**Rehabilitation Utilizing Nutritional Supplementation**

Rachel Olivier, MS, ND, PhD

Acute pain is characterized by recent onset, typically initiating no more than days or weeks earlier, of variable intensity, with the likelihood of associated sympathetic hyperactivity, including hypertension and tachycardia. Alternatively, chronic pain is classified as pain persisting for greater than three months, also of variable intensity, which includes the probability of added components, such as insomnia or weight loss.[1] Nutritional intervention, as a means to accelerate the rehabilitation process, has shown to be a beneficial adjunct in the treatment of both acute and chronic pain. In all likelihood the severity and length of the injury, whether acute or chronic, will dictate the means of nutritional intervention.

There are characteristically two means of utilizing nutritional supplementation to accelerate the rehabilitation process, be it in acute or chronic injuries. In certain circumstances it may be appropriate to utilize both types of nutritional support. One method of choice is the use of proteolytic enzymes, vitamins, minerals and amino acids to support cellular repair and regeneration. The second or adjunct method of nutritional intervention is via the downregulation of NF-KappaB.

Proteolytic enzymes have a variety of physiological mechanisms. These mechanisms include: protein digestion, blood coagulation, lysis of fibrin clots, and activation of zymogens.[2] Taken orally, proteolytic enzymes function to break down proteins (protein digestion), typically resulting as a consequence of injury, otherwise referred to as inflammatory modulators. The four classical signs of inflammation are redness (rubor), swelling (tumor), heat or warmth (calor), which may potentially result in fever, and pain (dolar). Proteolytic enzymes serve to accelerate the inflammatory process necessary for healing, and have been regarded as enzyme activators and regulators, as opposed to enzyme inhibitors.

As part of the inflammation process, the humoral immune response is activated and the body is alerted to increase the production of B-cells and T-cells, potentially resulting in an inflammatory state. Inflammation thus serves as an essential component of the healing process. Specifically defined, inflammation is a protective response whereby a living system is programmed to defend itself against invasions of foreign protein or materials (bacteria, virus, parasites, etc.). It is activated in several ways, including the production of antigens to the foreign substance, as well as to its own cellular contents, as a result of degradation. Consequentially, there is typically a gradual increase in inflammation in the respective areas, which subsequently results in a series of inflammatory events. This cascade of events, responding to activating factors released indicating cell damage, is programmed to be rapidly and efficiently activated, as a low-key response could potentially result in cell death. As cells become destroyed, as a consequence of the toxin cleanup, the removal of the released cell contents should be dealt with immediately to lessen the system becoming set on a cycle of self destruction. This innate survival mechanism means to fiercely attack with free radical proinflammatory molecules designed for the quick "shoot first and ask later" approach. Naturally, this acts to damages other healthy cells. Subsequently, inflammation continues until the cellular debris and macrophages are cleaned up. C-reactive protein (CRP), which is typically nominally elevated in acute inflammation, may be used as an

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[1] http://www.ama-cmeonline.com

[2] Neurath H. Evolution of proteolytic enzymes. Science. 1984 Apr 27;224(4647):350-7.

indicator or serum marker of the inflammatory process. Chronic inflammation may cause a significant elevation in CRP. Proteolytic (protein digesting) enzymes are effectively used, on an empty stomach, to assist systemic cleanup of "foreign" protein, particularly with injury. This lessens the 'call to arms' of the activating factors of inflammation by assisting with the rate of debris removal. Proteolytic enzymes typically consist of bromelain, papain, trypsin, alpha chymotrypsin and pancreatin, which are often found in combination with lipase and amylase.

Proteolytic enzymes have been used extensively to accelerate healing, specifically in the sports arena. The use of proteolytic enzymes in this regard has been used successfully for both acute and chronic traumatic inflammations, including contusions, distortions, ligament rupture, edemas, hematomas, hydrarthroses, pulled or torn muscles, and vertebral subluxations.[3] In one study oral bromelain use was shown to be a probable modulator of gastrointestinal inflammation, as a result of its proteolytic activity within the colonic microenvironment.[4]

Although inflammation is a beneficial component of the healing process, it may also become a destructive and self-perpetuating process, as a result of countless environmental factors and triggers. The high degree of toxins in the environment, including air, food and water, make systemic detoxification difficult, thus compounding the effect of a "total toxic burden". Additionally the problem is multiplied by purported "environmental factors," which include oxidative stress, radiation, injury, nutritional deficiency (of macronutrients and antioxidants, EFAs, vitamins, minerals, etc.), a pro-inflammatory diet, gut permeability and low serum levels of 25-OH-D. The result is a perpetuating cycle, as a consequence of a runaway inflammatory cascade. Regardless of the etiology, these stimuli may lead to the activation of the nuclear transcription factor kappaB (NF-kappaB) cascade, which has been noted as a major pathway for amplification of the inflammatory process.[5]

The inappropriate activation of NF-kappaB has been correlated to many disease states, as well as to inflammatory disorders. Subsequently, inhibition or down-regulation of NF-kappaB has become a major therapeutic goal in the treatment and prevention of a wide range of illnesses, including among others, autoimmune diseases, arthritis, and neurological illnesses, as well as generalized pain and inflammation. NF-kappaB has been characterized as a major intracellular "amplifier", serving to increase the production of direct inflammatory mediators, including cytokines, prostaglandins, leukotrienes, nitric oxide and other reactive oxygen species, otherwise termed "free radicals". Via a series of events, NF-kappaB binds to DNA and activates genes encoding for inflammatory responses. These genes in turn elaborate the inflammatory process.

Nutritional intervention has shown remarkable benefits in down-regulating the NF-kappaB inflammatory pathway. The terms "nutrigenomics" or "nutritional genomics" have been used to describe the implications of dietary components and nutritional supplementation on gene expression. Nutritional genomics has been termed "the next frontier in the postgenomic era."[6] Nutritional intervention has shown to be a potent modulator of gene expression, and in turn have the capability to alter the phenotypic materialization of disease via the upregulation or

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[3] Lopez DA, Williams RM, Miehlke M. **Enzymes The Fountain of Life**. Neville Press, Inc. 1994.
[4] Hale LP. Proteolytic activity and immunogenicity of oral bromelain within the gastrointestinal tract of mice. Int Immunopharmacol. 2004 Feb;4(2):255-64
[5] Tak PP, Firestein GS. NF-kappaB: a key role in inflammatory diseases. J Clin Invest. 2001;107(1):7-11.
[6] Kaput J, Rodriguez RL. Nutritional genomics: the next frontier in the postgenomic era. Physiol Genomics. 2004 Jan 15;16(2):166-77.

downregulation of specific genes, the interaction with nuclear and hormone receptors, as well as the ability to modify the influence of transcription factors.[7] Various nutrients have shown to have a potent effect on NF-kappaB, serving to inhibit its activation. These nutrients include vitamin D, Curcumin (*Curcuma longa*; Turmeric), Lipoic acid, Green tea extract (Epigallocatechin Gallate), Rosemary, Grape seed extract, propolis (a source of caffeic acid phenethyl ester), resveratrol, Phytolens®(a patented extract from legumes), Vitamin C, Milk Thistle (*Silybum mariamum*), *Boswellia serrata*, White Willow (*Salix alba*), and essential fatty acids.

Vitamin D may perhaps be one of the most crucial nutrients used as part of the rehabilitation process. Deficiencies in vitamin D have shown to be rampant, likely as a consequence of the low "adequate intake" value defined by the Food and Nutrition Board.[8] Deficiency has been associated with the lack of exposure to sunlight, the use of sunscreens, or with those living in higher latitudes. As a consequence Vitamin D status may be insufficient to meet physiological needs. Additionally, evidence has indicated that absorption requires emulsification. In addition to its role in decreasing inflammation and downregulating NF-kappaB, an increasing number of studies have indicated that low serum levels of $25{\cdot}OH{\cdot}D_3$ are directly linked to suboptimal patient outcomes, specifically regarding inflammation. Of particular interest are the studies that link vitamin D deficiency to the loss of type II muscle fibers, and thereby to proximal muscle atrophy,[9] muscle weakness, decreased functional ability and mobility,[10] and to generalized musculoskeletal pain thresholds.[11] Additionally, vitamin D deficiency has been associated with low mood and poorer cognitive performance in older adults,[12] both important factors deserving consideration as part of the rehabilitation process, as the crucial role of the mind-body connection in healing is well documented.

In summary nutritional intervention has documented beneficial results, scientifically proven to be an integral part of the rehabilitation process. When NF-kappaB activation ensues inflammation has shown to be a destructive, self-perpetuating process. Incorporating proteolytic enzymes, vitamins and minerals, in conjunction with, or in lieu of nutrients aimed at downregulating NF-kappaB has demonstrated consistent results in promoting rehabilitation and overall wellness.

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[7] Vasquez A. Reducing Pain and Inflammation Naturally – Par IV: Nutritional and Botanical Inhibition of NF-kappB, the Major Intracellular Amplifier of the Inflammatory Cascade. Nutritional Perspectives: J CNACA. July 2005.

[8] http://ods.od.nih.gov/factsheets/vitamind.asp

[9] Verhaar HJ, Samson MM, Jansen PA, de Vreede PL, Manten JW, Duursma SA. Muscle strength, functional mobility and vitamin D in older women. Aging (Milano). 2000 Dec;12(6):455-60.

[10] Janssen HC, Samson MM, Verhaar HJ. Vitamin D deficiency, muscle function, and falls in elderly people. Am J Clin Nutr. 2002 Apr; 75(4):611-5.

[11] Heath KM, Elovic EP. Vitamin D deficiency: implications in the rehabilitation setting. Am J Phys Med Rehabil. 2006 Nov; 85(11):916-23.

[12] Wilkins CH, Sheline YI, Roe CM, Birge SJ, Morris JC. Vitamin D Deficiency Is Associated with Low Mood and Worse Cognitive Performance in Older Adults. Am J Geriatr Psychiatry. 2006 Dec;14(12):1032-1040.