WONDER WHY?

Nutritional Support for Soft Tissue Healing

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ABSTRACT

People who heal well obviously differ in some important way from those who we see with chronic non-healing lesions. The distinguishing feature is primarily the effectiveness of the healing cascade. Unless the factors contributing to this are considered, the outcome of Prolotherapy will also be affected. Research shows the most important nutrients for the generation of new collagen for healing are protein, vitamin C, zinc, copper and manganese—all cofactors for various enzymes in collagen generation and stability. Nutrition in modern societies is shown to be inadequate in many of these areas and can easily be corrected. Malabsorption is also a cause of poor healing and musculoskeletal difficulties, and undetected celiac disease is common in our patients. Chronic widespread pain is similar but a separate entity, and thyroid and vitamin D deficiency need to be considered.

Journal of Prolotherapy. 2011;3(3):709-713.
KEYWORDS: copper, diet, gluten, protein, manganese, nutrition, soft tissue, thyroid, vitamin C, vitamin D, zinc.

WHAT DISTINGUISHES THOSE WHO HEAL NORMALLY FROM THOSE WHOM WE SEE WITH CHRONIC MUSCULOSKELETAL PAIN?

The distinguishing feature is primarily the effectiveness of the healing cascade. Unless the factors contributing to this are considered, the outcome of Prolotherapy will also be affected. Research shows the most important nutrients for the generation of new collagen are protein, vitamin C, zinc, copper and manganese. All enzymes have several nutrient cofactors, necessary for the enzyme to function. The effectiveness of the enzyme will be enhanced by optimum levels of its nutrient cofactors. Genetic disorders where a defective gene causes poor collagen formation, e.g. Ehlers-Danlos Syndrome, are rare, but do turn up in a Prolotherapy practice. For example some patients with Ehlers-Danlos have found improvement with vitamin C.[1] However we all have a few slightly defective genes, and in cases of milder degrees of musculoskeletal weakness and poor wound healing, it makes sense to attempt to influence the outcome with enhanced levels of the appropriate cofactors, especially the nutrients that have been shown to improve wound healing.

ADEQUACY OF THE DIET

It is often thought that the Western diet is adequate in the provision of nutrients. In the cases of extremely physically active individuals, such as athletes and heavy manual workers, who need to eat more food to get enough calories, this is often the case. However, there is ample evidence of dietary deficiencies and some of the more typical and clinically important are highlighted in this article.

PROTEIN

The adult Recommended Dietary Allowance (RDA) for protein is 0.8 g/kg/day. But on this level healthy free-living elderly men and women decrease their urinary nitrogen excretion and lose muscle mass.[2] The authors concluded that it is clear that older adults require at least 1.0 gm protein/kg/day.[3] Many older people have a reduced appetite and taste disorder (symptoms of zinc deficiency) and consume less protein, preferring sweet and starchy food, resulting in an accelerated rate of sarcopenia,[4] (loss of muscle) and poorer wound healing. To get 0.8 grams protein/day a 70kg (154 pound) person would have to eat 56gm protein per day. This would be approximately the equivalent of 1 egg (7 grams protein), a 5 ounce can of tuna (28 grams protein) and a very small piece of meat, fish or chicken a little smaller than the palm of the hand which is typically about 3 ounces (21 grams protein). Protein-rich foods are also the richest sources of zinc. The busy practitioner with little experience with nutrition can simply advise the patient to eat protein 3 times a day. Athletes or those doing 4 hours of vigorous exercise/day or more need 1.2gm protein/kg/day. Protein deficiency is known to delay wound healing and many studies show that a protein supplement hastens healing and reduces hospital time after surgery. Encouraging people who have

coffee and/or cereal for breakfast, to have a quick protein drink is an easy way to increase protein intake, however eggs are ideal and do not increase cholesterol.[5]

ZINC

Zinc deficiency is well-known to be associated with delayed wound healing. It is a cofactor in numerous transcription factors (i.e. the making of protein from DNA and RNA) and enzyme systems including zinc-dependent enzymes (matrix metalloproteinases) that augment fibroblast migration and debridement (remodelling) during wound repair. Zinc confers resistance to excess apoptosis[6] (manifesting as persistent granulation tissue) by protecting cells against reactive oxygen species through the antioxidant activity of the cysteine-rich metallothioneins (enzymes). In particular, zinc deficiency decreases nuclear factor $(NF)^{k}B$ activation, reduces proinflammatory cytokines [interleukin (IL)-1ß and tumor necrosis factor (TNF)-^{a}], and decreases neutrophil infiltration. However, extremely high zinc was found to delay wound closure and these cytokine changes,[7] illustrating the nutritional principle that excess of one nutrient may reduce absorption and effectiveness of the related nutrients (for example, excess zinc affects iron, manganese and/or copper). Indeed, it was demonstrated in human studies that a zinc intake 20-fold greater (300 mg/d) than the current US RDA (15 mg/d) decreased several markers of immune function, including the chemotactic response and phagocytic activity of neutrophils[8] (the ability of white blood cells to find problems and get rid of them).

A good rule of thumb in supplementation of minerals is to use a dose between the RDA and twice the RDA, in conjunction with other nutrients. Higher doses are used in research, but are not needed in clinical practice due to the synergistic (team) effect of other nutrients. This also means that if the patient is not deficient in that particular nutrient, supplementation will do no harm, avoiding the need for expensive testing and monitoring.

Most nutritional doctors do not bother testing for zinc deficiency as serum or hair zinc are not accurate enough for individual use, whereas clinical history and examination are very useful – past history of wound infection,[9] growing pains, Osgood Schlatters disease, recurrent infections, plus white spots on nails, striae (stretch marks), acne scars etc are good pointers.

Mild deficiency of zinc is common.[10] Australian research from 1991 showed 67% of men & 85% of women ate less than the RDA for zinc.[11] Only 42% of US people over 70 had adequate zinc intake in the 1980s.[12] More than 60% of Southern US women reported dietary copper, zinc, and selenium intakes below recommended levels.[13] (Manganese was not measured and race made no difference.) Average zinc intake in the USA ranges from 7 to 13mg, and in elderly Australians 11.5mg,[14] but in these studies the individual intake was as low as 6mg in Sweden, 2.5mg in Tasmania and was proportional to energy intake —i.e. the very lean patients are likely to be getting less zinc. Remember that averages mean that approximately half are below that intake, and our patients are likely to be in the lower half.

At my Prolotherapy workshops, I teach that it is prudent to supplement all Prolotherapy patients with zinc.

MANGANESE

Manganese activates glycosyl-transferase enzymes, a vital step in collagen cross-linking and formation of proteoglycans—the structural basis of all connective tissue. Manganese is especially important in cartilage as it is also involved in protection of the cartilage from oxidative damage in its role in superoxide dismutase. There is a significant decrease in manganese-superoxide dismutase (SOD2) in the superficial layer of cartilage in patients with osteoarthritis compared with normals.[15] Most of the research on effects of manganese deficiency is in animals or in vitro (showing connection with osteochondroses,[16] reduction in damage from NSAIDs and accelerated cartilage synthesis[17]). However a combination of glucosamine, chondroitin and manganese ascorbate improved osteoarthritis of the knees significantly more than the placebo group in 16 weeks in 34 Navy divers.[18] Zinc, copper and manganese all improved different aspects of cellular mobility and proliferation in wound healing.[19] US deficiencies are not known but 9.7% are deficient in Spain.[20] In my experience, hair analysis is reasonably accurate for manganese, and it is often deficient in those with arthritis. Food sources are nuts, seeds, legumes and whole grains. Many people rarely eat these. RDA is 2.5-5mg/day. Safe supplement level is up to 11mg in the long term, but up to 20mg for say, a few months.

COPPER

Copper is important for copper superoxide dismutase, another important antioxidant enzyme. It also activates lysyl oxidase, increasing strength and weight of tendons and other connective tissue.[21] Copper deficiency is associated with osteochondrosis and subchondral bone changes in calves[22] and in some human genetic disorders. Evidence suggests that deficiency is more of a public health concern than excess.[23] It should always be supplemented with zinc as the side effects of excess zinc are mostly due to copper deficiency. RDA is 1mg/day.

Find a mineral supplement with about 25mg zinc, 5mg manganese and 1mg copper to recommend to your patients.

VITAMIN C

Vitamin C deficiency is associated with defective connective tissue, particularly in wound healing. Ascorbate is required for hydroxylation of proline in procollagen, and stabilizes the collagen triple helical structure.[24]

Vitamin C deficiency is associated with impaired wound healing (50% decrease in wound strength) joint pain and effusions, bone pain and muscle weakness, fatigue and lassitude, perifollicular hyperkeratosis (tiny pimples around hair follicles) and other signs and symptoms of scurvy, e.g. poor resistance to infection.

In 1988–1994, 13% of the US population was vitamin C deficient, but this had improved to 7% by 2003-2004[25] except in smokers and low income persons. The new higher RDA for vitamin C of 75 mg for women and 90 mg for men is, for the first time, based on recognition of the vitamin's role as an antioxidant as well as protection from deficiency. Again our chronic non-healing patients are more likely to be in the deficient group.

Supplementation with 1000mg vitamin C daily can maximize the likelihood of a good response to Prolotherapy.

GLUTEN INTOLERANCE

I am noticing that many Prolotherapy patients have features of undiagnosed celiac disease – zinc deficiency (old striae, white spots on nails), irritable bowel syndrome, fatigue etc. They also have features that I consider to be zinc (and possibly manganese) deficiency in childhood and teenage years – growing pains, Perthes hips, Osgood Schlatters disease, scoliosis and uneven leg length. We know that zinc and manganese are important for bone and other growth, and that the Western diet is marginal, especially in fussy eaters and at times of extra demand such as teenage growth spurts. Adolescent requirement for zinc is approximately 20mg/day. We also know that gluten intolerance (to wheat, rye, barley and oats) is associated with malabsorption of zinc and many other nutrients. I propose that marginal absorption of zinc/manganese contributes to uneven growth in these young people, resulting in mild skeletal inequalities. Every one of the scoliosis patients I have seen has gained improvements in other symptoms (mainly irritable bowel, depression and tiredness) after adopting a gluten free diet.

CASE STUDY

A 29 year old health worker was having severe cramps and stiffness and eventually was unable to complete a triathlon. Femoro-acetabular impingement (of the hip joint) had been treated surgically twice. He had clunking sacroiliac joints and multiple trigger points in gluteal and back muscles since hurting his back moving a piano age 16. He is a type 1 diabetic who is very lean and has occasional abdominal pain and diarrhea and frequent episodes of gas (as does his baby daughter). Serology for celiac disease was normal twice and gastroscopy and small bowel biopsy were also reported normal. 25 hydroxy vitamin D was low at 36 nmol/L and responded poorly to oral supplementation. Parathyroid hormone (PTH) was elevated (This is common in celiac disease as low calcium due to poor absorption causes the parathyroid glands to over-produce PTH to keep the blood calcium normal so the heart and nerves can function. This steals calcium from the bones (the only reservoir of calcium), causing osteoporosis.) There was no response to a gluten free diet for several weeks but eventually he reported less tiredness, less post meal soreness and gas, and better bowel actions. His right leg was 8mm shorter than the left on CT measurement, and building up the shoe on that side helped the back considerably, as did Prolotherapy into hip and sacroiliac joints and many trigger points. Gene test for celiac disease was positive at HLA-DQ2 and HLA-DQ8. This case suggests significant malabsorption (suspect low magnesium, by the cramps and PTH, and probably low zinc, by the poor bone and joint healing, and general reduced absorption, by his leanness although

he is married to a dietician and ate plenty of good food, as do most athletes). And yet there was no evidence of celiac disease on biopsy or serology.

Despite the current opinion from gastroenterologists, that celiac disease is only diagnosable by a small bowel biopsy, I think that:

- Gluten intolerance is part of the same continuum as celiac disease in many cases, and cannot necessarily be diagnosed on the basis of the result of a small bowel biopsy. I have seen families that include true biopsy-positive celiacs with siblings who, despite being biopsy negative, gained dramatic health improvements on a gluten free diet. They probably have at least some genes in common with their true-celiac relatives.
- Biopsy is not necessary for a diagnosis. Now that we have gene testing I think that the result of transglutaminase serology, elimination and challenge testing combined with gene testing is more accurate.
- Trial of a gluten free diet is something that people are willing to do without needing the motivation of a small bowel biopsy. If they feel better on a gluten free diet they will do it properly, but it often takes 6-12 months to get really expert at it.

Celiac disease is being diagnosed in people with unexplained infertility, osteoporosis, depression, fatigue, anemia, strange neuropathies, musculoskeletal pain, fibromyalgia as well as irritable bowel and 20% have constipation at diagnosis. Vitamin D, folate and other B vitamins, iron, zinc and many other deficiencies are common, and can take many months to improve until the gut wall heals after gluten is excluded. Enteral candidiasis often complicates complex cases, as zinc deficiency reduces cell mediated immunity, which keeps candida under control. Some patients who have had normal small bowel biopsies recover their health on a gluten free diet, so I urge doctors to keep watching out for the rest of the iceberg of undiagnosed gluten intolerance. On average it takes patients 4 years to get diagnosed correctly, even though it is common at 1 in 100 people and it is estimated that 75-80% of celiacs are still undiagnosed. I am convinced that our chronic musculoskeletal pain patients include a higher proportion of gluten intolerant people than the general population so if doctors haven't diagnosed one in the last year, you are probably missing it. Extra suspicion is needed in the very lean patients, but plenty of overweight patients are gluten intolerant. The best screening questions are "Does bread upset you? and Do you have flatulence or bloating?" Many people have discovered that bread upsets them, and rarely eat it but are getting gluten in other ways e.g. rye or spelt bread which have less gluten, or choose to follow a low carbohydrate diet. Since it takes weeks after starting a gluten free diet for the atrophic villi to recover, the nutrient absorption can still be very poor even if they have very little gluten. Hence the value of longer term nutrient supplementation and encouragement to persist with the diet.

WIDESPREAD MUSCULOSKELETAL PAIN

Many of our patients actually have pain in multiple sites. They may only tell us about the most important one at first, but as the consultations go on, more and more pains are revealed. In these cases results are either poor or temporary unless other factors are also considered. Defining it as fibromyalgia helps to focus the search on metabolic factors.

THYROID DEFICIENCY

JC Lowe has proposed that fibromyalgia is a composite of an underlying thyroid deficiency and deconditioning syndrome, with loss of muscle mass and subsequent loss of fitness.[26] This is relevant for those patients who have multiple areas of pain. Feeling worse after exercise is a symptom of thyroid deficiency. Doctors can ensure that even minor degrees of thyroid deficiency are treated. There is discussion among endocrinology experts as to the upper limit of normal thyroid stimulating hormone (TSH), as rigorously tested normal volunteers all have TSH between 0.4 and 2.5,[27] and increasing values of serum TSH above 2mU/l increased the probability of developing hypothyroidism.[28]

This is further complicated by ubiquitous environmental toxic chemicals called thyroid disruptors, reported by the US Endocrine Society in 2009.[29] These chemicals not only interfere with thyroid hormone production and receptor function, but also reduce TSH,[30] meaning that TSH itself is not such a reliable indicator of thyroid function adequacy as we have believed. Thus relying on TSH to diagnose thyroid deficiency is not as accurate as a list of thyroid deficiency symptoms e.g. feeling the cold, cold hands and feet, feeling sluggish mentally as well as physically, depression, fatigue, being unable to lose weight despite correct diet and exercise, and signs such as loss of

hair, high cholesterol, myxoedematous appearance (puffy face), thickened tissue and temperatures under 36.7˚C or 97.8˚F. Mark Starr's excellent book *Hypothyroidism Type 2*[31] details the work of Barnes, Sonkin, and Hertoghe, who have published extensively on the clinical diagnosis and treatment of tissue resistance to thyroid hormone due to defective mitochondria. Closely supervised clinical trials of thyroxine, T3 or natural thyroid extracts are used to see if raising thyroid hormone levels results in improvements in pain, energy and loss of excess weight.

VITAMIN D DEFICIENCY

Many people are suffering needlessly from back pain and other muscle pain caused by low vitamin D, especially people with darker skin and people with little exposure to sunlight e.g. doctors and other office workers, veiled women, and disabled young adults. Unexplained musculoskeletal pains are often due to vitamin D deficiency as well as deconditioning syndrome. Pains of this type are a recognized symptom of osteomalacia which is diagnosed by tests for calcium, vitamin D and parathyroid hormone. In fact vitamin D deficiency is even more common in general rheumatology patients than osteoporosis patients, especially those with chronic pain/fibromyalgia.[32] Levels of vitamin D below 30 nmol/l (12ng/ml) are associated with decreased muscle strength. Supplementation with vitamin D for 1 to 2 months has been shown to normalize muscle strength and pain in patients with myopathy. In 139 patients with muscle pain, 74% were vitamin D deficient and 90% of those improved with vitamin D.[33] Australian aboriginal patients with muscle pain averaged 41nmol/L (16.4ng/ml) and controls 58nmol/L (23.2ng/ml).[34] Your laboratory's normal range may include many patients suffering from subclinical vitamin D deficiency and research shows that vitamin D needs to be at least 75nmol/L (30ng/ml) to normalize calcium metabolism for muscles and bones.

These clinical descriptions of chronic widespread pain fit the picture of fibromyalgia but not all studies of fibromyalgia have shown a connection with vitamin D —understandable since there are several different already known causes of FM. For example, a patient whose fibromyalgia is primarily linked to thyroid deficiency will not necessarily respond to vitamin D. An excellent referenced summary of the many aspects of vitamin D deficiency is available at http://www.healthresearchforum.org.uk/reports.html.

OTHER FACTORS

Once you have seen the effects of the nutrient therapies above you will also be interested in MSM (methyl sulfonyl methane) for pain, magnesium for muscle spasm, Omega-3 fish oil and herbs e.g. Boswellia, Devil's Claw etc. for inflammatory arthritis, correcting food intolerance by elimination diets (especially for cow's milk protein) for head and shoulder aches, Minocycline or elimination diets for rheumatoid arthritis and many other complementary remedies that have some clinical research but not necessarily Level 1 evidence.

CONCLUSION

Trace mineral deficiencies involved in connective tissue metabolism are commonly found in the general population and even more commonly found in the chronic pain patient group, due to many factors including malabsorption and the consequences of modern diet and lifestyle. The possibility of undiagnosed gluten intolerance should be kept in mind. Insufficient levels of vitamins C and D are also involved in chronic connective tissue pain, as is hypothyroidism. Your patient's response to Prolotherapy will be enhanced and Prolotherapy courses may be shorter and more effective if you also address key nutritional factors. ■

BIBLIOGRAPHY

The bibliography is available at www.journalofprolotherapy.com.