The Case is Closed: Editorial Bias Prevents Reasonable Evaluation of Dietary Supplements

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Being involved with dietary supplement research for almost 18 years, I have witnessed my share of hype for, and against, the use of dietary supplements. Few, however, have attempted such blatant finality to the subject as the recent editorial in the Annals of Internal Medicine—titled “Enough is Enough: Stop Wasting Money on Vitamin and Mineral Supplements.”1 The editorial authors, acting as both judge and jury, declare in no uncertain terms that “we believe the case is closed—supplementing the diet 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.” The verdict, they tell us, was sealed by 3 papers published in the same Annals issue. Not surprisingly, the publication of the editorial was touted by many news outlets that quickly found the usual supplement bashers all too willing to add insult to injury by regurgitating decades-old sound bites.

Anybody who has spent even a brief amount of time evaluating medical research, especially as it pertains to the use of vitamins and minerals, knows that such a conclusion (“the case is closed”) is as arrogant as it is absurd. In fact, the editorial does not even do justice to the data presented in the 3 papers published within the same issue—let alone the broader evidence used to evaluate the use of vitamins and minerals for the prevention of chronic disease. In any system of justice, this would be declared a mistrial.

Let us first re-examine the testimony of the 3 witnesses (the 3 papers published in this particular Annals issue) before asking the broader questions that may expose the real agenda behind this editorial. We call the 3 witnesses to the stand: (1) the vitamin-only and placebo-only arms of the Trial to Assess Chelation Therapy (TACT) tracking event rates after an initial myocardial infarction (MI); (2) the measurement of cognitive changes when giving men a multivitamin—part of the Physicians Health Study II (PHS2); and (3) a systematic review of a select group of studies using various vitamin preparations for primary prevention of cardiovascular disease and cancer—a review prepared for the U.S. Preventative Services Task Force.

Witness Number 1: TACT

The TACT, funded by the National Institutes of Health (NIH), was purported to be the clinical trial that would finally “prove” the value of ethylenediaminetetraacetic acid (EDTA) chelation for cardiovascular risk modification. After the 10-year trial that most thought (and many hoped) would result in the debunking of IV chelation therapy for cardiovascular disease, the results turned out to be quite promising for EDTA chelation therapy; JAMA published the initial results in March of 2013.2 TACT subjects were at least 50 years old and all had sustained a previous MI. The primary end point was a composite of death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina. The composite of cardiovascular death, reinfarction, or stroke was a prespecified secondary end point. TACT was a 2 × 2 factorial trial where patients received weekly infusions of EDTA or placebo, along with a high-dose vitamin and mineral supplement or placebo, for 40 weeks. Because of the unique challenges created by recruiting patients for the trial, the normal P value for statistical significance of <.05 was lowered to P < .036 (a more stringent level of statistical significance). Even so, the 5-year estimate of reaching the primary end point shows that those given the EDTA chelation had 18% less risk (hazard ratio = 0.82), which met the stringent level of statistical significance (P = .035). The expectant lukewarm conclusion by authors was that the therapy “modestly reduced the risk of adverse cardiovascular outcomes, many of which were revascularization procedures. These results provide evidence...
to guide further research but are not sufficient to support the routine use of chelation therapy for treatment of patients who have had an MI."

Since this study was a 2 × 2 factorial trial, the 2 arms receiving no EDTA chelation (saline/placebo) given either placebo capsules or high-dose multivitamin capsules were compared in the new study. A high-dose multivitamin mineral supplement, similar to those sold by a number of physician-only product companies, was used for this study. According to the authors, the high-dose vitamins showed an 11% relative reduction in the primary end point compared to placebo, but this difference did not reach statistical significance. The authors make it clear to us that while the trial does not support the routine use of a high-dose oral multivitamin regimen for all patients who have had an MI, the total number of events were smaller than the trial was originally powered to detect, and thus “the reduced statistical power due to a small difference between groups, as well as the nonadherence to the study regimen, limits the conclusion of nonefficacy” (emphasis added). The number of people who stopped their vitamin or placebo therapy was staggeringly high at 46%.

Let us now review a few more things that might be of interest in the evaluation of this case but are left out of the editorial. First is the fact that both the vitamin group and the placebo group were consuming a high number of pharmaceutical agents (as one might expect of a postinfarct cohort). Subjects were on aspirin (>82% of subjects), β-blockers (70%), statins (70%), ACE inhibitors/ARBs (60%), clopidogrel (25%), and oral hypoglycemic (>20%). On top of this, nearly half the patients (42%-45%) were taking other multivitamin supplements! So, in essence, this study was looking for a statistical difference in outcomes between one group of subjects taking high-dose vitamins (discontinued by 46% of subjects) and another group of subjects (nearly half of whom were consuming another multivitamin of unknown ingredients)—while both groups consumed high amounts of pharmaceuticals that are known to reduce both the primary and secondary end points measured.

Furthermore, there was one important cohort that realized a statistically significant reduction in the primary end point when given the multivitamins: those individuals not on a statin drug (38% reduction in events, \(P = .012\)). Therefore, when we remove the effect of statins on these subjects, a much clearer benefit appears for the supplemental nutrients. Of course, these authors tell us to ignore this subgroup data, even though they are both clinically and statistically significant, until more studies can be done. A very strong positive trend also existed in supplemented patients enrolled in TACT less than 5 years since their MI (\(P = .046\)), suggesting that these nutrients are more effective the less time an individual has been pharmacologically-treated since their MI. Finally, while this study used a supplement containing much higher doses than nearly any other multivitamin trial to date, it is important to note that, unlike the widely repeated concerns of risk, this trial reported no difference in severe adverse events or incident cases of cancer. The witness can step down.

Witness Number 2: The PHS2 Data

The second paper was a subgroup of the PHS2. Previous analysis of this data already showed that this multivitamin therapy statistically reduced the risk for cancer and cataracts. In this analysis of the PHS2, cognitive function was measured using the Telephone Interview for Cognitive Status (TICS). Although the PHS2 involved numerous other arms, the data presented here only included the 2 groups given either a multivitamin (Centrum Silver) or placebo. Subjects over 65 years of age were recruited from within the PHS2 for this substudy. They found, using such telephone assessments over an average of 8.5 years of follow-up, that there was no statistical difference between the 2 groups in the mean level of cognition. They conclude that “in male physicians aged 65 years or older, long-term use of a daily [Centrum Silver] did not provide cognitive benefits.”

The limitations of this study are many. First, because this was a substudy of the PHS2, the first (baseline) cognitive test was conducted an average of 2.5 years after patients were randomized to their multivitamin or placebo intervention (in some cases it was over 5 years!). This means that the baseline cognitive assessment was already influenced by years of the therapy. Even though their baseline data showed no statistical, between-group differences, this fact alone would likely have prevented anyone from drawing firm conclusions from this data. On top of this, subjects in the PHS2 were only prevented from taking other multivitamins if those products contained more than the USRDA of vitamin E, vitamin C, β-carotene, or vitamin A. This means they could have consumed high levels of B vitamins, known to lower homocysteine (a metabolite associated in some studies with cognitive risk), or any of a number of other supplements known to affect cognition (Ginkgo biloba, phosphatidylserine, omega-3 fatty acids, vinpocetine, etc) without the knowledge of the researchers (up to 33% of subjects were taking other multivitamins in the PHS2). These gross oversights are due to the simple fact that the PHS2 was clearly not designed to answer the question of whether daily multivitamin use affects cognitive function in healthy older physicians in the first place.

Since few observational studies have examined the relationship between multivitamin use and cognition, and since the PHS2 was also not (originally) designed to ask this question, these data do not allow any broad conclusions about the benefits of all multivitamins (and doses) on potential cognitive benefits. While most integrative clinicians do not typically recommend products like Centrum Silver, it should have been obvious to these researchers that this product was not specifically designed to modulate cognitive function in healthy 65-year-old male physicians; nor were there previous trials to suggest such an outcome. It is curious, then, that a study (PHS2) that was not designed for this primary end point, coupled with an intervention (Centrum Silver, 1 capsule/d) not designed for this primary end point can be evidence for anything—let alone for an argument that the “case is closed.” Let the second witness step down.
Witness Number 3: A Systematic Review

The last of the 3 published articles is a systematic review of the potential benefits and harms of vitamins and mineral supplements in community dwelling, nutrient-sufficient adults for the primary prevention of either cardiovascular disease or cancer. After weeding through thousands of potential articles, these reviewers selected 103 articles (representing only 26 studies) that fit their study selection criteria. As one would expect, these trials varied considerably in study design, recruitment criteria, and primary end points—and most importantly, the trials differed dramatically in the multivitamins or mineral products used. Not surprisingly, the authors found “no consistent evidence that the included supplements affected CVD, cancer, or all-cause mortality in healthy individuals without known nutritional deficiencies.”

Rather than attempt to parse the nuances of each selected study, a broader critique will be sufficient for this review. Blinded by their desire to debunk the use of “vitamins” and “minerals,” these reviewers ignore the fact that each nutrient has a completely different mechanism of action, therapeutic dose potential, and historical data. Comparing studies where subjects consumed the hormone-like cholecalciferol, with studies using the water-soluble antioxidant ascorbic acid, merely because both are classified as “vitamins,” is not scientifically credible. On top of that, they excluded from their analysis any studies that used doses higher than the upper tolerable limit set by the U.S. Food and Nutrition Board. This would exclude studies using products with more than 4000 IU of vitamin D, 35 mg of niacin, 1 mg of folate, or 350 mg of magnesium—doses often exceeded in products known for their therapeutic benefit. Furthermore, since they excluded studies where subjects were nutrient deficient, this virtually eliminates the application of this data to “average” Americans (many of whom are deficient in more than one vital nutrient), which begs the question of this review’s intended application.

The authors admit that this study design was used primarily to evaluate drug therapies, and that “the design might not be ideally suited to evaluate nutrients.” We agree whole-heartedly. They also acknowledge that since subjects in the various placebo arms of each of these studies are healthy and not known to have any nutrient deficiencies; they are, in fact, comparing subjects with “average” nutrient intake (placebo) versus those with higher than average nutrient intake (supplemented). In most cases, the “placebo” group is not even prevented from taking other supplements or is later determined to have consumed higher amounts of some nutrients than the researchers originally anticipated (they note, for instance, that women in the Women’s Health Initiative control group had twice the average calcium intake than the study design anticipated).

In the end, this review of highly selected and widely divergent low-dose studies (only a few which reflect “real-world” supplementation) adds little to the evaluation of the use of appropriately dosed nutrient supplements for reducing the risk of (ie, preventing) chronic disease. The final witness can now step down.

Closing Argument

After a brief cross-examination of the 3 “witnesses,” you may agree with us that the case is far from “closed.” In fact, these studies just continue to reveal the complexity of evaluating nutritional supplementation in free-living Western populations. Simply put, broad nutrient supplementation (alone), in populations not known to have deficiencies in a particular nutrient, is unlikely to result in consistent measurable disease outcomes. The clinical goal of multivitamin-mineral supplementation, however, is not reducing the risk of a particular outcome per se but, instead, to diminish the likelihood that the individual will have limited metabolic capacity due to inadequate nutrient availability (from a poor diet, absorption difficulty, genetic disposition, or metabolic need).

I find it ironic that, while the FDA mandates that manufacturers of dietary supplements constantly reassure their customers that “these products are not intended to cure, treat or prevent any disease,” this same statement could somehow be proof they contain no health benefit at all! What this statement and these types of trials prove is that, alas, nutrients are not drugs! Furthermore, the studies that are designed to “prove” drug efficacy are wholly inadequate and inappropriate to evaluate the benefits of nutrients. We must be wary that the “evidence-based medicine” we once relied upon has now morphed into “medicine-based evidence” where drug companies set the rules and the FDA gladly enforces them. And even though the $300 billion pharmaceutical industry is 10 times larger than the supplement industry (only ~40% of which is vitamins), we are advised (by the editorial) to “stop wasting our money” only on the latter. Does this sound like unbiased, scientific advice? You be the judge.

References