Essential Nutrient System™ Short Research Review

OMEGA+D SUFFICIENCY™

Omega-3:

"The agent best documented by hundreds of references in the literature for its anti-inflammatory effects is omega-3 essential fatty acids (EFAs) found in fish and in pharmaceutical-grade fish oil supplements." (*Maroon JC, Bost JW. Omega-3 fatty acids (fish oil) as an anti-inflammatory: an alternative to nonsteroidal anti-inflammatory drugs for discogenic pain. Surgical Neurology. 2006;65(3):326-331*).

"There is extensive documentation in the rheumatology, ophthalmology, and cardiovascular literature on the beneficial anti-inflammatory effects of high-dose fish oil in the reduction of joint pain from rheumatoid and osteoarthritis, and also major positive effects on … coronary atherosclerosis, which is now considered an inflammatory disease." "In an editorial published in the same issue of *Surgical Neurology*, J.I. Ausman, MD, PhD, states "the importance of this work to neurosurgeons is that now there is an analgesic agent that can take the place of the COX-2 inhibitors and be used with no side effects." (*Maroon JC, Bost JW. Omega-3 fatty acids (fish oil) as an anti-inflammatory: an alternative to nonsteroidal anti-inflammatory drugs for discogenic pain. Surgical Neurology. 2006;65(3):326-331*).

"Omega-3 fatty polyunsaturated fatty acids (PUFAs) have been shown to decrease the production of inflammatory eicosanoids, cytokines, and reactive oxygen species; have immunomodulatory effects; and attenuate inflammatory diseases." (*Mickleborough, T.D. Omega-3 polyunsaturated fatty acids in physical performance optimization. Int J Sport Nutr. Exerc. Metab. 2013; 23: 83-96*).

"A meta-analysis of 16 studies at 3–4 months showed significant effects for four of six pain outcomes: patient assessed pain, morning stiffness, number of painful and/or tender joints, and NSAID consumption [significantly reduced NSAID consumption]." (*Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain 129 (2007) 210-233*).

By affecting cell membrane composition, metabolism, signal pathways, and by direct control of gene expression, sufficient omega 3 essential fatty acid levels play

a key role in the prevention of human diseases such as obesity, diabetes, cancer, neurological and brain disorders, and heart disease. (*Ntambi, J.M. & Bene, H. Polyunsaturated fatty acid regulation of gene expression. J Mol Neuroscience 2001 Apr-Jun; 16 (2-3): 273-8*).

Fish oil supplementation reduces exercise-induced inflammation, decreases delayed onset muscle soreness, increases the rate of recovery, and reduces the risk for infection due to immunodeficiency. Fish oil supplementation is associated with improved cognitive abilities including reaction time, decision making, and stabilizing mood. (*Mickleborough, T.D. Omega-3 polyunsaturated fatty acids in physical performance optimization. Int J Sport Nutr. Exerc. Metab. 2013; 23: 83-96*)

"A Purdue University study showed that kids low in Omega-3 essential fatty acids are significantly more likely to be hyperactive, have learning disorders, and to display behavioural problems." (*Stevens, LJ et. al. Omega-3 fatty acids in boys with behavior, learning, and health problems. Physiol Behav. 1996 59(4/5) 915-920*).

"Omega-3 fatty acids lower the risk of cancer through their suppressing effect on the biosynthesis of eicosanoids [molecules from omega-6 fatty acids that promote inflammation, suppress the immune cells that eliminate cancer cells, and stimulate cancer cell growth]." (*Larsson, SC, et.al. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am J Clin Nutr 2004; 79:935-45*).

Due to the overwhelming evidence of benefit, the American Heart Association now recommends the use of omega-3 fatty acid supplements for the primary and secondary prevention of coronary heart disease. (*Bronsna, U. & Dengel, D. Influence of vascular oxidative stress and inflammation on the development and progression of atherosclerosis. Am J Lifestyle Med. 2010 4 (6) 521-34*).

Vitamin D:

"Some researchers have found this (vitamin D deficiency) to occur in up to 85% of chronic musculoskeletal pain cases, especially those involving the lower back." (*Stewart Leavitt, Ph.D. Vitamin D – A Neglected 'Analgesic' for Chronic Musculoskeletal Pain. Pain Treatment Topics June 2008*).

"In the research investigations to date, patients found to have deficient 25(OH)D (Vitamin D) concentrations had been variously diagnosed with fibromyalgia syndrome, hyperesthesia, rheumatic disorders, osteoarthritis, back pain, bone and joint pain, muscle weakness, and other chronic somatic complaints." (*Stewart Leavitt, Ph.D. Vitamin D – A Neglected 'Analgesic' for Chronic Musculoskeletal Pain. Pain Treatment Topics June 2008*).

"The active 1,25(OH)2D form of vitamin D is a potent modulator of inflammation, and may play a role in shutting off chronic inflammatory responses." (*Pedersen LB, et al. 1,25-dihydroxyvitamin D3 reverses experimental autoimmune encephalomyelitis by inhibiting chemokine synthesis and monocyte trafficking. J Neurosci Res 2007;85:2480-2490*).

Research indicates that vitamin D supplementation modulates or decreases pro-inflammatory cytokines (e.g. C-reactive protein, interleukin 6 and 12, and tumor necrosis factor-alpha) while increasing anti-inflammatory cytokines (e.g. interleukin-10). Clinical investigators have further suggested that vitamin D may help to moderate painful chronic inflammatory autoimmune conditions that are influenced by excessive cytokine activity, such as inflammatory bowel disease and Crohn's disease. (*Boxer RS, Dauser RA, Walsh SJ, et al. The association between vitamin D and inflammation with the 6-minute walk and frailty in patients with heart failure. J Am Geriatr Soc. 2008;56:454-461*).

Subjects were treated for 3 months with 5000 IU/day to 10,000 IU/day of vitamin D3 (patients >50 kg received the larger dose). There were no episodes of hypercalcemia reported, and pain symptoms were relieved in 95% of the patients. (*Al Faraj S, Al Mutairi K. Vitamin D deficiency and chronic low back pain in Saudi Arabia. Spine 2003;28:177-179*).

Supplementation of Vit D in subjects with deficient Vit D levels resulted in a 50% increase in muscle force and reaction time. A similar change was seen in the ability to relax the muscle – in other words the muscle responds quicker to the brain signal both to contract and relax. Vit D regulates calcium metabolism and calcium is responsible for muscle contraction. (*Glerup H., Mikkelsen K, Poulsen L, et al. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. Calcif Tissue Int. 2000; 66:419-424*).

Vitamin D levels are correlated with muscle efficiency and muscle mitochondrial activity and phosphocreatine recovery significantly improved with vitamin D supplementation. In a parallel study the researchers showed that low vitamin D levels were associated reduced muscle function and recovery. (*Akash Sinha, et al. Improving the vitamin D status of vitamin D deficient adults is associated with improved mitochondrial oxidative function in skeletal muscle. Endocrine Abstracts, 2013; DOI: 10.1530/endoabs.31.OC1.6*).

"Birge and Haddad found that supplementation with vit D acts directly on muscle to increase protein synthesis." "Several cross-sectional studies have assessed associations between Vit D levels and various parameters of neuromuscular performance, finding direct associations between Vit D levels and physical performance. Correlations were more frequent and strongest for reaction time, balance, and timed tests of physical performance." (*Cannell et al. (2009) Athletic Performance and Vitamin D. Medicine and Science in Sports and Exercise. 41 (5) 1102-1110*).

"Several randomized controlled trials in older adults found that vitamin D improves various parameters of neuromuscular functioning, including balance, muscle strength, and reaction time…." "Another test of the theory are interventional studies in reducing falls, assuming falls are failures of athletic performance. Bischoff-Ferrari et al. recently reviewed that literature and concluded that vitamin D, even in relatively low doses (800 IU/day), reduces falls in the elderly." (*Cannell et al. (2009) Athletic Performance and Vitamin D. Medicine and Science in Sports and Exercise. 41 (5) 1102-1110)*.

"Vitamin D dramatically up-regulates the genetic expression of antimicrobial proteins (AMPs) in immune cells of the innate immune system [the part of the immune system that immediately attacks and kills viruses, bacteria, and fungi – the branch of the immune system responsible for fighting colds and flu]." "Also, macrophages use vitamin D to enable the synthesis of the bactericidal peptides needed to deal with bacterial invaders." (*Nature Immunology, (Vitamin D controls T cell antigen receptor signaling and activation of human T cells 10.1038/ni.1851*).

In a 3 year trial taking 800 IU/day of Vitamin D reduced the incidence of colds and flu by 70%. In the group taking 2000 IU/day the incidence of colds and flu was

reduced by almost 100% (only 1 of 104 subjects developed cold or flu). (*Alogia, J. et al. Epidemic Influenza and Vitamin D. Epidemiology and Infection 2007, Vol 135 (7) pp. 1095-1098*).

A group of Type 2 diabetic subjects with chronic, painful neuropathy were supplemented with 2000 IU/day of Vitamin D for 3 months. Symptoms improved from an average of "distressing" to an average of "mild". Overall results were a nearly 50% reduction in pain scores. (*Lee P, Chen R. Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. Arch Intern Med. 2008;168(7):771-772*).

Vitamin D-sensitive cancers are responsible for 257,000 deaths (46% of all cancer deaths in U.S. in 2007). (*Jemal A, et al. Cancer statistics, 2007. CA Cancer J Clin. 2007 Jan-Feb;57(1):43-66*).

A four-year study on vitamin D supplementation showed a 77% reduction in all invasive breast cancers in women who received vitamin D supplementation versus those who did not supplement. (*Lappe, J.M. et al. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J of Clin Nutr 2007;85:1586-1591*).

Women who maintained sufficient vitamin D levels had an 80% reduction in breast cancer incidence compared to those who had deficient vitamin D levels. (*Lowe, LC et al. Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. Eur J Cancer. 2005;41:1164-9*).

"High serum vitamin D was associated with lower mortality from breast cancer." "Patients with the highest concentration of Vitamin D had approximately half the fatality rate compared to those with the lowest concentration." (*Mohr SB et al. Meta-analysis of Vitamin D sufficiency for improving survival of patients with breast cancer. Anticancer Research. 2014;34:1163-1166*).

"In an earlier study, patients with clinical depression were randomized to receive vitamin D3 supplementation or placebo. Those patients administered vitamin D had significantly enhanced mood and a reduction in negative- affect symptoms."

(*Stewart Leavitt, Ph.D. Vitamin D – A Neglected 'Analgesic' for Chronic Musculoskeletal Pain. Pain Treatment Topics June 2008*).

"Thus pathogenic (bad) and commensal (good) gut bacteria can play opposing roles in allergy development, and these roles might be modulated by the vitamin D receptor gene, other host genes, and vitamin D itself." "It is also possible that independent of its immune effects, **vitamin D** has a direct effect on gut bacterial flora to increase or decrease the number of specific species of bacteria or species diversity." *Weiss, S.T. Bacterial components plus vitamin D: the ultimate solution to the asthma (autoimmune disease) epidemic? J Allergy Clin Immunol 2011; 127 (5): 1128-30*

Importance of Supplementing Vitamins A and D Together Using Cod Liver Oil – Why Innate Choice® OmegA+D Sufficiency™ was created (composed of half fish oil and half cod liver oil):

Vitamins A and D act synergistically and physiologically modulate each other's absorption and utilization via epigenetic changes to each other's receptors on cell membranes.

It is imperative that the source of vitamin A is from traditional Norwegian-Processed cod liver oil because this type of cod liver oil contains naturally occurring vitamin A. Most methods of deodorization of cod liver oil remove the vitamin A and then replace it with synthetic vitamin A added.

Synthetic vitamins, including synthetic vitamin A, have been shown in multiple studies to increase cancer rates. In a study of 22,000 pregnant women who were given synthetic Vitamin A the study was halted because birth defects increased 400%." (*Rothman, K. Teratogenecity of High Vitamin A Intake. N Eng J Med. 1995: 333;1369-1373*). In a study of 29,000 male smokers who were given synthetic beta carotene and synthetic Vitamin E the study was stopped when rates of lung cancer, heart attacks, and death increased." (*Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Eng J Med. 1994: 330;1029-1035*).

"Vitamin A, provitamin A, and carotenoids are well-known antioxidants. However, humans cannot synthesize vitamin A and must obtain it from their diets." "Cod

liver oil is a good source of vitamin A supplementation, as the dose of vitamin A is moderate and the quality of vitamin A is excellent." (*Huang, WB et al. Cod liver oil: a potential protective supplement for human glaucoma. Int J Ophthalmol 2011;4(6):648-651*).

"Cod liver oil is used widely as a dietary supplement. It is a rich source of vitamin A, vitamin D, and essential omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA)."
"In previous studies, cod liver oil supplementation has been suggested to reduce cardiometabolic risk factors, have anticancer effects, and ameliorate cognitive impairment induced by chronic stress." (*Huang, WB et al. Cod liver oil: a potential protective supplement for human glaucoma. Int J Ophthalmol 2011;4(6):648-651*).

"The active form of vitamin D3 is an immunoregulatory hormone with beneficial effects on Th1 cell-mediated inflammatory diseases." "Thus, we initially reveal that Vit D and Vit A have synergistic effects on the generation of Th17 cells, suggesting that the combination would provide a promising novel therapy for Th17 cell-related immune diseases including skin inflammation." *(Ikeda, U et al. 1,25 dihydroxyvitamin D3 and all-trans retinoic acid synergistically inhibit the differentiation and expansion of Th17 cells. Immunology Letters 2010. 134(1):7-16*).

"Vitamin A and vitamin D balance, enhance, and contain each other through the retinoid X receptor (RXR)." "Because they share a receptor, if we supplement either vitamin D or vitamin A in an unbalanced fashion, we create a functional deficiency of the one not supplemented." "Low blood levels of vitamin D, vitamin A, and carotenoids are all correlated with greater risk of heart disease." "Both vitamin A and vitamin D are far more than vitamins, with profound effects on every tissue of the body...they are involved in regulation of everything from bone to the brain, the kidney to the immune system, the heart to the pancreas." (*Levine, SA. The importance of a balanced approach to vitamin D supplementation. Journal of Orthomolecular Medicine. 2011;26(1):15-20*).

"In summary, we describe a unique and unexpected facet of intermolecular cross-talk between VDR and RXR and demonstrate that RXR actively participates in RXR-VDR-mediated gene transcription by directly recruiting coactivators in response to

1,25-(OH)-2D-3." [In layperson terms vitamin A (retinoid) is required to activate the expression of vitamin D controlled genes. In other words, without sufficient amounts of vitamin A, the actions of vitamin D can be impaired or even blocked. Vitamin A and Vitamin D work synergistically.] (*Bettoun, Burris, et al. Retinoid X Receptor Is a Non-silent Major Contributor to Vitamin D Receptor-Mediated Transcriptional Activation. Molecular Endocrinology 17: 2320–2328 2003*).

"Vitamins A and D each increase the genetic expression of cell receptors for the other. Together, vitamins A and D cause a three-fold increase in production of receptors compared to either vitamin alone." "This would imply that the policy of giving vitamin D supplement alone in pregnancy instead of cod liver oil would need adjustment. Cod liver oil, as natural supplement of vitamin A and vitamin D, is well know for its beneficial effects on the growth of infants and children." (*Ng et al. Vitamin D and vitamin A receptor expression and the proliferative effects of ligand activation of these receptors on the development of pancreatic progenitor cells derived from human fetal pancreas. 2011 Stem Cell Rev 7 (1): 53–63*).

"TUNEL showed vitamin A and vitamin D induced prostate cancer cells apoptosis [cancer cell death]. The combination of vitamin A and vitamin D markedly enhanced the expression of Bax and reduced the expression of Cyclin D1 by real time-PCR and western blot assay." "In conclusion, vitamin A and vitamin D could synergistically induce apoptosis in prostate cancer cells." (*Sha, J et al. Synergistic effect and mechanism of vitamin A and vitamin D on inducing apoptosis of prostate cancer cells. Mol Biol Rep. 2013;40(4):2763-2768*).

PROBIOTIC SUFFICIENCY™

*"*Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. There is now mounting evidence that selected probiotic strains can provide health benefits to their human hosts.*" Reid, G., Jass J., Sebulsky M.T., and McCormick J.K. 2003. Potential Uses of Probiotics in Clinical Practice. Clinical Microbiology Reviews. 16(4):658-672*

"The daily present-age consumption of bacteria, live or dead, is a million times less than what was consumed by our Stone Age (Paleolithic) ancestors."

"The intestines contain about 1 kg probiotic bacteria, or 10 times as many bacterial cells as the body contains eukaryotic cells." "The protective flora is often reduced as a result of stress and consumption of a Western diet, which not only contains too little fiber but also is deficient in important nutrients such as omega-3 fatty acids."*Bengmark, S. M.D. Ph.D. 1998. Immunonutrition: Role of biosurfactants, fiber, and probiotic bacteria. Nutrition. 14:585-594.*

"Probiotic bacteria have also been shown to preserve intestinal integrity and mediate the effects of inflammatory bowel diseases, irritable bowel syndrome, colitis, and alcoholic liver disease." Kruis, W. *et al. Double-blind comparison of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther 1997;11:853-8.*

"The microbiota interacts with the innate and adaptive arms of the host's intestinal mucosal immune system and through these mechanisms drives regulatory cell differentiation in the gut that is critically involved in maintaining immune tolerance. If appropriate immune tolerance is not established in early life and maintained throughout life, this represents a risk factor for the development of inflammatory, autoimmune, and allergic diseases." *Mcloughlin, RM & Mills, KH. Influence of gastrointestinal commensal bacteria on the immune responses that mediate allergy and asthma. J Allergy Clin Immunol. 2011; 127 (5): 1097-107*

Regular ingestion of probiotic supplement reduced the frequency of Upper Respiratory Tract Infection (cold and flu) in athletes. Subjects taking probiotics had significantly greater levels of salivary IgA. *Gleeson, M. et al. Daily Probiotic's (Lactobacillus casei Shirota) Reduction of Infection Incidence in Athletes. Int J Sport Nutr Exer Metabol 2011 21 (1)*

"The meta-analysis indicated a significant reduction in serum CRP [C-Reactive Protein – An Inflammatory Marker) following probiotic administration." "It is suggested that probiotics not only improve the balance of gut microbiota in favor of healthy bacteria but are also helpful in either preventing or improving the outcome of a number of health conditions such as obesity, insulin resistance, type 2 diabetes, and non-alcoholic fatty liver disease." *Mazidi, M. et al. Impact of Probiotic Administration on Serum C-Reactive Protein Concentrations: Systematic Review and Meta-Analysis of Randomized Control Trials. Nutrients 2017, 9, 20;doi:10.3390/nu9010020*

VITA SUFFICIENCY™

Naturally Occurring Micronutrients Have Proven Wellness & Prevention Benefits

Research evidence shows that naturally occurring fruit and plant sourced essential micronutrients are far superior to synthetic vitamins. *Liu, RH. Potential Synergy of Phytochemicals in Cancer Prevention: Mechanism of Action. Journal of Nutrition. December 2004, 134(12), 3479S-3485S.*

Diets high in naturally occurring essential micronutrients sourced from fruits and plants decreases the risk of chronic diseases, such as cardiovascular disease and cancer. *Boyer, J and Liu, RH. Apple phytochemicals and their health benefits. Nutrition Journal 2004, 3:5.*

Diets high in naturally occurring essential micronutrients sourced from fruits and plants help prevent heart disease and cancer, and also help protect against a variety of other illnesses such as cataracts, diabetes, Alzheimer's disease, and asthma. *Woods R, Walters H, Raven J, Wolfe R, Ireland P, Thien F, Abramson M: Food and nutrient intakes and asthma risk in young adults. Am J Clin Nutr 2003, 78:414-421. Willett W: Balancing life-style and genomics research for disease prevention. Science 2002, 296:695-698.Ames B, Shigenaga M, Hagen T: Oxidants, antioxidants, and the degenerative diseases of aging. Proc Natl Acad Sci 1993, 90:7915-7922*

Dietary consumption of naturally occurring vitamins from fruits and vegetables lowers risk of lung cancer, CHD, cataracts, and age-related macular degeneration. *van Helden, YG. et al. Beta-carotene metabolites enhance inflammation-induced oxidative DNA damage in lung epithelial cells. Free Radic Biol Med. 2009 Jan 15; 46(2):299-304*

Synthetic Vitamins Increase Birth Defects, Cancer, and Death.

"22,000 pregnant women were given synthetic Vitamin A. The study was halted because birth defects increased 400%." *Rothman, K. Teratogenecity of High Vitamin A Intake. N Eng J Med. 1995: 333;1369-1373.*

The Alpha-Tocopherol Beta Carotene (ATBC) Trial observed a higher death rate in the isolated synthetic beta-carotene group and no treatment effect in the isolated

alpha-tocopherol group. *Blumberg, J. and Block, G. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study in Finland. Nutr Rev. 1994;52(7):242-245.*

"29,000 male smokers were given synthetic beta carotene and synthetic Vitamin E. The study was stopped when rates of lung cancer, heart attacks, and death increased." *Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Eng J Med. 1994: 330;1029-1035.*

The Heart Outcomes Prevention and Evaluation (HOPE) study reported greater all-cause death with isolated vitamin E (tocopherol). *Yusuf, S. et al. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000 342(3): 154-160.*

A research study conducted in March 2009 showed that taking synthetic vitamin C and synthetic vitamin E actually blocked the beneficial effects of exercise in terms of insulin sensitivity and antioxidant activity. Most importantly the subjects who received naturally occurring vitamin C and vitamin E from consuming fruits and plants did not have this problem! *Ristow, M. et al. Antioxidants prevent health-promoting effects of physical exercise in humans. PNAS, published ahead of print May 11, 2009*

The Physicians Health Study reported no benefit of supplementation with isolated synthetic beta-carotene. *Hennekens et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med. 1996;334(18):1145-1149.*