The Synergistic Approach: The Future of Nutrition Therapy

by Robert Crayhon, MS

There is no cell in the body that requires one nutrient only, yet single nutrient therapy has comprised the bulk of all nutrient intervention studies. This is understandable, because the goal of research is to isolate the activity of nutrients so their individual roles in the prevention of deficiency and the treatment and prevention of disease can be discovered.

Clinically, however, single nutrient therapy is not as effective as multiple nutrient intervention. Single nutrient deprivation and intervention studies are useful for research purposes, but as the research cited below will show, whenever synergistic nutrient combinations are compared to single nutrient interventions, the combined nutrient approach is both more effective and safer. Perhaps this is because multiple nutrient intervention better approximates the nutrient distribution found in food.

No cell in the body uses only one nutrient. No nutrient in the body acts alone. Therefore, it should come as no surprise that we need all of the nutrients in order to promote optimal cellular, organ, and overall health. Because nutrients have powerful interactions with other nutrients, the success of a nutrient therapy may depend more on the synergistic interaction with a particular nutrient than merely the dose given. This argues for both individualized therapy as well as synergistic ones. For example, The First National Health and Nutrition Examination Survey (NHANES I) data shows that the Na:K ratio was more strongly related to blood pressure than either nutrient alone.[1]

One of the reasons suggesting that nutritional therapy should be done in synergy is that deficiencies occur in synergy.[2] It is difficult to study riboflavin deficiency in humans, for example, because it is so often accompanied by deficiencies of other nutrients. Therefore, repleting all nutrients is often beneficial in cases where a single deficiency is discovered.

Synergistic Interventions are Safer

The most important reason to use nutrients in combination is not efficacy, but safety. The ingestion of single, isolated nutrients by the human genus is but 70 years old. This is at odds with the 2.6 million years of only ingesting nutrients in synergistic combinations found in foods of plant and animal origin. Throughout our genetics' long history, they have never encountered a single instance where a food consumed supplied one or even a small handful of nutrients. This is mirrored in our metabolism: all cellular functions, including glycolysis, the Krebs cycle, the energy transfer cycle, cellular housekeeping, eicosanoid metabolism, neurotransmitter metabolism, antioxidant defense, immune strength, and detoxification all depend on an optimal supply of virtually all nutrients.

The homocysteine raising effects of niacin have been noted in human studies. In a multicenter randomized, placebo-controlled trial, the effects of niacin compared with placebo on homocysteine levels in a subset of 52 participants with peripheral arterial disease were examined. During the screening phase, titration of niacin dose from 100 mg to 1000 mg daily resulted in a 17% increase in mean plasma homocysteine level from 13.1 to 15.3 micromol/L. At 18 weeks after randomization, there was an absolute 55% increase from baseline in mean plasma homocysteine levels in the niacin group and a 7% decrease in the placebo group.[3] Animal studies have shown that taking pyridoxine with niacin eliminates its homocysteine-raising effects. Human trials using niacin along with all of the homocysteine lowering nutrients – folate, cobalamin, and pyridoxine – are warranted.[4]

Beta carotene is another nutrient which does not offer complete safety when taken alone. Beta carotene alone does lead to regression of oral leukoplakia, a precancerous lesion.[5] However, beta carotene supplements appear to increase the incidence of lung cancer in smokers.[6] This may be due, however, to the fact that taking beta carotene alone does not supply the other nutrients – vitamin E and vitamin C – which are needed to help prevent beta carotene from oxidizing and itself becoming a cell damaging free radical. The Linxian study showed that vitamin E, selenium and beta carotene supplementation led to lower cancer rates.[7] This shows that the synergistic combination of beta carotene can lead to positive results. However, not all synergistic research in cancer prevention has yielded positive results. Beta carotene and vitamin E taken together did not lead to protection against pancreatic cancer[8] or colorectal adenomas[9] in the ATBC (alpha tocopherol beta carotene) trial.

Beta-carotene in its unoxidized form appears to be an anticarcinogen, but its oxidized products appear to facilitate carcinogenesis. The carcinogenic response in lung tissue to high-dose beta-carotene supplementation reported in the human intervention trials is caused by the instability of beta-carotene in the free radical-rich environment in the lungs, particularly in cigarette smokers.[10] This is especially possible because smoke decreases tissue levels of other antioxidants, such as ascorbate and alpha-tocopherol, which normally have a stabilizing effect on the unoxidized form of beta-carotene. Nutritional intervention using a combination of antioxidants such as beta-carotene, alpha-tocopherol, lycopene, and ascorbate as anticarcinogenic agents would be a more appropriate way to reduce cancer incidence in smokers. Then we can perhaps duplicate with supplementation the epidemiological results suggesting that a high beta carotene intake through diet is chemoprotective against lung cancer. Foods rich in beta carotene are rich in other antioxidants, including ascorbate, polyphenols, and other carotenoid and xanthophyll antioxidants.[11]

Iodine and selenium are two nutrients which are essential for thyroid function. Yet supplementing with iodine in the absence of selenium can do more harm than good. High iodine intake during selenium deficiency can permit thyroid tissue damage as a result of low thyroidal GSH-Px activity during thyroid stimulation.[12]

The Synergistic Effect Benefits Nutrient Absorption

Vitamin C and other antioxidants are known to enhance iron absorption.[13] Zinc is a nutrient which can be thought of as synergistic with almost every other nutrient, for a lack of adequate zinc can lead to a lack of absorption of other nutrients, particularly fat soluble vitamins such as vitamin A and vitamin E.[14] EFAs have now been shown to increase calcium absorption from the gut,

in part by enhancing the effects of vitamin D, to reduce urinary excretion of calcium, to increase calcium deposition in bone and improve bone strength and to enhance the synthesis of bone collagen.[15] This has been found to be particularly true for calcium absorption and calcium balance. Supplementing with both EPA and GLA for three years led to increased bone density and decreased calcium turnover in women aged 79.5. After three years on supplemental EPA and GLA, lumbar spine density increased 3.1% and femoral BMD increased of 4.7%.[16] Glutamine, SCFAs, and nucleotides, affect normal and pathologic intestinal mucosal development, function, adaptation, and repair, and when optimally supplied to the gut mucosa, help promote optimal nutrient absorption.[17]

Synergistic Antioxidant Studies in Cancer Prevention: Successes and Failures

Antioxidants are a great example of how nutrients work together, particularly for inhibition of cancer cell growth. The effect of the carotenoid lycopene alone or in association with other antioxidants was studied on the growth of two different human prostate carcinoma cell lines (the androgen insensitive DU-145 and PC-3). Lycopene alone was not a potent inhibitor of prostate carcinoma cell proliferation. However, lycopene together with alpha-tocopherol, at physiological concentrations (less than 1 microM and 50 microM, respectively), resulted in a strong inhibitory effect of prostate carcinoma cell proliferation, which reached values close to 90%.[18] Perhaps this synergistic effect of nutrients on cancer prevention in human epidemiological studies explains why fruits and vegetables[19] appear to have more protective ability than interventions with single nutrients such as beta carotene.[20]

Niacin and Chromium

Both chromium and niacin have been found to lower cholesterol. Often, high doses of niacin are needed to achieve this effect. A study of two subjects given 100 mg of niacin with 200 mcg of chromium chloride found that that combination lowered cholesterol.

The two subjects given niacin and chromium experienced significant blood lipid lowering effects. The first subject had a cholesterol level of 10.33 mmol/L (399 mg/dL). Daily supplementation for four weeks with 100 mg of nicotinic acid (niacin) and 200 micrograms of chromium chloride led to a decrease in serum cholesterol to 8.86 mmol/L (342 mg/dL). Further supplementation for four months led to a further decrease in serum cholesterol to 7.25 mmol/L (280 mg/dL). The second subject had a cholesterol level of 8.73 mmol/L (337 mg/dL). Four weeks of supplementation lowered the level to 6.73 mmol/L (260 mg/dL). When supplementation was discontinued, the cholesterol level rose slightly. When supplementation was reinstituted, the cholesterol level decreased to 6.68 mmol/L (258 mg/dL).[21] While this is a small study, it demonstrates that the cholesterol lowering effects that are typically achieved with large doses of niacin can be obtained with smaller doses of niacin taken along with chromium.

Chromium does not work effectively in the absence of niacin, according to animal research. This could explain why humans do not uniformly achieve lipid and/or blood sugar lowering effects on chromium supplementation. Sixteen healthy elderly volunteers were divided into three groups and given either 200 micrograms Cr, 100 mg nicotinic acid, or 200 micrograms Cr + 100 mg nicotinic acid daily for 28 days and evaluated on days 0 and 28. Fasting glucose and glucose tolerance were unaffected by either chromium or nicotinic acid alone. In contrast, the combined chromium-nicotinic acid supplement caused a 15% decrease in a glucose area integrated total (p less than .025) and a 7% decrease in fasting glucose. These data suggest that the inability to respond to chromium supplementation may result from suboptimal levels of dietary nicotinic acid, and once again demonstrate the power of the synergistic effect.[22]

Fatty Acid Synergy

One of the questions raised by research in fatty acids is, which fatty acid has the most anti-inflammatory effects: EPA or DHA? A mouse model of lupus-induced renal disease suggests that EPA and DHA combined have a greater anti-inflammatory and renal-protective effect than either fatty acid alone.[23]

GLA and Lipoic Acid

The power of the synergistic effect is demonstrated in a couple of studies where gamma linolenic acid (GLA) and lipoic acid were given alone and in combination. Two multicenter, randomized, placebo-controlled trials in humans with diabetic neuropathy have shown significant benefits of GLA as compared with placebo in neurophysiological parameters, thermal thresholds, and clinical sensory evaluations in diabetic neuropathy.[24] Fifteen clinical trials have been performed examining lipoic acid as a treatment for diabetic neuropathy, showing that intravenous and oral administration are both of equal benefit. Doses ranged from 600-1800 mg per day, with trials lasting anywhere from 4-24 months.[25] These two nutrients were given together in a provocative animal study. After 6 weeks of diabetes, 2 weeks of lipoic acid treatment corrected 20% sciatic motor and 14% saphenous sensory deficits. Lipoic acid also corrected a 49% diabetic deficit in sciatic endoneurial blood flow. Treatment of diabetic rats with low doses (20 mg kg(-1) day(-1)) of lipoic acid and GLA, while having modest effects on their own, showed evidence of marked synergistic action in joint treatment, completely correcting motor nerve conductivity velocity (NCV) and blood flow deficits.[26] Another animal study also showed that the GLA-lipoic acid combination is effective in improving both electrophysiological and neurochemical correlates of experimental diabetic neuropathy.[27] The synergistic effects of GLA and lipoic acid are also greater than either alone when used in the treatment of insulin resistance.[28]

More Synergistic Effects

A 16-week randomized, double-blind, placebo-controlled crossover trial of a combination of glucosamine HCL (1,500 mg/day), chondroitin sulfate (1,200 mg/day), and manganese ascorbate (228 mg/day) in degenerative joint disease (DJD) of the knee or low back was conducted in 34 males. This combination therapy led to a marked reduction in symptoms of knee osteoarthritis with no side effects.[29]

Male erectile dysfunction has been studied by an interventive study using arginine, ginkgo extract, vitamin E, and an RDA multivitamin supplement. The results were positive, with over 70% of those studied noting improvement.[30]

Focus for future research for examining the synergistic effects of nutrient therapy should include:

- Folic acid,[31] inositol,[32] selenium,[33] and St. John's Wort[34] have all been found effective for alleviating depression. Low zinc[35] and omega 3 fatty acid[36] levels have also been observed in depressed patients. Combining all of these therapies may yield greater success than either one alone.
- Acetyl-L-carnitine,[37] phosphatidyl choline,[38] phosphatidyl serine,[39] inositol,[40] ginkgo standardized extract,[41] and vitamin E[42] have all

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demonstrated the ability to help relieve some of the symptoms of Alzheimer's disease and slow its progression. A trial using all of these therapies may yield even more substantial results.

- Nutrients that have been found to help treat PMS include calcium and manganese[43]
- Vitamin C,[44] taurine,[45] potassium,[46] and magnesium[47] help lower blood pressure. A trial using all four of these nutrients may show that together they have a synergistic effect greater than the sum of the parts.
- Carnitine and CoQ10 work together to improve cellular energetics and promote heart health.[48] A trial combining them with heart helping nutrients such as vitamin E, taurine and magnesium and potassium[49] should be conducted in patients with arrhythmias and congestive heart failure.
- Because riboflavin,[50] calcium[51] and feverfew[52] all appear to help prevent migraine headaches, they should be studied together in a human trial.
- Research suggests that vitamins A, C, E, selenium, zinc, copper, and dietary fatty acids have powerful effects on immune function. Studies using all of these nutrients should be employed.[53]
- HIV patients demonstrate a defect in zinc, selenium, and glutathione. There is a progressive decrease for carotenoids, zinc, selenium, and vitamin E with the severity of disease. Few serious and large trials of antioxidants have been conducted in HIV-infected patients. The more promising candidates for presenting synergistic effects seem to be N-acetyl cysteine, beta-carotene, selenium and zinc.[54]

Correspondence:
Robert Crayhon, MS
1750 - 30th Street, PMB 319
Boulder, Colorado 80301 USA
303-415-0229

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