The Chemistry of Discogenic and Disc Herniation Pain: Diet and Nutritional Supplement Considerations

David R. Seaman, DC, MS

TABLE OF CONTENTS

PREVALENCE OF DISC ISSUES

Back Pain is one of the most common complaints reported to physicians and a leading cause of disability. The tissues primarily responsible for generating spine pain include muscles, facet joints, sacroiliac joints, the intervertebral disc, and spinal nerve roots that are irritated most commonly by herniated discs.

The percentage of chronic spinal pains caused by muscle nociception is not known. Of the remaining tissues, the intervertebral disc, manifesting as discogenic pain and radicular pain, is the most common generator of chronic low back pain (1,2).

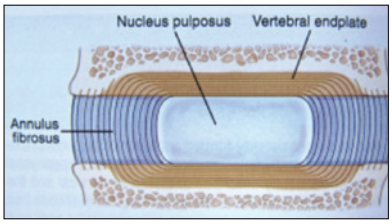
- 20% sacroiliac joint
- 15-40% facet joint
- 40% primary disc
- 1-5 % radicular pain due to disc herniation

Treatments should be applied in the context of disc biology, pathology and natural history issues. Manual therapy and rehabilitation can be viewed largely as mechanical interventions, which can substantially reduce pain and suffering. This aspect of treatment that is commonly missed is nutritional chemistry, which addresses the inflammatory issues of the disc. These are not adequately understood.

DISC BIOLOGY

The intervertebral disc consists of three key anatomic components: the nucleus pulposus, the annulus fibrosis, and the vertebral endplate (Figure 1) . The nucleus consists largely of proteoglycans (65%) and collagen (15%).

The annulus contains more collagen (70%). Approximately 20% of the annulus is made of proteoglycans, which are present to prevent annular buckling by functioning as a

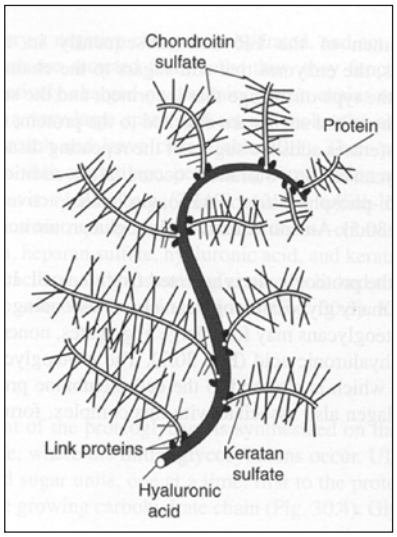


gel that helps to maintain adherence between the annular layers/lamellae (3).

The vertebral endplate is also made up of proteoglycans and collagen. Thus, the majority of disc structure is proteoglycans and collagen, which means that disc biology and disc health are really about understanding proteoglycan/collagen biochemistry.

The large concentration of proteoglycans in the nucleus allows for imbibition of water, very similar to a sponge. The numerous chondroitin sulfate chains are negatively charged and so attract extracellular sodium ions and water. Figure 2 illustrates a proteoglycan molecule.

Figure 2. Proteoglycan



To put the hydrating capability of the nuclear proteoglycans in context, we are approximately 2 cm taller in the morning. This equilibrates within 1 hour as we move about, which is why it is advisable to avoid lumbar flexion movements upon arising (4). In one study, avoiding AM flexion led to a significant reduction in low back pain versus controls (5).

Because the nucleus is fluid-rich, it would compress and expand radially during loading; however, this is prevented by the strong collagen-rich layers of the annulus. This nuclear space containment by the annulus allows for the nucleus to be the primary responder to loading, which spares the annulus from an excessive compressive burden (Figure 3). Without proper nucleus biochemistry, the annulus would buckle during sustained compressive loading. The ability of the nucleus to bear compressive loads is stronger than the vertebral trabecular bone and the endplates (4).

The health of the nuclear proteoglycans is maintained by structurally and functionally intact endplates. The nucleus primarily receives nutrients by diffusion through the endplates. In addition to this relationship between the nucleus and endplate, the endplate very importantly insures a distinct anatomic separation between the nucleus and the vessel-rich trabecular bone of the vertebral bodies.

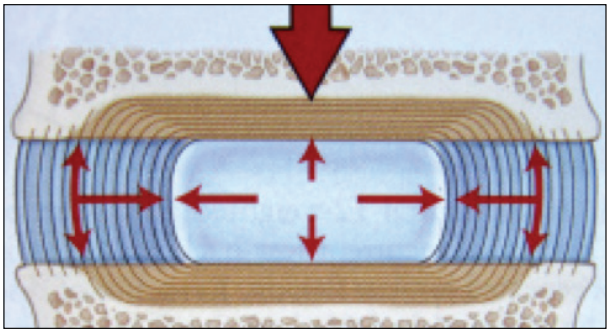


Figure 3. Disc loading

UNDERSTANDING THE PATHOLOGICAL PROCESS

The proteoglycans and collagen of the nucleus and annulus are synthesized and maintained by chondrocytes and fibroblasts. Normal connective tissue homeostasis involves the removal and replacement of old proteoglycans and collagen. Removal is achieved by matrix metalloproteinases (MMPs), which are a family of connective tissue degrading enzymes, formerly referred to individually as collagenase (now MMP-1), gelatinase (now MMP-2), stromelysin (now MMP-3), and elastase (now MMP-12).

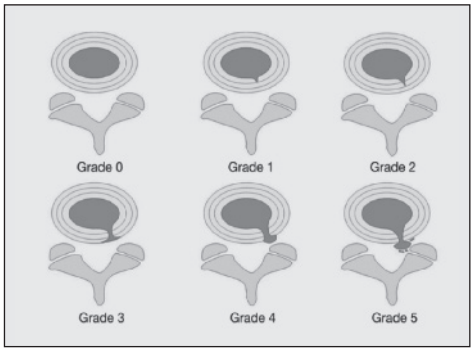
MMPs are also involved in the remodeling of injured connective tissue. As with normal homeostatic turnover, MMPs are "turned on" to degrade the damaged proteoglycans and collagen. MMPs are then turned off by tissue inhibitors of metalloproteinases (TIMPs). Thus, the proper MMP/TIMP balance allows for replacement and restoration of connective tissue function. In the case of the disc degradation, discogenic pain, and disc herniation, which can be collectively referred to as discopathy, an imbalance favoring MMP overactivity appears to be the driving force (3,5-8).

The process of disc degradation begins with damage to the weakest link within the disc's anatomy, which is the vertebral endplate. In fact, the first unequivocal sign of disc damage occurs in the vertebral endplates (1,3). Endplate damage disrupts the delicate homeostatic environment of the nucleus because such injury leads to the activation of MMPs and the degradation of the nucleus pulposus (1,3). By degrading the nuclear proteoglycans, MMPs limit the ability of the nucleus to imbibe water and maintain its cohesive structure that normally resists and properly distributes compressive loads. Thus, the chemical degradation of the nucleus leads to altered spinal mechanics.

Injury to the endplate most commonly occurs without symptoms and only becomes noticeable if MMPs are not properly turned off. This gradually leads to degradation of the of the entire nucleus and a radial fissure into the annulus and the subsequent time-delayed development of discogenic pain, which may proceed to frank herniation and radicular pain. The gradual chemical degradation of the nucleus and annulus can create the illusion that pain is largely "mechanical" and that disc herniation is due to an obvious traumatic mechanical event.

Inaccurate terms, such as a "full thickness radial tears" and "circumferential tears" in the annulus, further create the impression that radial fissures and delamination of the annulus are created by altered mechanics. No evidence supports the notion that this occurs (1,3). Figure 4 illustrates the nuclear and annular MMP-driven degradation process in the context of the grading procedure for discograms (9).

Figure 4. Discogram grading



The degraded nuclear material, which is highly inflammatory and acidic, follows the path created by the activated MMPs into the annulus. Upon reaching the innervated outer third of the annulus (Grade 3), the inflammatory/acidic nuclear material will activate nociceptors and cause "discogenic" pain, which accounts for about 40% of all chronic back pain presentations (1-3). If the MMPs degrade the outer annulus, the nuclear material will herniate and inflame nerve roots, leading to radicular pain (Grade 4 & 5). Approximately 1-5% of back presentations are radicular in nature (1-3).

Once the MMPs enter the annulus as visualized in a Grade 1 discogram, they begin to degrade annular proteoglycans and collagen, the outcome of which is an annulus that loses it mechanical integrity, which places a greater compressive burden on the annulus and facet joints. If pain is present at this point in the process, it will not be discogenic (3). Facet joint pain constitutes 15-40% of back pains (2), and they are the likely pain generator in this case, as they are required to bear an uncommon compressive burden. Thus, it is most desirable for MMP inhibition to occur before the MMPs and the degraded inflammatory nuclear material breach the inner annular layers and substantially alter loading mechanics.

MMP ACTIVATION

From an operational and practical perspective, it is important to remember that discogenic pain and disc herniation occur because of upregulated MMP activity and other inflammatory mediators.

Multiple factors are involved in the activation and inactivation of MMPs. The precise details have yet to be uncovered by scientists; however, it appears that chronic inflammation is a primary cause. In reality, the chronic activation of MMPs is part of chronic inflammation, which is a response to inflammatory lifestyle/dietary choices to be described in this section.

In the case of the disc, inflammatory mediators such as interleukin-1 and tumor necrosis factor are known to activate MMPs, which leads to degradation of the nucleus (6). In fact, MMP-3 overactivity has been implicated as a therapeutic target for disc degradation and herniation (8). To this end, cytokine inhibitors have been used to treat surgically removed herniated disc specimens, resulting in a reduction of MMP-3 (10).

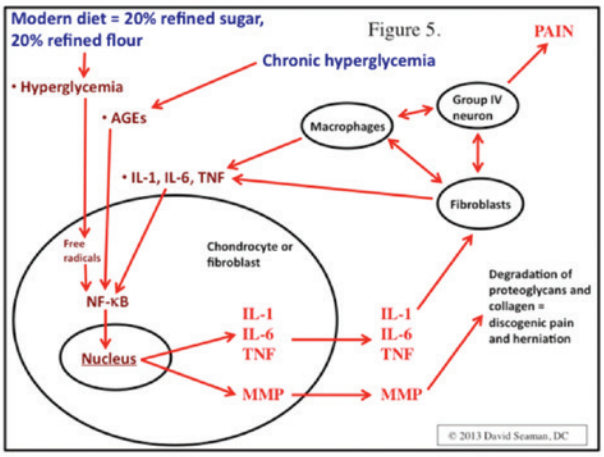
It is important to remember that the sources of cytokines and MMPs are the cells within the disc tissues, especially chondrocytes and fibroblasts, and likely macrophages but they are involved later in the process when the nuclear material reaches the outer annulus. An area of potential confusion here is that chondrocytes and fibroblasts are typically viewed as cells that deposit proteoglycans and collagen that leads to healing. However, these same cells produce cytokines and MMPs in response to inflammatory stimuli, and will continue to do so as long as inflammatory stimuli are present.

Despite the well-known mechanisms described above, to suggest that inflammatory stimuli, such as overeating sugar and flour, can promote the disc herniation, is nonetheless viewed as unreasonable. And this is because the predominant view of discopathy is that it is a mechanical process that only becomes somewhat chemical upon herniation. The following evidence should help to counter this erroneous notion:

- Patients with the metabolic syndrome and type 2 diabetes have an increased risk of expressing disc herniation (11-13).
- Advanced glycation end products (AGE), which develop due to chronic hyperglycemia, are associated with disc degradation and herniation (14,15).
- Patients with the metabolic syndrome, type 2 diabetes, hypertension, dyslipidemia, and obesity have a generalized elevation of MMPs, including MMP-3 (16).

These relationships are illustrated in Figure 5. While the chemical processes in this image are simplified for ease of learning, they are still biochemically accurate.

Figure 5



Nuclear factor-kappa B (NF-κB) is activated refined carbohydrate and AGE, which then drives the production of cytokines and MMPs. The MMPs degrade the local connective tissue, while cytokines can perpetuate local inflammatory signaling and further MMP release. If MMPs do not turn off, disc degradation will continue.

Key point: Discs do not degrade and then generate discogenic pain and herniation unless MMPs are activated.

It should be understood that the reason why MMPs turn on and stay on is not known. We do know that patients with metabolic syndrome and diabetes are more prone to MMP upregulation disorders such as disc herniation (6-8) and atherosclerosis (16), indicates that dietary problems are a primary cause. To combat MMP overactivity, Hopps and Caimi state (16):

> "The evidences of an improvement in MMP/TIMP ratio with diet, exercise and medical therapy should encourage further investigations with the intent to contrast the atherosclerotic process and to reduce morbidity and mortality of this kind of patients."

It should be understood that dietary, exercise, and pharmaceutical recommendations are not provided to "treat" atherosclerosis, but to reduce "out-of-control" MMPs/inflammation. Thus, the same treatment recommendations apply to patients with "out-of-control" MMPs/ inflammation manifesting as discopathy.

PHARMACEUTICAL INTERVENTIONS

NSAIDs and Tylenol are the common meds used to treat back pain that may be discogenic or coming from facet or sacroiliac joints. The same may be used with disc hernation and the associated radiating pain due to an inflamed nerve root.

When the herniation/radiating pain is severe, steroid dose packs may be prescribed. Cytokine inhibitors have also been tried with less success. Figure 6 illustrates the mindset associated with prescribing these medications.

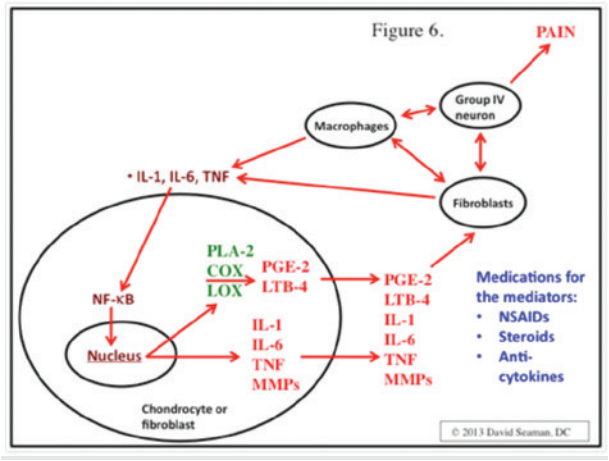


Figure 6

Medications are given for the purpose of reducing the chemistry of inflammation. The goal is to calm down the excessive inflammation so that healing can occur. No consideration is given to the fact that dietary chemistry can promote the perpetuation of inflammation chemistry. This may be especially important for discogenic and disc herniation patients as the pain can be quite severe. Figure 7 illustrates dietary chemistry that drives inflammation chemistry.

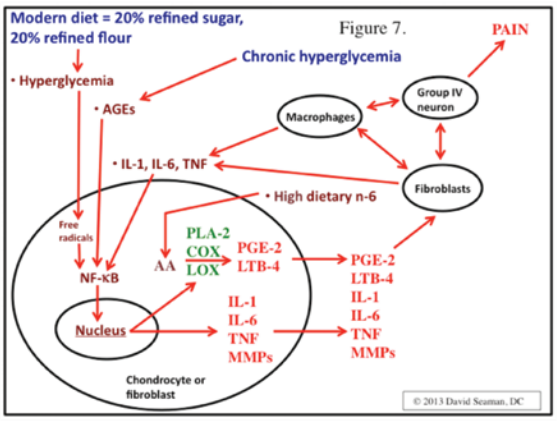


Figure 7

Figure 7 illustrates how sugar, AGEs, and omega-6 fatty acids drive inflammation chemistry. While the relationship between diet and inflammation has been studied for many years, the relationship is still confusing to many practitioners as "inflammation" is typically viewed in the context of over injury. The concept that diet can be "injurious" is new and new facts, despite being facts, can take time to gain momentum.

THE DIETARY CONNECTION

Studies have now identified that overweight/obese individuals and patients with the pro-inflammatory metabolic syndrome and atherosclerotic risk factors are more likely to have localized back pain and radiating pain because the systemic inflammation associated with these conditions is superimposed on to local areas of stress and injury (17-21).

It is important for patients to know that their diet can directly increase or decrease systemic inflammation, which can inflame local areas of inflammation. The average American's diet contains approximately 60% of calories coming from sugar, flour, and refined oils. The primary refined oils include corn, safflower, sunflower, cottonseed, and soybean oils, which contain an excessive amount of linoleic acid, an omega-6 (n-6) fatty acid, which the body converts into arachidonic acid and then into pain-producing prostaglandin E2 (PGE2). Another 15-20% of calories come from over-fat animal products and 10% from dairy. No more than 10% comes from fruits and vegetables (22). The consumption of this pro-inflammatory diet in the high calorie fashion engaged by most, leads to an immediate postprandial surge in blood sugar, free fatty acids, and triglycerides (23).

The postprandial blood sugar surge, in particular, overwhelms mitochondria and causes them to generate an excess of free radicals. This induces systemic inflammation (Figure 7), endothelial dysfunction, hypercoagulability of the blood, and sympathetic hyperactivity (14). Specific test meals that cause immediate postprandial inflammation include three slices of buttered white toast (900 calories) and a typical McDonald's breakfast that consists of an Egg Muffin, Sausage Muffin and two hash brown patties (910 calories) (24-26). In other words, patients in pain should avoid refined sugar, flour, and oils, which create immediate systemic inflammation that has the potential to augment the inflammation already present in a disc or nerve root.

Patients in pain, and particularly those with inflammatory disc conditions, i.e., discogenic and nerve root pain, should consume an anti-inflammatory diet that is relatively low in calories. The food focus should be omega-3 fish and eggs, lean meat and chicken, vegetables, fruit, and nuts (27). This anti-inflammatory diet can be augmented by key supplements with a strong anti-inflammatory profile.

USE OF SUPPLEMENTS IN TREATMENT

Supplementation can be viewed from two perspectives; those being general health/prevention versus active inflammation reduction and each is illustrated in Figure 7. The general health/prevention perspective should be viewed in the context of using supplements to help reduce factors that stimulate inflammation. Chromium and lipoic acid can be helpful in patients with pro-inflammatory glycemic dysregulation involving hyperglycemia and AGE production. Omega-3 fatty acids can help to restore omega-6/omega-3 balance, so that COX/LOX enzymes generate anti-inflammatory mediators. Magnesium and vitamin D also should be to support glycemic control and a host of anti-inflammatory signaling mechanisms.

Supplements for reducing active inflammation include proteolytic enzymes and botanicals. NutraDisc is a unique product formulation contains proteolytic enzymes, curcumin, and glucosamine/chondroitin sulfate.

PROTEOLYTIC ENZYMES

Enzymes have a long history of use in the treatment of acute injuries. Discogenic pain and disc herniation can be viewed as acute injuries, as each can come on suddenly and be associated with severe pain. Supplemental proteolytic enzymes have not been specifically studied in the context of disc herniation; however, this should not dissuade practitioners from using enzymes as the connective tissues of the disc are no different than the connective tissues of the ankle. When enzymes are used immediately post-ankle sprain (Bucci), the outcome was a quicker return to work in the enzyme group (1.7 days) versus placebo (4.4 days). Subjects taking enzymes were able to resume exercise training earlier (9.4 days) compared to those taking placebo (15.9 days). Studies with enzymes routinely show anti-inflammatory benefits that translates into quicker recovery and return to work or training (28).

The mechanisms of action of proteolytic enzymes are extremely diverse. Several anti-inflammatory mechanisms are proposed to be at work (29-33):

- reduces the level of prostaglandin E2 (PGE2) and of thromboxane A2 in exudates during acute inflammation
- breakdown of excessive cytokines in vicinity of inflammatory site
- reduces the blood level of bradykinin
- stimulate neutrophil apoptosis
- reduces neutrophil migration to sites of inflammation
- reduces the blood level of fibrinogen
- supports fibrinolysis
- activates plasmin
- prevents aggregation of blood platelets
- prevents adhesion of platelets to endothelial cells of blood vessels

CURCUMIN

Curcumin is one of the most researched natural products (34). It is known to be a modulator of multiple inflammatory signaling mechanisms including NF-κB, COX, and LOX. The outcome of this activity is a reduction in pro-inflammatory cytokines, prostaglandin, and leukotrienes. More recently, the activity of curcumin was reviewed in the context of articular chondrocyte function. Multiple anti-inflammatory and protective mechanisms were cited (35-37), such as:

- inhibition of NF-κB
- inhibition of MMPs
- inhibition of IL-1-induced glycosaminoglycan release
- inhibition of chondrocyte apoptosis
- inhibition of IL-1, IL-6, IL-8, and PGE2

Knowledge of these mechanisms has led researchers to study the effects of curcumin on intervertebral disc inflammation. While this was an in vitro study, the authors concluded that, "based on its anti-inflammatory and anti-catabolic effects, intradiscal injection of curcumin may be an attractive treatment alternative." In an in vivo murine model of arthritis, oral administration of curcumin reduces MMP-1 and MMP-3 (36).

In a human clinical trial of curcumin's efficacy as an anti-rheumatic agent, investigators compared curcumin with that of phenylbutazone (an NSAID) in a short-term, double-blind, crossover study involving 18 relatively young RA patients (age range, 22–48 years). Each subject received a daily dose of either curcumin (1200mg) or phenylbutazone (300mg) for 2weeks. Curcumin was well tolerated, had no side effects, and exerted an antirheumatic activity comparable to that of phenylbutazone (34).

GLUCOSAMINE CHONDROITIN SULFATE

Glucosamine sulfate as a monotherapy has mostly been studied for its treatment effect in patients with osteoarthritis (OA) of the knee in patients who average about 60 years of age. A patient is typically considered to have a positive outcome if pain is reduce by at least 20% (38).

The beneficial effect of glucosamine focuses largely around the notion that cartilage synthesis is enhanced – this should be viewed as an urban legend because it exaggerates the cartilage synthesis benefits and misses the anti-inflammatory connection.

The loss of cartilage in OA joint is not due to wear and tear or compression – this is impossible. We know this because the loss of cartilage starts when joint space is normal – very important point to understand – we see late stage OA and assume wear and tear are the cause. Figure 8 below specifically demonstrates that inflammation and MMPs degrade cartilage in OA (39), which is the same process that causes disc nuclear degradation and herniation.

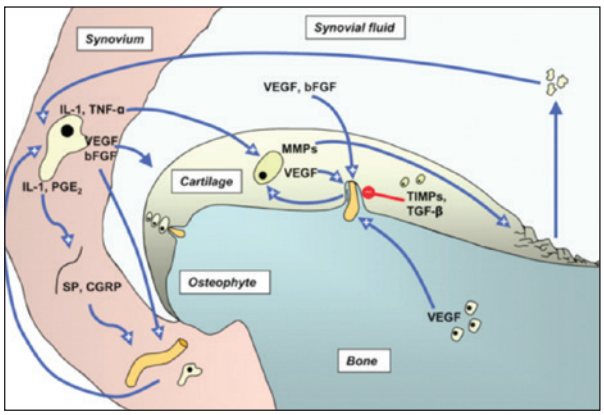


Figure 8. Inflammation/MMPs cause cartilage loss not wear

An interesting study looked for predictors of glucosamine success and identified that body mass index (BMI) was a key predictor – less than 27.9 is associated with a greater chance for improvement (40). This led me to look at other studies and I found that the best outcome in terms of pain reduction and joint space protection involved patients with a BMI of 25.7, which means they were just slightly over weight (41). Clearly, the lower the BMI, the better then outcome. It is important to understand that an expanding BMI is:

- absolutely linked to greater levels of systemic inflammation (42)
- associated with a greater expression of OA (19)
- associated with increased activity of MMPs (16)

These data suggest that less inflamed patients will respond better to glucosamine/chondroitin supplementation, which means that patients need to pursue a normal BMI by eating anti-inflammatory foods. And interestingly, regarding glucosamine/chondroitin, multiple anti-inflammatory mechanisms are ascribed to their supplementation based on basic scienced studies (43-46):

- inhibition of NF-κB
- inhibition of MMPs
- inhibition of PGE2 and inducible nitric oxide
- inhibition of pro-inflammatory cytokine signaling

With the above information in mind, glucosamine/chondroitin should be positioned as an anti-inflammatory supplement that works better in knee OA patients with a normal BMI. Only a handful of studies have been conducted on joints other than the knee.

Regarding back pain, little research has been done with glucosamine. One study using a dosage of 1,500 mg of glucosamine sulfate in patients with chronic back pain (> 6 months) and degenerative lumbar OA showed no difference compared to placebo (47). The average age of the patients was 47.5-49.4 depending on the group and the average BMI was 25.4. This does not mean that glucosamine is not useful; it means that treating a multifactorial condition called back pain with a monotherapy is not effective. This should not be surprising to anyone.

Treating a complex condition with only 1,500 mg of glucosamine (about 6 calories worth of carbohydrate) should not be expected to have a substantial relieving or curative effect. This is not to say that people should psychologically swing to the other extreme and believe that glucosamine or glucosamine/chondroitin is not beneficial. An interesting case history about a patient with chronic back had symptomatic and biochemical improvements with glucosamine/chondroitin supplementation during a 2 year period (48).

From a broader health view, researchers looked at supplementation with glucosamine, chondroitin, and fish oil in the context of high sensitivity C-reactive protein levels, which is a marker of chronic inflammation. They found hs-CRP reductions of 17% with glucosamine, 22% with chondroitin, and 16% with fish oil compared with participants who did not take the supplements (49). Long term glucosamine/chondroitin users also appear to have a greater chance for increased longevity (50).

NATURAL HISTORY OF DISC HERNIATION

All the details about the disc injury, internal disruption and the herniation process are not understood. It is known, however, that when discs do herniate as in a grade 4/5 discogram, they should resorb. Some do and some do not. The desorption process is actually accomplished by MMPs, a situation where we want MMPs to do their job.

This can seem paradoxical a bit. There are three aspects of MMP function that should be understood:

1. We want MMPs to be active at a homeostatic level for normal repair/regeneration processes.
2. When individuals "flame up," MMPs do not turn off after endplate damage, which can lead to discogenic pain, wherein the goal is to reduce inflammation with diet and supplements to turn off the overactive MMPs.
3. Upon herniation, the body generates a robust inflammatory response, which involves infiltration of macrophages that release MMPs, which we want for the purpose of degrading the herniated material. However, since most patients are "flamed up," they also get an overactive inflammatory response due to the release of an excess of pro-inflammatory prostaglandins and cytokines and a lack of anti-inflammatory prostaglandins and cytokines (27).

The anti-inflammatory diet and all supplements mentioned earlier can help to normalize the inflammatory response so patients have a better chance of healing (27); and in the case of disc herniation this means allowing for the normal resorption the herniated discal material, and reducing pain and nerve root compromise.

COMMON TREATMENTS

In the context of discogenic pain, it appears that the McKenzie method of end-range loading is the preferable treatment.

When the intervertebral foramen is compromised due to degenerative changes, it appears that traction, sometimes called decompression, is the preferred treatment.

However, there are no absolutes when it comes to manual care interventions. Standard chiropractic manipulation can also be used with equal success. The best approach should be considered based on how a patient responds. The main goal should be to reduce pain and dysfunction, so as to make the patient comfortable, whether the patient has discogenic pain or disc herniation. As both conditions are inflammatory, deflaming with diet and supplements are also indicated for all patients.

Some patients do not respond to manual care and move to get minimally invasive procedures such as epidural steroid injections (ESI). The fact that steroids are being used demonstrates that the patient is excessively flamed up. These patients also need deflaming with diet and supplements.

Compared to conservative manual care and minimally invasive injections, surgery is considered an invasive treatment, micro discectomy being the least invasive. Patients undergoing surgery are really getting a controlled traumatic event that naturally leads to an inflammatory event. These patients are also candidates for deflaming with diet and supplements.

NUTRADISC® with MERIVA® BIOAVAILABLE CURCUMIN

PART 1: DISC EDUCATION

Key Points to Remember

1. Function of nucleus is to respond to and distribute compressive forces.
2. Endplate damage begins the nuclear degradation process.
3. The degradation and herniation process are both inflammatory and are driven by MMPs.
4. The pro-inflammatory diet turns on MMPs.
5. Metabolic syndrome and diabetes are associated with increased MMP activity and a greater risk of developing discopathy.
6. Anti-inflammatory diet modulates MMPs into the homeostatic mode.
7. Chromium and lipoic can be used to improve blood sugar regulation.
8. Basic supplements such as omega-3s, vitamin D, and magnesium offer well-known diverse anti-inflammatory benefits.
9. Specific supplements, including proteolytic enzymes, curcumin and glucosamine/chondroitin can modulate inflammatory mediators including MMPs.
10. Patient responsiveness is not predictable as it depends on genetics, degree of inflammation, and multiple lifestyle factors, particularly mindset and activity levels

IMPORTANT POINT:

Disc herniation continues to be taught in medical and chiropractic schools from the perspective of mechanical tearing of the annulus that causes the nucleus to travel along radial fissures and then on to herniation. Despite the fact that MMPs drive the entire process, this fact is unknown to many.

Some to many MDs, but particularly DCs and PTs, are trapped in the mechanical mindset and reject the fact that discopathy is a chemically-driven process. Despite this fact, they also understand that disc herniation is an inflammatory event because many patients are given NSAIDs and steroids and experience relief. In the chiropractic setting, when patients respond to manual care, it is most likely because these patients are not excessively inflamed. And research has shown that manipulation can modulate local spinal tissue inflammation. However, when patients do not respond to manual care or respond slowly, this is because excess inflammation is at work and many patients fall into this category. These are the patients who are candidates for diet and supplementation.

REFERENCES

1. Adams M, Bogduk N, Burton K, Dolan P. The biomechanics of back pain. New York: Churchill Livingstone; 2002: p.78.

2. Souza TA. Differential diagnosis and management for the chiropractor: protocals and alogorithms. Gaithersburg: Aspen Pub; 2009: p.144.

3. Bogduk N. Clinical anatomy of the lumbar spine. New York: Churchill Livingstone; 2005.

4. McGill SM. Low back disorders: evidence-based prevention. Champaign (IL): H Kinetics; 2002.

5. Snook SH, Webster BS, McGorry RW. The reduction of chronic, nonspecific low back pain through the control of early morning lumbar flexion: 3-year follow-up.J Occup Rehabil. 2002;12(1):13-9.

6. Goupille P, Jayson MI, Valat JP, Freemont AJ. Matrix metalloproteinases: the clue to intervertebral disc degeneration? Spine 1998;23(14):1612-26.

7. Roberts S, Caterson B, Menage J, Evans H, Jaffray DC, Eisenstein SM. Matrix metalloproteinases and aggrecanase: their role in disorders of the human intervertebral disc. Spine. 2000;25(23):3005-13.

8. Bachmeier BE, Nerlich A, Mittermaier N et al. Matrix metalloproteinase expression levels suggest distinct enzyme roles during lumbar disc herniation and degeneration. Eur Spine J. 2009;18:1573-86.

9. Kim HI, Shin DG. Causes and diagnostic strategies for chronic low back pain. J Korean Med Assoc. 2007;50(6):482-93.

10. Genevay S, Finckh A, Mezin F, Tessitore E, Guerne PA. Influence of cytokine inhibitors on concentration and activity of MMP-1 and MMP-3 in disc herniation. Arthritis Res Ther. 2009;11(6):R169.

11. Jhawar BS, Fuchs CS, Colditz GA, Stampfer MJ. Cardiovascular risk factors for physician-diagnosed lumbar disc herniation. Spine J. 2006, 6:684-91.

12. Sakellaridis N. The influence of diabetes mellitus on lumbar intervertebral disk herniation. Surg Neurol. 2006, 66:152-4.

13. Sakellaridis N, Androulis A. Influence of diabetes mellitus on cervical intervertebral disc herniation. Clin Neurol Neurosurg 2008, 110:810-2.

14. Tsuru M, Nagata K, Jimi A et al. Effect of AGEs on human disc herniation: intervertebral disc hernia is also effected by AGEs. Kurume Med J. 2002;49(1-2):7-13.

15. Jazini E, Sharan AD, Morse LJ et al. Alterations in magnetic resonance imaging T2 relaxation times of the ovine intervertebral disc due to non-enzymatic glycation. Spine. 2012;37(4):E209-15.

16. Hopps E, Caimi G. Matrix metalloproteinases in metabolic syndrome. Eur J Intern Med. 2012;23(2):99-104.

17. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between obesity and low back pain: a meta-analysis. Am J Epidemiol. 2010;171:135-54.

18. Mantyselka P, Miettola J, Niskanen L, Kumpusalo E. Persistent pain at multiple sites-connection to glucose derangement. Diabetes Res Clin Pract. 2009;84(2):e30-2.

19. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis). Osteoarthritis Cartilage. 2013;21:16-21.

20. Shiri R, Karppinen J, Leino-Arjas P et al. Cardiovascular and lifestyle risk factors in lumbar radicular pain or clinically defined sciatica: a systematic review. Eur Spine J. 2007;16:2043-54.

21. Heuch I, Heuch I, Hagen K, Zwart JA, Associations between serum lipid levels and chronic low back pain. Epidemiology. 2010;21:837-41.

22. Cordain L, Eaton SB, Sebastian A et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr. 2005;81:341-54.

23. O'Keefe JH, Gheewala NM, O'Keefe JO. Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. J Am Coll Cardiol. 2008;51(3):249-255.

24. Aljada A, Mohanty P, Ghanim H, et al. Increase in intranuclear nuclear factor kappaB and decrease in inhibitor kappaB in mononuclear cells after a mixed meal: evidence for a proinflammatory effect. Am J Clin Nutr. 2004;79(4):682-690.

25. Aljada A, Friedman J, Ghanim H, et al. Glucose ingestion induces an increase in intranuclear nuclear factor kappaB, a fall in cellular inhibitor kappaB, and an increase in tumor necrosis factor alpha messenger RNA by mononuclear cells in healthy human subjects. Metabolism. 2006;55(9):1177-1185.

26. Erridge C, Attina T, Spickett CM, Webb DJ. A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. Am J Clin Nutr. 2007;86(5):1286-1292.

27. Seaman DR. Anti-inflammatory diet for pain patients. Pract Pain Management. 2012;12(10)36-46. http://www.practicalpainmanagement.com/issue/1210.

REFERENCES

28. Bucci L. Nutrition Applied to Injury Rehabilitation and Sports Medicine. Boca Raton: CRC Press; 1995: p.167-76.

29. Leipner J, Iten F, Saller R. Therapy with proteolytic enzymes in rheumatic disorders. Biodrugs. 2001; 15(12):779-89.

30. Maurer HR. Bromelain: biochemistry, pharmacology, and medical use. Cell M ol Sci. 2001; 58:1234-45.

31. Tilwe GH, Beria S, Turakhia NH, Daftary GV, Schless W. Efficacy and tolerability of oral enzyme therapy as compared to diclofenac in active osteoarthrosis of knee joint: an open randomized controlled clinical trial. J Assoc Physicians India. 2001; 49:617-21.

32. Fitzhugh DJ, Shan S, Dewhirst MW, Hale LP. Bromelain treatment decreases neutrophil migration to sites of inflammation. Clin Immunol. 2008;128(1):66-74.

33. Pavan R, Jain S, Kumar A. Properties and therapeutic application of bromelain: a review. Biotechnol Res Int. 2012;2012:976203.

34. Goel A, Kunnumakkara AB, Aggarawal BB. Curcumin as "curecumin": from kitchen to clinic. Biochem Pharmacol. 2008;75:787-809.

35. Henrotin Y, Clutterbuck AL, Allaway D et al. Biological actions of curcumin on articular chondrocytes. Osteoarthitis Cartilage. 2010;18:141-49.

36. Mun SH, Kim HS, Kim JW et al. Oral administration of curcumin suppresses production of matrix metalloproteinase (MP-1) and MMP-3 to ameliorate collagen-induced arthritis: inhibition of the PKC/JNK/c-Jun pathway. J Pharmacol Sci. 2009;111:13-21.

37. Klawitter M, Quero L, Klasen J et al. Curcuma DMSO extracts and curcumin exhibit an anti-inflammatory and anti-catabolic effect on human intervertebral disc cells, possibly by influencing TLR2 expression and JNK activity. J Inflamm (Lond). 2012;9(1):29.

38. Clegg DO, Reda DJ, Harris CL et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. New Eng J Med. 2006; 354:795-808.

39. Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis and inflammation. Rheumatology. 2005;44(1):7-16.

40. Bennett AN, Crossley KM, Brukner PD, Hinman RS. Predictors of symptomatic response to glucosamine in knee osteoarthritis: an exploratory study. Br J Sports Med. 2007;41:415–419.

41. Pavelka K, Gatterová J, Olejarová M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med. 2002; 162:2113–23.

42. Bays HE: Adiposopathy: is sick fat a cardiovascular disease? J Am Coll Cardiol. 2011;57:2461-73.

43. Verbruggen G. Chondroprotective drugs in degenerative joint diseases. Rheumatology (Oxford). 2006;45(2):129-38.

44. Phitak T, Pothacharoen P, Kongtawelert P. Comparison of glucose derivatives effects on cartilage degradation. BMC Musculoskeletal Disorders 2010, 11:162.

45. Iovu M, Dumais G, du Souich P. Anti-inflammatory activity of chondroitin sulfate. Osteoarthritis Cartilage. 2008;16(Suppl 3): S14-8.

46. Vallières M, du Souich P. Modulation of inflammation by chondroitin sulfate. Osteoarthritis Cartilage. 2010;18(Suppl 1): S1-6.

47. Wilkens P, Scheel IB, Grundnes O, Hellum C, Storheim K. Effect of glucosamine on pain-related disability in patients with chronic low back pain and degenerative lumbar osteoarthritis: a randomized controlled trial. JAMA. 2010;304(1):45-52.

48. van Blitterswijk WJ, van de Nes JC, Wuisman PI.Glucosamine and chondroitin sulfate supplementation to treat symptomatic disc degeneration: biochemical rationale and case report. BMC Complement Altern Med. 2003 Jun 10;3:2.

49. Kantor ED, Lampe JW, Vaughan TL, Peters U, Rehm CD, White E. Association between use of specialty dietary supplements and C-reactive protein concentrations. Am J Epidemiol. 2012;176(11):1002-13.

50. Bell GA, Kantor ED, Lampe JW, Shen DD, White E. Use of glucosamine and chondroitin in relation to mortality. Eur J Epidemiol. 2012;27(8):593-603.