Food synergy: an operational concept for understanding nutrition[1–4]

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ABSTRACT

Research and practice in nutrition relate to food and its constituents, often as supplements. In food, however, the biological constituents are coordinated. We propose that ''thinking food first''' results in more effective nutrition research and policy. The concept of food synergy provides the necessary theoretical underpinning. The evidence for health benefit appears stronger when put together in a synergistic dietary pattern than for individual foods or food constituents. A review of dietary supplementation suggests that although supplements may be beneficial in states of insufficiency, the safe middle ground for consumption likely is food. Also, food provides a buffer during absorption. Constituents delivered by foods taken directly from their biological environment may have different effects from those formulated through technologic processing, but either way health benefits are likely to be determined by the total diet. The concept of food synergy is based on the proposition that the interrelations between constituents in foods are significant. This significance is dependent on the balance between constituents within the food, how well the constituents survive digestion, and the extent to which they appear biologically active at the cellular level. Many examples are provided of superior effects of whole foods over their isolated constituents. The food synergy concept supports the idea of dietary variety and of selecting nutrient-rich foods. The more we understand about our own biology and that of plants and animals, the better we will be able to discern the combinations of foods, rather than supplements, which best promote health. *Am J Clin Nutr* 2009;89(suppl):1543S–8S.

INTRODUCTION

We all eat food, several times each day, in considerable variety. We also consume several purified substances as intentional enrichment or as fortification of the food, unintentional contamination of the food, supplements, or drugs. Our bodies consist of these substances, modulated by processes such as digestion, synthesis of new compounds from the intake of building blocks, genetic capability to process the ingested material, and pathologic changes that may influence metabolism. Because we consist of what we consume, what we consume likely influences health. Food can be taken directly from nature (eg, an apple from a tree) or produced from a recipe (eg, a cake). A fundamental feature of food is that the constituents are coordinated. This results in a physically intact entity. The nutrient composition of naturally occurring food also reflects the biology of the organism. Foods with high quantities of unsaturated fats, such as nuts, have high amounts of compounds with antioxidant properties, which protect against the instability of these fats. A person or animal eating a diet consisting solely of purified nutrients in their Dietary Reference Intake amounts, without benefit of the coordination inherent in food, may not thrive and probably would not have optimal health. This review argues for the primacy of food over supplements in meeting nutritional requirements of the population.

FOODS, NUTRIENTS, AND HEALTH POLICY

The question of food compared with nutrients is central to the study of diet and health, ie, nutrition. The discovery of fundamental food constituents, such as vitamin C, and their role in deficiency diseases was, quite simply, astounding. The ability to combat malnutrition through supplementation and the supply of sufficient food energy has improved human welfare. In these ways, an approach to nutrition that is fundamentally guided by nutrients has helped to enhance understanding and set policy. The aspect of science that reduces to fundamental principles, however, can lead to oversimplification and ultimately stifle understanding and progress (1, 2). A thriving diet supplement industry has arisen on the supposition that nutrients have the same health effect delivered in isolation or as a constituent of food. This supposition has led to pharmaceutical-like products that are not well investigated. Clinical trials of these agents has produced the valuable information that many do not work as intended or even have adverse effects (3). Macronutrient policies, such as encouraging low total fat intake, have tended to block intake of apparently healthful foods, such as olives, nuts, and salmon. Alternatively, many observational studies show a powerful link between Mediterranean or prudent dietary patterns and reduced rates of several complex and slowly accreting chronic diseases (4–7). Because the benefit of these dietary patterns does not appear to be definable by the action of simple nutrients, research and policy should focus on foods and nutrients.

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FOOD SYNERGY

A central tenet in this argument is the concept of food synergy (1, 2, 8), a perspective that more information can be obtained by looking at foods rather than at single food components. Thus, the action of the food matrix (the composite of naturally occurring food components) on human biological systems is greater than or different from the corresponding actions of the individual food components. In addition, we do not have complete knowledge of food composition and some effects may result from unidentified or underappreciated components. Organisms, whether they are being eaten or doing the eating, have coordinated constituents, determined by the cell as the director of the orchestra and the central integrator of the constituents. Isolated constituents that are formed outside of normal biological processes are not integrated. This relates to intentional supplements, unintentional contaminants, or compounds, such as the *trans* fat formed in hydrogenation of vegetable oils. The viability of the food synergy concept is bolstered by the lack of effect of many isolated compounds shown in clinical trials (3). Nevertheless, to attain ideal health benefits, the combination of food components needs to address their interactions within the food and with the human system. Food components must survive digestion to arrive in the human system in such a way that the mutual effects of the different components can be realized by the eater.

DIET AND DISEASE RISK: SERUM CHOLESTEROL, SATURATED FAT, AND THE MEDITERRANEAN DIET

The tension between the study of nutrients and the study of foods is exemplified by the classic work of Ancel Keys. His careful observations led him to arrive at a scientifically precise equation that quantitatively linked a 1-mg/dL increase in serum cholesterol to 2.7 times the increase in saturated fat energy and 1.35 times the decrease in polyunsaturated fat energy (9–13). Concurrently, he observed cultural differences in the population distribution of heart attacks, with a substantially higher prevalence among the wealthier than with less wealthy citizens in southern Europe. These holistic observations led to the Seven Countries Study, in which there were large population differences in heart attack rates, apparently attributable to diet and its effect on serum cholesterol (14). His enduring belief in the Mediterranean diet is reflected in the cookbooks he wrote with his wife (15–17). For him, the ''scientific answer'' to the dietary link between cholesterol and heart disease primarily was saturated fat intake. The intuitive answer, however, was the Mediterranean diet, which seemed in some complex and difficult manner to have a role in heart disease. We admire Keys' enduring and accurate work on diet and cholesterol. We believe, however, that the reductionist approach gave an incomplete answer and that the intuitive answer fits the data better, as recent studies have shown (4). Saturated and polyunsaturated fat are not the only substances in food that affect serum cholesterol (18–20), and plant-based, nutrient-rich diets affect other important blood parameters (21).

Do we know that a Mediterranean or prudent dietary pattern achieves health benefits? With the exception of the large reduction in risk shown in the Lyon Diet Heart study (22), there are no randomized trials testing the effect of the Mediterranean diet on chronic disease events. Two trials have focused on fat reduction: one in healthy postmenopausal women (23), and the other, the Women's Intervention Nutrition Study (WINS), in breast cancer survivors (24). A third trial in breast cancer survivors, the Women's Healthy Eating and Living (WHEL) Study, achieved a low-fat diet with substantial increases in fruit and vegetable consumption (25, 26). Risk reduction was reported only in the WINS (24). The primary change in the WHEL Study was an increase in vegetables of 3–4 servings/d, approximately half of which were from tomato and carrot juices (25). These findings lead to questions about the viability of a general hypothesis, that all plant foods are beneficial and increasing intake reduces risk.

DIETARY SUPPLEMENTS: RISKS AND BENEFITS

The reductionist logic has been alive and well in past years. In contrast to the few trials of dietary patterns or specific foods (23–26), there have been many long-term, tightly controlled, randomized clinical trials of supplements (3), partly because of the simplicity of intervening with a pill rather than with dietary change. By extrapolating from observational studies of food intake to the nutrients those foods contain (8, 27), and reasoning from known mechanisms addressing risk, these studies postulated that certain nutrients would be beneficial in the prevention of cardiovascular disease, cancer, and premature death.

The 2006 National Institutes of Health (NIH) State-of-the-Science Conference (3) on multivitamins/multiminerals focused on 13 vitamins and 15 essential minerals. The history begins with James Lind's studies of scurvy in the 1700s and the discovery of the first vitamin, thiamine, in 1913. Iodine was added to table salt in 1924, vitamin D to milk in 1933, and thiamine, riboflavin, niacin, and iron to flour in 1941. The NIH report stated that in America, 20–30% of the population used a multivitamin daily such that the supplement industry reported 2005 annual sales of $23 billion (3). Many more Americans effectively take a multivitamin by eating fortified grain products.

The NIH report reviewed long-term randomized clinical trials of supplements with vitamins or minerals that did not contain herbs, hormones, or drugs (3) (summarized below). The combination of calcium and vitamin D was shown to increase bone mineral density and reduce fracture risk in postmenopausal women. There was some evidence that selenium reduces risk of prostate, lung, and colorectal cancer. Vitamin E may decrease cardiovascular deaths in women and prostate cancer incidence in male smokers. Vitamin A paired with zinc may decrease the risk of noncardia stomach cancer in rural China. Otherwise, most of the trial findings were null for planned or secondary endpoints. Trials of niacin, folate, riboflavin, and vitamins B-6 and B-12 showed no positive effect on chronic disease occurrence in the general population. There was no evidence to recommend β-carotene and some evidence that it may cause harm in smokers.

Studies of vitamin D, at an average daily dose of 528 IU, showed a significant reduction in total mortality in a meta-analysis of 18 clinical trials (28). There was an inverse estimated association in 7 of the 9 larger studies, with a significant pooled relative risk of 0.92 (95% CI: 0.86, –0.99). Despite the statement (3) that a calcium/vitamin D combination was needed to improve risk of fracture, total mortality was shown to be lowered in 5 studies of vitamin D alone and similar to the rate shown in the 13 studies that included calcium in the intervention. In contrast, in a meta-analysis of 19 randomized controlled trials involving more than 135,000 participants (29), high-dosage vitamin E supplementation ($\geq$400 IU/d for $\geq$1 y) increased all-cause mortality (5% excess risk of total mortality).

On the basis of overwhelming evidence of protection against neural tube defects when consumed periconceptionally, the United States and Canada in 1998 mandated compulsory fortification of refined flour with folic acid (30), bringing the amount of folate to a quantity higher than in whole-grain flour. This has been accompanied by an expected increase in blood folate concentrations and a decrease in homocysteine concentrations. Gratifyingly, neural tube defect incidence has decreased by 15% to 50% (30). B vitamins, however, including folate, did not fare well in several clinical trials of cardiovascular disease and venous thromboembolism (31–34). Furthermore, folate may promote cancer progression (30), although the mechanisms are unclear and likely different from those involved in folate analog–based chemotherapy. Blockage of folate metabolism with folate analog results in an inhibition of DNA synthesis in cancer cells and precipitates their death (30). Thus, folate may have dual modulatory effects on cancer, depending on timing and dose. Furthermore, excess folate in the elderly may mask vitamin B-12 deficiency and consequent neuropathy (35).

As a basis for addressing possible harm from supplements, Mulholland and Benford (35) defined a safe range (range of acceptable intake) with deficiency risk at the low end and toxicity risk at the high end. Even compounds generally recognized as safe (GRAS) can have problems at high doses: for example, vitamin C intake at several grams can result in gastrointestinal effects, such as osmotic diarrhea. The resulting U-shaped curve, characterizing deficiency, safe range, and toxicity, is asymmetric and varies in individuals and in stages of life. It defines optimal nutrition within the safe range. Greenwald et al (27) used these concepts when interpreting the most favorable studies of a multivitamin supplement. Specifically, they cautioned that success observed in the Linxian General Population and Dysplasia trials in reducing risk of cancer (36) may have reflected a borderline-deficient population in China. Adding supplements in the nutrient-replete Western studies may not have been efficacious because they did not correct a deficiency. Greenwald et al (27) explored whether or not borderline deficiency may be relevant to vitamin D, where a safe range is not well known; the relatively high baseline intake of calcium (mean: 1151 mg/d) and vitamin D (mean: 367 IU/d) may have hindered the ability to see a protective effect against 7-y colorectal cancer incidence in the calcium (1000 mg/d) plus vitamin D (400 IU/d) component of the Women's Health Initiative (27).

The amount of supplemental (purified or isolated) nutrients consumed is difficult to monitor because of extensive enrichment/fortification of products and the lax 1994 Dietary Supplement and Health Education Act, which allows manufacturers to label with minimum rather than actual amounts of nutrients contained in the supplements (3). There is haphazard reporting of adverse events apparently related to supplement use. In most respects, despite their designation as GRAS, supplements are pharmaceuticals but are not studied or regulated as such. Consequently, the report notes that assurance of safety and quality of multivitamins/multiminerals is inadequate without mandatory adverse event reporting and labeling changes. It recommends that "It is important that the FDA's purview over these products be authorized and implemented" (3).

Should we recommend a daily multivitamin, delivering low doses of a variety of compounds, for the general population as "insurance" against nutrient deficiency? This is the strategy followed in the United States, but in our opinion this is risky given the lack of evidence of benefit, the occasional evidence of harm, and the relative lack of solid health research on supplements. This does not deny some indications of benefit (28, 30), especially in nutrient deficiency (36). In our view, the better "insurance" would be to eat food with a broad coverage of nutrients and take no supplements at all, unless they are deemed necessary to fix a specific medical problem.

BENEFITS OF FOOD SYNERGY

One aspect of food synergy may be a buffer effect: the effect of a large intake of a particular nutrient may vary depending on if it is taken in concentrated form or as part of a food matrix (35). Rich food sources of a nutrient are likely to be spread over several meals rather than taken as a bolus, eg, the European Union Recommended Dietary Allowance of iron, 14 mg, can be obtained in a bolus from a single tablet rather than from 670 g roast beef, 875 g spinach, or 209 g cornflakes. The authors note further that the food matrix slows absorption of the nutrient, which lowers the likelihood of a bolus effect.

Another aspect of synergy may be nutrients that affect each other's absorption, such as copper-zinc and manganese-iron (35). Similarly, vitamin C may act as a pro-oxidant in the presence of iron (37), and alcohol can disrupt iron homeostasis through effects on iron-binding proteins such as ferritin and transferrin (38). The buffering and competitive effects reflect forms of control over the entry of components into the human system.

A third aspect of synergy relates to whether or not constituents have been produced by technologic or biological processes. A salient example may be *trans* fat, which is produced in ruminant animals and in food processing during hydrogenation of vegetable oils. Biological processing can relate to constituents that exist in close proximity, eg, within cell walls and membranes or small cellular bodies such as liposome. These constituents are prepared to act dynamically and in concert, eg, in up-regulating signaling or response to a threat. Naturally occurring *trans* fats, such as conjugated linoleic acids found in dairy products, are reflective of ruminant biology and may have beneficial health effects in humans (39) whereas *trans* fats introduced in food processing have different origins and contexts. Public health commentary on recent research in this area (40) indicates that ruminant *trans* fat is dietetically linked to saturated fat. Here again we are led back to the consideration of whole foods and the whole diet in examining diet-health relations.

Several conditions have to be met for the hypothesis of orchestrated food synergy to work. First, there must be balance in the way that a food (an organism) is constituted. In humans and other animals, there are homeostatic systems maintaining concentrations of glucose and distribution of lipids. Balance and regulation work equally well in the plant kingdom. Plants must have protection against predators. For example, seeds living naked in the earth, without roots for sustenance, may be attacked by bacteria, fungi, or insects. Small molecules, such as polyphenolics, may play a protective role and, presumably, the plant's control mechanisms block the pesticidal compound from attacking the plant itself. The balanced set of food constituents created in the food is ingested by the eater. Some of these food constituents retain this balance after ingestion, but other food constituents are digested and distributed as the human system

determines. Balance also is needed at this point, as the human system adapts the food constituents to its systems and processes. This is where constituents with antioxidant activity may be helpful, eg, when other unstable constituents, such as polyunsaturated fat, also have been consumed.

The second condition that must be met for food synergy to work is that the balanced constituents have to survive digestion in some active form. Many food constituents are broken down during digestion, such as proteins into amino acids, assisted by proteases, and carbohydrates, with the assistance of enzymes, such as maltase, lactase, and sucrase. Other constituents, however, survive digestion, in particular fats and small molecules, such as phenolic acids and flavonoids, especially if they are fat soluble. The cell is the great integrator in all organisms, with many regulatory systems and many ways to pick and choose among available constituents. Small molecules and their association with fat molecules are relevant to health because the cell has the ability to be responsive to different compounds. Cancer, for example, emerges only after many cell cycles in which cell replication was not exactly right. The small compounds that survive digestion are active throughout remodeling of the cell and are especially dependent on how much fat the cell is exposed to if the particular process happens to be fat dependent.

Hydroxycinnamic acids found in coffee provide an example of survival of small compounds. In one study, after avoiding foods rich in phenolics for 2 d and fasting overnight, 10 volunteers had concentrations of caffeic acid, *p*-coumaric acid, and ferulic acid in LDL cholesterol that were 17.8, 1.8, and 1.5 pmol/mg protein, respectively (41). Thirty minutes after consuming 200 mL of coffee containing ≈200, 5, and 35 mg of these phenolics, the concentrations in LDL cholesterol rose to 31.1, 9.7, and 21.6 pmol/mg protein, which is reflective of the phenolic composition of the coffee. The caffeic acid rose slightly by 60 min whereas the other 2 substances dropped. The human body does not just downgrade whole systems as they enter the digestive tract. Some of the food constituents are altered, such as with deamination and methylation. Most of the phenolic acids were present in bound forms. The binding and other amendation of molecules native to food are clearly relevant to understanding nutrition. If molecules need pairing for functionality, eating them in the same food would increase the likelihood of that pairing; eating different foods within the same 24-h period also may be sufficient for the pairing to occur within the digestive tract or systemically. In this way, the food synergy theory supports eating a variety of nutrient-rich foods.

The third condition that must be met for food synergy to work is that the substances that survive digestion must be biologically active. Natella et al (41), in their assessment of coffee, showed that the LDL cholesterol was less oxidizable ex vivo in blood samples drawn after coffee consumption than in blood samples drawn before coffee consumption. It was also less oxidizable in vitro in cells incubated with a coffee-like medley of phenolic acids than in cells incubated without these compounds.

We (8) have provided several examples that reported on food synergy. These examples involved grain, apples, tomatoes, pomegranates, and broccoli. In the grain example (42), the cereal fiber from refined grain was not related to mortality in long-term follow-up, but the cereal fiber in whole grain was, suggesting that the whole-grain fiber is a marker of biologically active substances, especially in the aleurone layer and bran. In the apple example (43), cell proliferation in a cancer cell line was not inhibited by the small amount of vitamin C contained in the apple and was inhibited more by extracts of the apple with skin than by extracts of the apple flesh only. Drug-induced mammary tumor incidence also was reduced by apples in a rat model, more so by using the whole apple than the flesh only (44). Tomato consumption apparently had a greater effect on human prostate tissue than did an equivalent amount of lycopene (45, 46). Whole pomegranates and broccoli had greater antiproliferative and in vitro chemical effects than did some of their individual constituents (47, 48). More recent work showed that pomegranate juice polyphenols, peel polyphenols, and oil exhibit synergy in inhibition of cancer cell proliferation (49). Bioactive human milk glycans interacted with intestinal microflora and intestinal mucosa surface glycans to foster the development of the infant's innate mucosal immunity (50). Flavonoids derived from almond skin acted synergistically with vitamins C and E to enhance resistance of human and hamster LDL cholesterol to oxidation (51, 52). F_2-isoprostanes, a free radical oxidation product, were reduced by consumption of brassica vegetables, independent of micronutrient mix (53).

The food synergy hypothesis implies that it is relevant to the eater how the food survives its own life cycle. Because the constituents of organisms are not all concordant with the needs of the eater, some constituents would be harmful to us. Some foods contain antinutrients, such as phytates, that inhibit the absorption of micronutrients; depending on the function involved, this could affect health positively or adversely. For example, chelating highly reactive iron could prevent oxidative stress but at the same time some minerals that are needed for health could be excreted as chelates. To some extent, the human community has identified safe foods by trial and error: we do not eat some foods, eat only small amounts of some and tolerate the poison, or prepare foods in special ways to break down a poison and reduce the risk. In the case of peanut allergy, it was shown that the "allergen proteins" in isolation did not cause an allergic or inflammatory response; the whole peanut was needed for that (54).

Foods themselves are variable; for example, varietals may differ substantially in their nutrient composition (55, 56). An assumption in the food synergy logic is that people eat an average of different varietals over a long period of time. It is this average that is of most interest in long-term health studies. This may present a problem in biochemical characterization of foods and specifically in short-term studies of food, which would, for example, use specific instances of an apple rather than various kinds of apples more generally representing the category "apple."

CONCLUSIONS

We have reviewed the scientific literature to support the argument that food rather than supplements should be the first consideration in addressing nutritional requirements of the population. In establishing further evidence, food should be the standard for detailed biochemical studies that uncover efficacious food components, such as those in whole grains (57) or blueberries (58, 59). Intake of any single biochemical or combination of biochemicals believed to represent the action of the corresponding food should have at least as strong a health effect as does the whole food. Furthermore, there are many ways to decompose food and many ways to characterize physiologic results of eating, and these may

show more variability across experiments than do findings for whole foods. In this way, once it is clear that deficiency diseases are being avoided, and as scientists continue to discuss nutrition from a nutrient perspective, the public may be better served by focusing on whole foods than on nutrient interpretations of them. (Other articles in this supplement to the Journal include references 60–86.)

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