickle cell anemia, Caisson disease, and Gaucher disease) have been seen to block end plate capillaries. Scoliosis accompanies heavy end plate calcification as well.

Inadequate Diffusion. A portion of the NP is left unnourished via routes from the end plate and periphery of the annulus.[19] This may explain the low pH of disks. In addition, inadequate diffusion leading to insufficient oxygen supply to the disk causes an increase in lactic acid buildup

and thus an acidic pH. Disks rely on a nutrition supply to produce proteoglycans.[16] Thus, limited diffusion is thought to cause disk degeneration by limiting proteoglycan synthesis.

Influence of Mechanical Loading

Compression. The disk deforms from daily activities and from degeneration and aging.[44] Compressing tissue lowers its water content, amount of nutrient delivery, and waste removal.[35,47,48] The impaired diffusion of small solutes during loading may cause hypoxia and nutritional deficiency, which is also suggested to play a role in disk degeneration. From a pharmaceutical perspective, diffusion-dependent drugs may be best administered at the end of the day when the disk is not loaded.[49]

Static loading refers to the acts of sitting down and standing, and dynamic loading refers to actively moving, such as walking and running. Static compression reduces oxygen concentration and increases lactic acid buildup.[43] Sustained static compression decreases nutrient diffusion into the disk and the exit of metabolic wastes.[49] Both sustained static loading and degeneration alter the water content of the disk, which can decrease the pore size, and, in turn, challenge solute diffusion, including that of glucose.[28] This may explain the low glucose levels found in long-term loading scenarios and in degenerated disks.

Collagen within the inner half of the annulus loses its tensile strength through the disorganization of lamella with sustained compression, as demonstrated in 1 week of in vivo loading.[50] Even after the stress is removed, cellularity is not restored because of the large amount of cell death. The annulus confines the nucleus radially; when axial loading exceeds the nucleus's swelling pressure, water is forced out of the disk, mainly via the cartilaginous end plate, in turn negatively affecting the biochemical environment of the disk. These findings suggest degenerative morphology is more the result of chronically applied stress than of acute trauma.

Sustained compressive loading is an oversimplification of a physiological scenario.[51] Dynamic loading more accurately depicts a real life diurnal cycle than does static loading.[45] Dynamic compression may increase nutrient diffusion by helping sustain the disk and synthesize ECM, thus preventing or reducing further disk degeneration. As the disk begins to lose its gel-like properties in degeneration, it depends on ECM to maintain its strength.[31] Dynamic loading plays a role in aiding matrix production, but it requires energy (ie, ATP) to do so. Such ATP usage, in turn, contributes to end plate calcification, which can lead to decreased nutrient transport to the nucleus, suggesting dynamic loading has some disk degenerative consequences. However, dynamic loading also increases oxygen consumption up to 30% in the NP.[43] This increases oxygen concentration and lowers lactate, suggesting a therapeutic role in disks with calcified end plates, as are often seen in aged and diseased conditions.

Dynamic compression also promotes glycolysis, resulting in more ATP production in the mitochondria of NP cells.[30] Mechanical loading boosts glucose consumption in annular cells and reduces the flow of glucose to the nucleus. However, the outer annulus, noted for its strong role in resisting bending forces, does not demonstrate diminished integrity with similar static loads.[50] Thus, the disk is able to maintain its stiffness and strength in bending.

Loading and Resting Phases. During an entire day's loading cycle, 3% to 10% (and occasionally even up to 20%)[52] of the total fluid is pressed out of the disk.[4] Pressure is released at night, and a compensating influx of fluid occurs.[2,4,52] This swelling phase, using a fluid flow pump, proves more useful in the integration of larger molecules compared with smaller ones, which diffuse easily into the tissue.[2,11,15] It takes 3 hours to catch up with the diffusion rate of an unloaded disk.[49] Although a loaded disk may show impaired small-solute transport after 1.5 hours, it also contributes to the main mechanism of convective flow for larger solutes.

There is greater resistance to fluid flow out of the disk than into it, resulting in the ability to recover the hydration lost throughout the day (up to 20% of disk's volume) while at rest.[52] This is necessary because an individual spends more time loading the spine (about 16 hours on average) than resting it (about 8 hours of sleep). In contrast to the healthy disk, the degenerated disk shows less of a response in the recovery phase as a result of less hydration (low water) and swelling pressure (from low amounts of proteoglycans).[44] These 2 factors coincide with less cell density and lower disk height, negatively affecting nutrient diffusion.

Spinal Position. The annulus changes dimensions in a fully flexed spine: The posterior aspect stretches vertically by about 50% and reduces the disk's thickness by 37% on average, whereas the anterior dimension compresses by 30%.[5] This allows for greater diffusion into the posterior half of the disk (a trend seen opposite to that in erect standing posture). Before flexion takes place, an area 4.4 to 6.0 mm into the posterior disk is left deprived of nutrients. This motion allows an adequate supply of glucose to reach this area. Also, by methods of fluid flow, larger molecules enter the posterior disk more readily with flexion. From the nucleus's perspective, flexed posture allows for increased diffusion from the annulus, a property particularly important for the transport of anions. These negative solutes typically avoid diffusion via the end plate because they are repelled by the negative fixed charge. However, any increase in nutrient delivery from the annulus is offset by a decreased supply from the end plates, seeing a greater distance to the midpoint of the nucleus. Overall, the anterior annulus is better supplied with nutrients than the posterior. Also, disk height decreases from anterior to posterior, which may contribute to the lesser degeneration seen in the anterior disk.

There is a lower incidence of lumbar disk disease in populations that adopt a flexed sitting posture.[5] Such flexed sitting postures, however, also increase intradiskal pressure by roughly 50%, as seen in lordotic posture. Lordotic posture is shown to decrease concentration gradients, consequently limiting diffusion.[18] Also, transitioning from supine to standing alters the distribution of glucose in the disk.[40]

Exercise/Motion. Fluid "pumping" via moderate exercise and movement may play an insignificant role in transporting small molecules, such as glucose, sulfate, and oxygen, but may significantly increase transport rates of larger molecules, such as hormones and enzymes.[4] Thus, immobilization may only have minor effects on the delivery of small molecules to the disk. Exercise and motion may increase small-solute incorporation into the disk over longer periods (months), suggesting a relationship with the increased vascularity to the disk.[53] Three months of exercise may increase oxygen and sulfate transport into the disk.[3]

Whole body vibration between 4 to 10 Hz may initiate a degenerative process.[54,55] Natural bending of the spine has a frequency similar to that of heavy machinery (eg, tractors). There is a significant correlation between disk herniations and truck driving. Physiologic loading (0.3 Hz) may likely improve diffusion rates into the disk. High-frequency loading (similar to static loading), however, may do the opposite.[56] Combining both high frequency (~ 10 Hz) and nutritional deficiency creates an additive effect on increasing cell death.[27]

Therapies

In an attempt to offer solutions to a degenerative condition, it may be possible to supply exogenous growth factors or differentiated stem cells to repair damaged or degenerated disks.[3] So far, these attempts have shown some success in restoring disk height and matrix growth in animal studies.

Notochordal cells have been suggested to play a role as stem cells for the NP.[32] Implanted notochordal cells have improved repair in acute disk degeneration (in animal models) by promoting matrix production via direct means (creating matrix) and indirect means (secreting soluble factors). However, the limited nutrient supply of a human degenerated disk may not meet the energy demand of the notochordal cells, which are already more sensitive to nutrient deprivation. Injecting growth factors directly into the disk is the most efficient method for reaching the nucleus.[36] Introducing the substance via the bloodstream would require consideration of the concentration once it reaches its target to avoid dissipation by that point.

Nimodipine, a calcium channel blocker, increases endplate vascularity and consequently increases diffusivity.[41] This serves as an indication for a potential future treatment strategy for degenerative disk disease. Biological treatment may be helpful in the aging disk, where sufficient nutrient supply is provided by normal diffusion patterns. However, such methods may be unsuccessful in degenerated disks because of their impaired structure and function. Vascularization of the disk corresponds with autoimmune reactions, immunoglobulin accumulation, and NP destruction. Constantly open marrow disk channels can result in extra fusion of protein complexes. Transforming growth factor beta may increase proteoglycan production at a pH of 7.4.[3] However, at a pH of 6.8 (physiologic pH), this upregulation disappears. It also has the tendency to lower the pH further for the disk, suggesting its use is counterproductive.

Discussion

Summary

Disk cells rely on glucose for energy to survive, and they rely on oxygen to produce matrix. Cells in the nucleus use less glucose and produce more ATP. A slightly alkaline pH is necessary for cells to survive and function. Cell metabolism affects lactic acid production and diffusion, influencing the pH. Cytokines and growth factors also boost glycolysis, in turn dropping pH and glucose levels to potentially dangerous levels.

Nutrients rely on 2 supply routes to reach the cells. The predominant one is via the capillary beds of the end plate and the other is via the outer annulus. Impeding these paths deprives the cells of nutrients. Because the IVD is avascular, it depends on diffusion and convection as transport mechanisms to move nutrients within the disk. Compression alters transport by forcing water out of tissue. Ionic charges of disk material affect the transport of solutes into the disk. A solute's size, shape, and ionic charge dictate how well it is transported.

Supplying exogenous growth factors, stem cells, or cartilage implantations to counter degenerating disks has been reported to be helpful in animal studies. Certain calcium channel blockers increase vascularity and, in turn, diffusion into the disk. Incorporating notochordal cells may not be sustainable because they are more sensitive to nutrient deprivation, and degenerating disks already lack nutrients.

Limitations and Future Studies

The content of this review article is limited to the findings of the articles reviewed. The referenced articles were included based on their perceived relevance to the topic. Both in vivo and in vitro research studies were assessed, as were animal, human, and computational models. Because in vitro contexts assess molecules outside of their normal environment, there are inherent limitations with extending such laboratory results to natural biological contexts. Although animal studies and computational models provide insight into biological processes, further research may want to establish clinical guidelines for treating and preventing degenerative disk disease in humans.

Much of the treatment interventions supplying exogenous factors used animal studies. Further research may want to focus on treating and preventing degenerative disk disease in humans.

Conclusion

Biomechanical and biological factors play substantial roles in nutrient transport mechanisms. Disruptions to these processes have implications in disk degeneration. Such disruptions include dysfunctional loading and spinal position, lack of motion, high-frequency loading, disk injury, aging, smoking, an acidic environment, and a lack of nutrient bioavailability.

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Concept development (provided idea for the research): C.M.D.G.

Design (planned the methods to generate the results): C.M.D.G.

Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): C.M.D.G.

Data collection/processing (responsible for experiments, patient management, organization, or reporting data): C.M.D.G.

Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): C.M.D.G.

Literature search (performed the literature search): C.M.D.G.

Writing (responsible for writing a substantive part of the manuscript): C.M.D.G.

Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): C.M.D.G.

Practical Applications

- Transport of nutrients to disk cells is speculated to occur through the capillary beds and marrow contact channels of the permeable cartilaginous end plates.
- Degradation and breakdown of the extracellular matrix due to nutrient deprivation in disk cells are some of the likely causes of intervertebral disk degeneration.
- Progressive nutrient transport disruptions may actively contribute in advancing the phases of degenerative disk disease.

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