

Dietary Supplements: Facts and Fallacies

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In the United States, products that have or are thought to have health benefits fall under three categories: prescription drugs, over-the-counter drugs, and dietary supplements. Prescription drugs are medications that have been approved by the US Food and Drug Administration (FDA) after well-controlled clinical trials assessing their safety and efficacy. Such drugs require that the consumer have a prescription from their doctor. Over-the-counter (OTC) drugs are medicines that do not require a prescription. These are often former prescription drugs that are off patent but have extensive documentation of safety and efficacy and are deemed safe to use without the oversight of a physician. The third category of health products are designated as dietary supplements. These products contain ingredients that are generally regarded as safe, such as vitamins, minerals, herbs, amino acids, and enzymes. In 1994, the Dietary Supplement Health and Education Act (DSHEA) defined the regulations for these agents. All such products must include the designation “dietary supplement” on their labels and can only make claims about structure and function but not about potential therapeutic or preventative effects. The DSHEA places the burden of proof on the FDA to show that a product poses significant health risk; however, new products coming to market after 1994 must provide the FDA with “reasonable evidence” that they are safe.

Since the DSHEA was enacted, the dietary supplement market has grown considerably in the United States and globally. In 2018, the market for supplements exceeded \$30 billion in the United States and \$115 billion worldwide. It is expected to expand at an annual rate of 7.8%.

The ubiquitous reach of the internet has facilitated the unfiltered claims and promotion of many products, generating a panoply of perceptions (or misperceptions) of their health value. As a result, the public often assumes that dietary supplements are safe and effective even though they have not undergone the scrutiny of a drug. Although many physicians tend to regard these products as having little or no true medical benefit, they may acquiesce to their patients' use of these agents, believing that “it probably won't help, but it can't hurt.” Both statements may be incorrect, especially with regard to cardiovascular health.

In actuality, there is an extensive amount of preclinical and clinical data on many dietary supplements and their impact on cardiovascular outcomes. The most recent meta-analysis (*Ann Intern Med*. July 2019) encompassing 277 randomized

controlled trials and almost a million participants assessed the effects of nutritional supplements or dietary interventions on all-cause mortality and cardiovascular outcomes. After evaluating 16 types of common dietary supplements, the authors found that long-chain omega-3 fatty acid and folic acid were associated with some cardiovascular benefit, whereas calcium plus vitamin D were associated with an increased risk for stroke.

In this edition of the *Methodist DeBakey Cardiovascular Journal*, we focus on the research behind several popular dietary supplements and offer our own objective analyses of the scientifically supported benefit, lack of benefit, or harm that these products may provide. We start by looking at recommendations regarding the use of long chain omega-3 fatty acids. The initial interest in their use for the primary and secondary prevention of cardiovascular disease was offset by subsequent clinical studies showing little or no benefit. In the opening manuscript, Drs. Penny Kris-Etherton, Chesney Richter, and colleagues review these data and present results from three recent major clinical trials that reignite enthusiasm for the use of omega-3 fatty acids. They also discuss mechanisms by which omega-3 fatty acids confer cardiovascular benefit and offer practical advice to clinicians about appropriate patient evaluation and recommendations for their use.

By far the most commonly used dietary supplements are vitamins and minerals. In the second manuscript, Drs. Anusha Sunkara and Albert Raizner survey the available data on multivitamins/multiminerals, antioxidants, folic acid, vitamin E, niacin, and beta-carotene—important substances that cannot be produced by the human body and must be ingested. The authors explore the question of whether or not exogenous supplementation over recommended daily allowances produces cardiovascular health benefits and provide an abundance of scientific data and clinical trials that address this theory.

Another of the more commonly used dietary supplements, often recommended or prescribed by physicians, is coenzyme Q₁₀. This substance is necessary for normal mitochondrial function and cellular production of ATP. In contrast to vitamins and minerals, coenzyme Q₁₀ is synthesized in the human body, but levels tend to decline with age. In addition, patients with congestive heart failure have a measurable deficiency of coenzyme Q₁₀. This supplement is most often recommended for patients who take statin drugs to ameliorate the most common side effects—muscle aches, cramps, and weakness,

referred to as SAMS (statin-associated muscle symptoms). Dr. Albert Raizner reviews the relevant chemical, metabolic, and physiologic properties of CoQ₁₀ and the clinical trials that address its possible roles in SAMS and congestive heart failure.

Many physicians do not know that one of our most successful and beneficial cardiovascular drugs has an herbal supplement analogue that has been used in China for a millennium. Red yeast rice contains a number of compounds that inhibit cholesterol synthesis, chief among them monacolin K. Just like the statin drugs that are effective at reducing low-density lipoprotein cholesterol, monacolin K inhibits the rate-limiting enzyme in cholesterol synthesis, HMG co-A reductase. Drs. Maciej Banach and Arrigo Cicero and research scientist Federica Fogacci provide a masterful review of the clinical data that supports the use of this herbal supplement in patients with elevated cholesterol.

In 1992, three American pharmacologists won the Nobel Prize in Physiology or Medicine for their discovery and characterization of nitric oxide (NO). Drs. Robert Furchgott, Lou Ignarro, and Ferid Murad found that the endothelial production of NO was critical for vascular homeostasis because it relaxes blood vessels, reduces their myointimal thickening, and suppresses the adherence of circulating blood elements to the vessel. Whereas their work focused on NO synthase and its generation of NO from L-arginine, it is now known that NO can also be generated from dietary nitrite and nitrate. In this issue, Dr. John Ivy provides a scholarly overview of the literature that supports dietary nitrite and nitrate as essential components that promote cardiovascular health.

Vitamin D and calcium are necessary for bone health and are used by patients with or at risk for osteoporosis. After several epidemiological studies revealed that individuals with low plasma levels of vitamin D were at increased risk of cardiovascular disease, the use of vitamin D supplements became popular for the prevention and treatment of

cardiovascular disease. However, subsequent randomized clinical trials to definitively assess the benefit of vitamin D in patients with or at risk of cardiovascular disease were disappointing. In addition, many adults take combined calcium-vitamin D supplements, and there is some concern that calcium supplements (but not food sources) may increase the risk of cardiovascular disease. Dr. Erin Michos and Amir Heravi review the literature on vitamin D, calcium, and cardiovascular health and draw some important conclusions regarding their efficacy (or lack thereof) and risks.

Finally, although many over-the-counter (OTC) dietary supplements are not inherently harmful, they may put patients at risk if not used as indicated. Whereas proton pump inhibitors (PPIs) are superior drugs in patients with gastroesophageal reflux, clinical trials of their safety and efficacy have been largely limited to short-term use. Now that these OTC drugs are readily available in grocery and drug stores, they are being used chronically by consumers for durations that were never approved by the FDA. Drs. John Cooke and Hannah Ariel discuss the evidence that long-term use of PPIs may carry increased risk for cardiovascular disease, renal failure, and dementia and present safe and efficacious alternative treatment strategies for gastroesophageal reflux.

This issue is intended to present a broad overview of the role of dietary supplements and OTC drugs in cardiovascular health, with the goal of stimulating additional interest in and exploration of the topic. With these products used by more than half of US adults, perhaps the most important point of this issue is that OTC drugs and dietary supplements deserve more careful monitoring by the medical community.

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