Response to Editorial: "Enough is Enough: Stop Wasting Money on Vitamin and Mineral Supplements"

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In a recent editorial in Annals of Internal Medicine, Dr. Emilio Guallar and colleagues review three new supplementation studies with negative or equivocal outcomes, and conclude that "the case is closed – supplementing the diets of well-nourished adults with (most) mineral or vitamin supplements has no clear benefit and might even be harmful. These vitamins should not be used for chronic disease prevention. Enough is enough."[1]

To the contrary, the research literature regarding the impact of vitamin-mineral supplementation on health is not nearly as uniformly negative as portrayed by Dr. Guallar and colleagues.

Although homocysteine-lowering vitamin supplementation (folate, B6, B12) has failed to prevent myocardial infarctions, some though not all meta-analyses of controlled trials suggest that this can modestly reduce risk for stroke,[2] and a large trial of such supplementation in women at high cardiovascular risk observed a 40% reduction in risk for visually significant macular degeneration in those receiving active supplementation (RR=0.59; 95% CI: 0.36-0.95), consistent with much epidemiology linking moderate elevations of homocysteine with risk for this disorder.[3, 4] Perhaps moderate elevations of homocysteine can adversely affect the blood-brain and blood-retina barriers.[5]

The AREDS1 study found that supplementation including high-dose zinc (80 mg daily) also was of modest utility for slowing the progression of macular degeneration.[6] More importantly, during the 6.3 years of the study, total mortality was 27% lower in those receiving as zinc as opposed to those not receiving zinc (RR 0.73; 95% CI: 0.61-0.89).[7] A plausible explanation for this findings is that high-dose zinc, via metallothionein induction, functions as an antagonist of the toxicity of cadmium, which is emerging as a key pathogenic factor in the general population (as Dr. Guallar's own important studies demonstrate).[8, 9] This remarkable finding was reported ten years ago, but there has been no subsequent effort to replicate it. More recent research has correlated the ratio of urinary cadmium to dietary zinc with total cancer mortality.[10]

Several decades ago, cardiologist Kurt Oster reported anecdotally on the marked benefits he observed in patients with vascular disorders treated with 40-80 mg folate daily.[11] Subsequent research has revealed that, in mega-doses, folic acid has remarkable antioxidant potential, reflecting the scavenging activity of its tetrahydro- metabolites.[12, 13] In particular, high-dose folate promotes recoupling of the endothelial nitric oxide synthase in dysfunctional endothelium, an effect which may be notably protective.[14] The impact of mega-dose folate administration in a rat model of cardiac ischemia reperfusion was so dramatic that the journal Circulation featured an accompanying editorial entitled "How Does Folic Acid Cure Heart Attacks?"[15, 16] Yet there have been no subsequent long-term studies evaluating the impact of mega-dose folate on health

Supplementation with the menaquinone form of vitamin K found in dairy products (K2, best administered as the commercially available menaquinone-7) has markedly lowered the fracture risk of postmenopausal women in Japanese clinical trials,[17] and there is good reason to suspect that it can also aid in the prevention of vascular calcification[18] – a possibility not yet addressed in published studies.

Gamma-tocopherol is the most prominent dietary tocopherol, and displays oxidant-scavenging activities not possessed by alpha-tocopherol;[19] nonetheless, alpha- rather than gamma-tocopherol has been accorded vitamin status. The gamma form antagonizes prostate cancer development in rats, and slows the growth of human prostate cancer implanted in nude mice.[20, 21] Gamma-tocopherol can also have favorable impact on endothelium-dependent vasodilation, a determinant of vascular risk.[22, 23] The alpha form is ineffective in these regards, and moreover, in high doses, inhibits the transport of gamma-tocopherol to the body's tissues.[24] Designers of the SELECT trial of prostate cancer prevention were urged to test gamma-rich mixed tocopherols, rather than pure alpha-tocopherol, but this advice was not heeded. The slight adverse impact of alpha-tocopherol subsequently observed in this study plausibly might reflect a depression of tissue gamma-tocopherol – and serve as indirect evidence that gamma-tocopherol is indeed protective in this regard.[25]

Designers of the Nutritional Prevention of Cancer Study intentionally chose a study population that was likely to include a significant fraction of patients with sub-optimal selenium status, such that selenium supplementation would be likely to boost their expression of selenium-dependent antioxidant enzymes. The marked reduction in total cancer incidence and mortality observed in this trial (for mortality, RR= 0.50, 95% CI: 0.31-0.80) was subsequently found to reflect cancer prevention in those subjects with relatively low selenium status at baseline.[26, 27] The subsequent larger SELECT chemoprevention trial made no effect to enroll subjects with poor selenium status and, not surprisingly, did not see benefit with supplemental selenium.[28] Selenium nutrition tends to be good in the U.S., owing to the high selenium content of mid-Western grains and of the livestock fed with them. However, many selenium chemoprevention trials have been conducted in countries where soil selenium is lower than in the selenium-rich U.S.; a meta-analysis of all selenium chemoprevention studies has concluded that supplemental selenium likely does lower overall cancer risk in populations with low baseline serum selenium status.[29] Swedish soils are typically selenium poor, and a recently reported 5-year placebo-controlled trial found that joint supplementation with selenium and coenzyme Q10 in elderly Swedes was associated with a reduction of more than 50% in cardiovascular mortality (5.9% vs. 12.6%; P=0.015).[30] More selenium trials targeting low-selenium populations are clearly needed.

A great deal of recent epidemiology has linked lower magnesium dietary intakes or serum levels to increased risk for vascular events, arrhythmias, diabetes, hypertension, metabolic syndrome, and mortality.[31] This is plausible, given that intracellular magnesium functions to antagonize certain pro-inflammatory signals triggered by cytoplasmic free calcium.[32, 33] Indeed, correction of low magnesium status has been found to have favorable effects on vascular endothelium, platelets, cardiac function, and blood pressure.[34] Yet a large controlled magnesium supplementation study, examining hard endpoints in an at-risk population, has not yet been conducted (though a study cited below may be pertinent). Plausibly, the modest increase in infarction risk associated with calcium supplementation in a recent meta-analysis[35] reflects impairment of magnesium balance in people with low baseline magnesium.[36]

The equivocal utility of supplemental vitamin D in much research may be traceable to the fact that suboptimal doses have been employed in most clinical studies to date. The physiological capacity for dermal generation of vitamin D is 10,000-20,000 IU daily;[37] many supplementation trials have used daily doses of low as 400 IU, but some experts now recommend supplemental intakes of 2,000-8,000 IU to insure optimal vitamin D status.[38] Although "adequate" vitamin D status may be sufficient to optimize its impact on vascular and bone health, the autocrine production of calcitriol in certain cancer-prone tissues

varies directly with 25-hydroxyvitamin D levels, so high-normal vitamin D status may be needed for optimal protection from some cancers.[38]

The Centrum Silver vitamin-mineral supplement evaluated in the recent trial by Grodstein[39] – which failed to observe an impact of this supplement on cognitive decline in an older population – provides modest doses (e.g. 500 IU vitamin D, 50 mg magnesium, 12 mg zinc, no gamma-tocopherol), and cannot be expected to do more that prevent overt deficiency in people with relatively bad diets. The subjects enrolled in this trial were physicians, who, by reason of education, financial capacity, and self-discipline, are likely to consume diets more nutritious than those of the average American. Moreover, there was no particular reason to believe that such supplementation would influence cognitive health. Nonetheless, an earlier analysis of the same trial concluded that people taking the supplement were at modestly lower risk for cancer as compared to those on placebo (HR= 0.92; 95% CI, 0.86-0.998).[40] Likewise, the moderate dose antioxidant supplement tested in the French SU.VI.MAX study was associated with significant cancer protection in men (RR=0.69, 95% CI, 0.53-0.91), though not in women (RR=1.04); men also had lower all-cause mortality in this study.[41]

The "high-dose multivitamin and mineral" employed by Lamas and colleagues in their secondary prevention trial provided 100 IU of vitamin D per day – an oddly low choice, given that this is the vitamin that most experts would consider most likely to favorably influence vascular risk.[42] The supplement did not contain gamma-tocopherol or vitamin K2. Arguably, its chief merit was an ample magnesium dose (500 mg). Given the very poor compliance of the subjects, the less than ideal design of the supplement, and the fact that the trial was powered to detect a reduction in risk of at least 25%, it is not surprising that the outcome (an 11% risk reduction - HR=0.89, 95% CI, 0.75-1.07) failed to achieve statistical significance. However, it is notable that, in the subgroup analyses summarized in Figure 3, the hazard ratio for those receiving the supplement was less than 1.0 in 17 of the 20 subgroups analyzed – strongly suggestive of a real effect. Rather than viewing this study as a defeat, perhaps we should perceive it as encouragement for a larger clinical trial of supplemental magnesium in the secondary prevention of vascular events; there is ample reason to suspect that poor magnesium status increases vascular risk.[31]

The claim that "antioxidants" are ineffective for prevention of chronic disease, and merit no further clinical study, is unwarranted. High-dose zinc may prove to have considerable merit, selenium may be helpful within low-selenium populations, and high-dose folate, and a range of non-vitamin natural antioxidants such as gamma-tocopherol, N-acetylcysteine, taurine, lipoic acid, coenzyme Q10, astaxanthin, melatonin, and phycocyanobilin have received minimal clinical evaluation despite displaying intriguing efficacies in the pre-clinical literature, and, in some cases, promising clinical effects on risk factors. As Fortmann and colleagues note in their overview of the current supplementation literature, "few fair- or good-quality studies are available for all supplements except vitamin E and beta-carotene".[43] And there was never any reason to believe that alpha-tocopherol and beta-carotene are the most effective of antioxidants; indeed, because they don't influence hydrogen peroxide production or signaling, they have minimal impact on the pro-inflammatory aspects of oxidative stress. Ascorbate suffers from the drawback that its capacity for intracellular uptake is maximized at serum concentrations achievable with reasonably nutritious diets.[44] Many biomedical researchers seem to think that "an antioxidant is an antioxidant", and that the failure of alpha-tocopherol, beta-carotene, or ascorbate in clinical trials implies that antioxidants *per se* are clinically without value or even harmful. Yet, ironically, much of the versatile proven protection of statin and angiotensin II antagonist therapy is believed to stem from a suppression of

superoxide production;[45] phycocyanobilin, an algae-derived bilirubin mimetic, has similar potential.[46] There can be little doubt that oxidative stress plays a key pathogenic role in a high proportion of health disorders; our challenge is to define the nutraceutical/drug regimens which can do the most effective job of controlling it.

Finally, it should be noted that Guallar and colleagues delimit their recommendation against supplementation to "well-nourished adults". In fact, a significant fraction of the public get a high proportion of their calories from added sugars and oils, refined grains, and alcohol; it is not irrational for such people to use a multi-vitamin-mineral. Obviously, it would be preferable for such people to eat a varied diet of natural whole foods – but people are who they are.

Rather than adopting a negative attitude toward supplementation per se, we should learn from past failures and design smarter studies using the right doses and forms of nutrients and phytochemicals in the right target populations – seeking to determine *what actually does work*, rather than simply evaluating the nutrients that happen to be the most faddishly popular. Supplements chosen for testing in large, expensive trials with hard endpoints should have first demonstrated the capacity to modulate risk factors (a qualification which alpha-tocopherol and beta-carotene could not have met). In response to "enough is enough", I suggest that clinical supplements research is only getting started, and will ultimately lead us to valuable resources for health.

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