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CLINICAL NUTRITION INSIGHTS

Nutritional Support for Connective Tissue Repair and Wound Healing

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ABSTRACT: *Tissue repair and wound healing are complex processes that involve a series of biochemical and cellular reactions, beginning with inflammation and followed by the repair and remodeling of the injured tissue. While damage to connective tissue was once believed to be irreparable, there is now scientific evidence to the contrary.[1,2] Connective tissue repair and remodeling involves chondrocyte reproduction and activity and the formation of collagen fibers and ground substance. When there is damage to connective tissue it is important to address the nutritional requirements for the synthesis of both the collagen fibers and the proteoglycans. Many nutrients are involved in connective tissue repair and wound healing: glucosamine sulfate, D-glucuronic acid, amino acids, bioflavonoids, and select vitamins and minerals. In addition to nutritional support, homeopathy has been used for generations for both acute and chronic injuries.*

Immediately following an injury, the healing process begins. A torn ligament or muscle is repaired, wounds heal, bones mend. The healing process first involves getting rid of damaged tissue, then rebuilding healthy connective tissue in a step-by-step manner. The redness, swelling, heat, and pain of inflammation are a natural part of the healing process. Prolonged or excessive inflammation, however, may slow down the healing process, which may cause continued loss of function and discomfort. On the other hand, total elimination of inflammation from massive drug treatment may also result in delayed healing.[1]

An appropriate inflammatory response is a vitally important part of tissue repair and wound healing, and deserves greater attention than is provided here. The inflammatory process, muscle spasm, and related nutritional support are addressed in the Clinical Nutrition Insight titled, "Understanding the Natural Management of Pain & Inflammation." The focus here relates to the repair and remodeling phase of the healing process, specifically that of connective tissue. While damage to connective tissue was once believed to be irreparable, there is now scientific evidence to the contrary.[1,2] Chondrocytes – the cells responsible for the formation, maintenance, and repair of articular cartilage – were long thought to be incapable of reproducing and forming new tissue. Current evidence suggests they are much more responsive to mechanical, endocrine, biochemical, and microenvironmental stimuli than was previously thought.[1,3]

In a well-referenced article by Ressel,[2] clinical and experimental evidence indicates that cartilage damaged by trauma, injury, or kinesiopathology may heal either with identical tissue or a mixture of fibrocartilage and hyaline cartilage. He states, "Clinical and experimental evidence is overwhelming that the IVD (intervertebral disk) has the capacity to both heal and regenerate. The degree of repair and regeneration of the IVD is greatly dependent on the character of the extracellular 'scaffold,' the available nutrition, the age, and the biomechanical state of the diskal material…ten case studies are presented that clearly demonstrate thepossibility of reversing osteoarthritic degeneration of the spine." Before and after radiographs of these ten case histories providedevidence of various types of improvement including disk height increases, decreases in osteophyte formation, reinitiation of thenormal cervical curvature, and a reduction of disk instability. The time interval necessary for improvement to manifest varied from as little as two months to over seven years, and was dependent on the degree of compliance to a multifaceted regime and the extent of the degeneration, among other things.

OSTEOARTHRITIS REVERSAL MAY BE POSSIBLE

Osteoarthritis has the highest morbidity of all illnesses affecting mankind. The cause of severe pain and compromised joint function, osteoarthritis often leaves patients confined to bed or a wheelchair.[3] Until recently, osteoarthritis has been looked upon as an irreversible consequence of aging, the inevitable result of continuous wear and tear on the joints. But with increasing knowledge of the factors contributing to osteoarthritis, these and other beliefs about the disease, and about connective tissue in general, are beginning to change. Indeed, there is some clinical and experimental evidence that suggests the possibility that the degenerative process of osteoarthritis may be stopped and even reversed.[2]

Another misconception is that conditions of joint degeneration require complete immobilization to support the healing process. On the contrary, continued use and weight bearing may be necessary for articular regeneration.[2] Findings from some immobilization studies have been summarized by Navarro and Sutton[4] as follows:

- Degeneration changes in cartilage appear after ten days of immobilization.
- There are cumulative degenerative changes from periodic immobilizations as brief as four days in duration at four week intervals.
- Immobilization (periodic or continuous) over 30 days leads to progressive osteoarthritis.
- Return to normal use and weight bearing after three weeks of immobilization reverses the effects of immobilization.
- Excessive mechanical stress after three weeks of immobilization accelerates cartilage degeneration.

Because articular cartilage is an avascular tissue, its chondrocytes do not receive a steady supply of nutrients directly from a capillary bed as do other tissues. Nutrients must, in effect, be absorbed into the cartilage much like water is absorbed into a sponge. An adequate supply of nutrients surrounding, or "bathing," the collagen must be present for the delivery of the nutrients to the chondrocytes. Alternating compression and decompression of the tissue is what facilitates the delivery. Thus, blending comprehensive nutritional support with proper joint motion and the appropriate weight bearing exercise may serve a physiologic function necessary for delivery of nutrition to the cartilage and recovery of cartilage tissue integrity.

CONNECTIVE TISSUE REPAIR: COLLAGEN AND PROTEOGLYCAN SYNTHESIS

Connective tissue repair and remodeling involves chondrocyte reproduction and activity and the formation of collagen fibers and ground substance.

• COLLAGEN FIBERS

The basic structural unit of a collagen fiber consists of long protein chains assembled from amino acids, such as proline, lysine, hydroxyproline, hydroxylysine, cysteine, and glycine (approximately one-third of the amino acids that make up collagen are glycine). Three chains are combined in a triple helix configuration called a tropocollagen unit. Tropocollagen units are then cross-linked in a staggered array to form bundles of collagen microfibrils. Further cross-linking forms larger collagen fibrils which aggregate to form collagen fibers. Collagen fibers give connective tissue its tensile strength; a load of at least 10 kg (22 pounds) is needed to break a collagen fiber 1 mm in diameter.[5]

• GROUND SUBSTANCE

Proteoglycans are a key component of the ground substance that helps make up connective tissue. Proteoglycans are large aggregates of mucopolysaccharides, also referred to as glycosaminoglycans (GAGs). The mucopolysaccharides, or GAGs, found in connective tissue are hyaluronate, chondroitin sulfates, keratan sulfates and, to a lesser degree, dermatan sulfates. As suggested by their names, sulfur is a major component of GAGs (except for hyaluronate). The sulfurization of GAGs imparts a high negative charge density. GAGs thus repel each other, causing a space-filling function. The negativity and space allow for great water absorption and retention, which accounts for the high degree of compressibility characteristic of connective tissue. It is the gel-like proteoglycans that give connective tissue its compressional strength and resiliency.[1,5]

Elastins are highly cross-linked proteins similar to collagens, and are found in connective tissues such as ligaments, skin, and large blood vessels. Elastins give various connective tissues rubber band-like elasticity and resiliency. As with collagen, one-third of the amino acid residues are glycine. Elastin is also rich in proline but, unlike collagen, it contains no hydroxylysine and very little hydroxyproline.[5]

GUIDELINES FOR CONNECTIVE TISSUE REPAIR

The following guidelines for connective tissue repair is a synopsis taken from published articles by leading experts on connective tissue research:[2,4]

- Provide thorough consultation and exam.
- Design specific corrective procedures to restore normal articular function and optimize neurological integrity and function.
- Encourage careful physical movement with moderate weight bearing to maintain joint flexibility, strength, and function, and to ensure adequate nourishment to the joint.
- Provide non-invasive pain management therapy.
- Ensure comprehensive nourishment (targeted, specialized supplements may be helpful).
- Provide patient education.

NUTRIENTS INVOLVED IN CONNECTIVE TISSUE SYNTHESIS

When there is damage to connective tissue, as from an intervertebral disk injury for example, it is important to address the nutritional requirements for the synthesis of both the collagen fibers and the proteoglycans. Collagen fiber and proteoglycan synthesis are dependent on the supply of nutrient building blocks such as amino acids and amino sugars. Vitamins and minerals are also needed for the many enzymatic reactions involved in connective tissue rebuilding. Following is a review of some of the nutrients that are involved in connective tissue repair and wound healing.

• GLUCOSAMINE SULFATE

Glucosamine is an amino-sugar and a basic constituent of proteoglycans. It is a preferred substrate and stimulant for proteoglycan synthesis.[6] Some recent studies suggest that orally administered glucosamine sulfate normalizes cartilage metabolism by possibly stimulating proteoglycan synthesis and inhibiting degradation.[7-11] Improvements in pain and inflammation, as well as restored function in patients with osteoarthritis, have been reported with supplemental glucosamine sulfate use.[7-11]

- **D-GLUCURONIC ACID**

D-glucuronic acid is one of the disaccharides that make up hyaluronic acid, the other being N-acetyl-D-glucosamine. Hyaluronic acid is a mucopolysaccharide that forms the backbone of proteoglycans and is also a major component of synovial fluid. Sato et al.[12] reported that hyaluronic acid and D-glucuronic acid act as free radical scavengers in a dose-dependent manner. They were shown to provide antioxidant protection of synovial tissues in patients with rheumatoid arthritis. This study demonstrated that the free radical scavenger activity was greatest within the synovial fluid. The investigators believe the free radical scavenger ability may be due to the D-glucuronic acid in the hyaluronic acid and not the N-acetyl glucosamine. It appears that healthy synovial fluid contains other antioxidant substances which may include superoxide dismutase, catalase, peroxidase, and/or other antioxidants such as albumin, flavonoids, alpha-tocopherol, ascorbic acid, polyphenols, and tannin.

- **AMINO ACIDS**

As stated earlier, collagen fibers are made up of long chains of amino acids, of which one-third is glycine. Proline, hydroxyproline, and hydroxylysine are also prevalent. Some proline and lysine residues become hydroxylated by certain enzymes to form hydroxyproline and hydroxylysine. This hydroxylation reaction requires a reducing agent, such as ascorbic acid, and alpha-ketoglutarate as a substrate. Some research suggests that hydroxyproline and hydroxylysine are not directly incorporated into collagen but rather they are incorporated as a result of the hydroxylation of proline and lysine, respectively. For example, ^{14}C-labeled hydroxyproline given to rats does not show up in synthesized collagen. However, when ^{14}C-proline is given, the hydroxyproline in synthesized collagen is radioactive.[5]

- **VITAMIN E**

Vitamin E is a major antioxidant and functions to quench free radicals in most tissues. Free radicals have many origins, but are also a major consequence of the inflammatory response. They predominantly affect polyunsaturated fats that compose the lipid portion of cellular membranes. The main rationale for vitamin E supplementation is to reduce the damaging effects of free radicals.[13]

A number of conditions, such as chronic inflammatory disorders, injury to the central nervous system, and connective tissue damage, are associated with free radical damage. It is thought that excess free radical production may also delay or prevent adequate healing. Vitamin E supplementation may reduce free radical damage and benefit wound healing and connective tissue repair.[1]

- **VITAMIN C**

Vitamin C, or ascorbic acid, has multiple functions as a coenzyme and cofactor in many of the body's biochemical pathways. As it relates to connective tissue, vitamin C is required for collagen fiber synthesis, a process vital for tissue repair and healing. Specifically, it is involved in the hydroxylation of proline to form hydroxyproline. Research by Schwarz et al. confirms that ascorbic acid acts as a specific inducer of the collagen pathway.[14] A deficiency in vitamin C is associated with poor collagen formation and delayed wound healing.[15]

Vitamin C also functions as an antioxidant. Whereas vitamin E is considered a very important fat-soluble antioxidant, vitamin C is considered a very important water-soluble antioxidant. Additionally, vitamin C is capable of regenerating other antioxidants, especially vitamin E. It does this by reducing vitamin E radicals formed when vitamin E scavenges oxygen free radicals.[16]

- **ZINC, COPPER, MANGANESE FOR SOD INDUCTION**

Superoxide dismutase (SOD) is an antioxidant enzyme. There are two forms of SOD: mitochondrial (contained within the mitochondria) and cytosolic (contained within the cytoplasm of the cell). Mitochondrial SOD is induced by manganese, whereas cytosolic SOD is induced by copper and zinc. Copper/zinc SOD (CuZnSOD) and manganese SOD (MnSOD) protect tissues by converting damaging superoxide free radicals into hydrogen peroxide, which is further catabolized by catalase into water and oxygen.

In order for the SOD enzymes to function, there needs to be an adequate dietary supply of copper, zinc, and manganese. Research suggests that raising the intake of minerals needed for SOD induction may improve SOD activity.[17,18] One study reported a significant increase in MnSOD lymphocyte activity in women who received 15 mg of manganese daily for 119 days, compared to women who received placebos.[18]

Another study reported increased CuZnSOD activity in rheumatoid arthritis patients who supplemented with copper when compared to control subjects. Patients with rheumatoid arthritis reportedly have lower SOD activity, probably the result of inflammation.[17] In this study, which was conducted at Purdue University, 23 rheumatoid arthritis patients were compared to 48 healthy, age-matched controls. Blood samples were assayed for erythrocyte Cu/Zn SOD activity before and after the four-week study. Patients who received 2 mg of supplemental copper daily had increased erythrocyte SOD activity an average of 21%. This increase was highly significant compared to the control group.

Another copper enzyme important to connective tissue is lysyl oxidase, which is involved in the cross-linking of elastin and collagen, a role that is necessary for proper collagen formation and maintenance.[19]

- **BIOFLAVONOIDS**

Bioflavonoids are plant-derived substances with strong antioxidant activity and possible pain-relieving properties. It is believed that bioflavonoids may help to relieve pain by inhibiting prostaglandin cyclooxygenase, lipooxygenase, and phospholipase.[20] Additionally, since some prostaglandins are known to induce elastase and other catabolic hydrolases, it is plausible that their suppression may benefit connective tissue.[20] Furthermore, bioflavonoids are thought to benefit connective tissue by binding to elastin, preventing its degradation by elastases released as a result of inflammation.[21] In addition to this apparent enzyme inhibition, bioflavonoids have demonstrated enzyme activation — namely that of proline hydroxylase, an enzyme necessary for collagen crosslinking.[20] Additional research regarding the biochemistry of bio-flavonoids and their therapeutic effects is still required, but the current science looks very promising. There is some clinical experience that supports their effectiveness in safely reducing both pain and inflammation in many cases.

HOMEOPATHY

In addition to nutritional support, another area of natural healing has shown historical benefit for connective tissue repair — homeopathy. Homeopathy has been used for generations for both acute and chronic injuries. Discovered and catalogued originally by Samuel Hahnemman, homeopathic remedies are believed to provide an "energetic" stimulus to the natural healing qualities of the body. Specific remedies have been used in combination to help relieve pain and speed recovery from acute injury, pain and swelling associated with injury, and even the pain associated with arthritis. Homeopathic ingredients, which have been listed in the USHP (United States Homeopathic Pharmacopoeia) for over a hundred years, have been shown to have a wide variety of therapeutic benefits, especially in acute circumstances such as pain and inflammation.[22]

A combination remedy containing berberis, cholchicum, rhus tox, spiraea, pendula cortex, salicum acidum, and urticae diocia may help reduce pain and inflammation in patients with rheumatic and arthritic disorders, and general muscular discomfort.

FOODS

There is a growing body of evidence and research demonstrating the vital role our diet plays in the healing of all types of tissue damage and inflammation, the specifics of which are discussed in the Clinical Nutrition Insight titled, "Understanding the Natural Management of Pain & Inflammation." It is wise to reduce foods that are relatively high in arachidonic acid (a non-essential fatty acid found in animal products and peanuts), and increase foods rich in alpha-linolenic acid and its end products (essential fatty acid compounds found in some fresh vegetables, flax and pumpkin seeds, walnuts, cold water ocean fish, and specialized supplemental concentrates).

Eating a diet rich in fresh fruits, vegetables, seeds, legumes, and whole grains will also help to ensure an abundance of phytochemicals – natural plant-based chemicals that may promote health and healing.

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