

Current Research

Dietary Supplements in Weight Reduction

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ABSTRACT

We summarize evidence on the role of dietary supplements in weight reduction, with particular attention to their safety and benefits. Dietary supplements are used for two purposes in weight reduction: (a) providing nutrients that may be inadequate in calorie-restricted diets and (b) for their potential benefits in stimulating weight loss. The goal in planning weight-reduction diets is that total intake from food and supplements should meet recommended dietary allowance/adequate intake levels without greatly exceeding them for all nutrients, except energy. If nutrient amounts from food sources in the reducing diet fall short, dietary supplements containing a single nutrient/element or a multivitamin-mineral combination may be helpful. On hypocaloric diets, the addition of dietary supplements providing nutrients at a level equal to or below recommended dietary allowance/adequate intake levels or 100% daily value, as stated in a supplement's facts box on the label, may help dieters to achieve nutrient adequacy and maintain electrolyte balance while avoiding the risk of excessive nutrient intakes. Many botanical and other types of dietary supplements are purported to be useful for stimulating or enhancing weight loss. Evidence of their efficacy in stimulating weight loss is inconclusive at present. Although there are few examples of safety concerns related to products that are legal and on the market for this purpose, there is also a paucity of evidence on safety for this intended use. Ephedra and ephedrine-containing supplements, with or without caffeine, have been singled out in recent alerts from the Food and Drug Administration because of safety concerns, and use of products containing these substances cannot be recommended. Dietitians should periodically check the Food and Drug Administration Web site (<http://www.cfsan.fda.gov>) for updates and warnings

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and alert patients/clients to safety concerns. Dietetics professionals should also consult authoritative sources for new data on efficacy as it becomes available (ods.od.nih.gov).

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Dietary supplements are a broad category of nutrients and other bioactive substances that contribute significantly to total dietary intakes. The prevalence of overweight and obesity is high in America today (1). Many consumers are seeking strategies for reducing their weights to healthier levels. Both hypocaloric diets (decreased energy intake) and increased physical activity (increased energy output) and/or metabolic changes can result in loss of body weight and body fat. The National Institutes of Health (NIH) has provided recommendations for the clinical treatment and management of obesity (2) and a strategic plan for future research (3).

Dietary supplements have two possible roles in weight reduction. First, they can provide nutrients for diets that are restricted in calories, which, therefore, may also be limited in essential nutrients. Second, they are purported to stimulate or enhance weight loss through mechanisms such as diminishing hunger or increasing resting metabolism.

A large number of dietary supplements are being marketed for weight loss today (4). The Food and Drug Administration (FDA) regulates dietary supplements under a different set of regulations than those covering "conventional" foods and drug products (<http://www.cfsan.fda.gov>). Generally, manufacturers do not need to register with FDA nor get FDA approval before producing or selling dietary supplements. Therefore, it is particularly important to be aware of and communicate reliable information regarding the safety and efficacy of dietary supplement products to consumers. General guidance is available on dietary supplements in the Healthcare Professional's Guide to Evaluating Dietary Supplements developed by the American Dietetic Association (http://www.eatright.org/Public/ConferencesAndEvents/92_suppl_guide.cfm) and in other publications (5-7).

DIETARY SUPPLEMENTS FOR ACHIEVING NUTRIENT ADEQUACY

The Food and Nutrition Board of the National Academy of Sciences has completed a decade-long update of the dietary reference intakes (DRI), including the recommended dietary allowances (RDA), or adequate intake levels (AI) when an RDA cannot be established, and tolerable upper levels (UL). These are accessible at <http://www.iom.edu>.

Nutrient-containing dietary supplements provide a means of consuming specific nutrients that otherwise might be low or lacking in reducing diets. Their formula-

tions vary from single nutrients to combinations of many different vitamins and elements. Some products also contain other nutrient and nonnutrient ingredients. Doses generally vary from levels close to the RDA or AI to several times these levels. The percentage of daily values stated on supplement and food labels for vitamins and elements is generally based on the highest RDA across various age and sex categories (with the exception of pregnancy and lactation) from the 1968 RDAs, with additional values for nutrients such as selenium for which there were no RDAs in 1968.

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Dietary supplements of single nutrients or combinations of nutrients at RDA/AI levels are particularly useful when calorie levels are very low (<800 calories, and especially <500 calories), when the reducing diet consists of usual foods rather than products especially formulated for weight reduction that are high in nutrient density, or when the dieter's needs for a nutrient are very high. For example, a reducing diet plan even with the addition of a multivitamin/mineral supplement may provide relatively small amounts (eg, 10% to 33% of the RDA) for a nutrient such as calcium among menopausal women. Therefore, a single-nutrient calcium supplement that provides levels at or close to 100% of the RDA is a reasonable choice for dieters whose weight loss diet is particularly low in this nutrient. If multivitamin/mineral supplement products are chosen, they should be at RDA/AI/daily value levels.

The clinical, physiologic, and biochemical effects of long-term failure to achieve nutrient adequacy (eg, RDA/AI levels of nutrient intakes) are comprehensively reviewed and well documented in the DRI reports. Unless noted, they also apply to individuals on reducing diets.

The care of obese individuals who undergo bariatric surgery requires nutritional counseling, periodic laboratory assessment of blood values, ongoing monitoring to ensure that nutritional status remains satisfactory, and, frequently, supplementation with nutrient-containing dietary supplements. At present, there are no formal standards for supplementation after bariatric surgery, but there are recommendations based on available data, and the need for ongoing medical supervision is recognized as critical. In general, risk of micronutrient deficiency is least for gastric banding, more significant with gastric bypass, and most significant with the biliopancreatic diversion procedures, which generate greater malabsorption. Dietary supplement use should be prescribed and supervised by the physician. Standards are available to guide such efforts (8,9).

Very-low-calorie diets (VLCDs) or "protein supplemented modified fasts" that provide less than 800 and often less than 500 calories per day are used in weight reduction. These diets may also pose risks of nutrient inadequacy and be unsafe if they are not formulated appropriately. Because the metabolic effects of such VL-

CDs are considerable, they are presumably safest when prescribed, dispensed, and monitored under a physician's direction, as a part of a comprehensive weight-reduction program. The physician should determine whether supplementation is required. Nevertheless, adverse events may still occur. The safety and efficacy of VLCDs have been reviewed, and reasonable recommendations for their use have been provided (10). VLCDs usually require supplementation, fortification, or special formulation of foods with certain micronutrients, electrolytes, and other nutrients because so little food is supplied. Protein needs may rise because, when energy is severely restricted, dietary as well as bodily protein stores may be used to maintain blood glucose levels, especially after the body's limited endogenous carbohydrate stores have been exhausted. Depending on the VLCD plan and its formulation, the need for nutrient supplements and/or electrolytes may vary and should be determined by the dieter's physician.

Dietary intakes of potassium in typical American diets are approximately 2.9 to 3.2 g/day in adults, considerably below the AI of 4.7 g/day, and extremely hypocaloric; VLCDs are probably often even lower (11). Fruits and vegetables, which are especially rich in potassium, and other foods are generally very limited on VLCDs. Therefore, potassium intakes may be inadequate. Also, when dietary intake is reduced, the kidney is inefficient in conserving potassium and hypokalemia (serum potassium concentration of less than 3.5 mmol/L) may result (12). Signs and symptoms of hypokalemia include cardiac arrhythmias, muscle weakness, and glucose intolerance. Moderate potassium deficiency may also occur without hypokalemia. Individuals on VLCDs are often prescribed potassium supplements to decrease the risk of hypokalemia. It is recommended that this be done under the direction of a physician because those who are trying to lose weight have many common medical conditions (diabetes, kidney disease, heart failure, adrenal insufficiency) and often use antihypertensive drugs that may alter potassium excretion. Risks of hyperkalemia also may result from self-medication with potassium supplements. In contrast, the risks of excessive amounts of potassium from consuming ordinary foods on weight-reduction diets are minimal among those with normal kidney function.

VLCD plans that are based on ordinary foods usually include recommendations for specific supplements to ensure that needs for vitamins, minerals, electrolytes, and other nutrients are met so that the combination of foods plus supplements achieves RDA/AI levels. As noted previously, for safety reasons, VLCDs should be used under a physician's direction.

There are no regulations for the composition of specialty food products such as the commercially prepared oral nutritional formulas marketed for use in weight-reduction regimens. However, the commercially prepared very-low-calorie "protein supplemented modified fast" products available today must bear a warning statement as to possible risk or harm if they fail to meet certain requirements in the Code of Federal Regulations (CFR) (21 CFR 101.17). This requirement resulted because some oral nutritional supplement products for weight loss that first became available in the 1970s were high in poor-quality dietary protein and likely also lacking in

other nutrients and electrolytes. Some products were associated with arrhythmias and serious adverse events, including death, and were withdrawn from the market (13). Information on the safety and efficacy of VLCD and recommendations for their use is available (2,10).

Low-calorie diets of 1,200 to 1,500 calories per day are designed to create a caloric deficit of approximately 500 calories a day for adult women and to bring about weight loss of approximately a pound a week. Reducing diets even lower in calories (eg, 800 to 1,200 calories) cause more rapid weight loss and are often even more limited in micronutrients. Such reducing diets often consist of foods that are commonly available in grocery stores. It may be difficult to achieve RDA levels for certain nutrients such as iron, calcium, and vitamin B-6. The lower the diet is in calories the greater the probability that some nutrients may fall short. Options for achieving RDA/AI intake levels include addition of several servings of foods rich in the specific nutrient, use of fortified foods, commercially prepared meal-replacement products that are relatively high in nutrients for the calories they provide, a single nutrient supplement, and/or a multivitamin/mineral supplement. The most appropriate strategy to choose in dietary planning to achieve the goal depends on the dieter's preferences; how much the diet falls short of the RDA, with respect to each nutrient; food availability; and cost.

There are potential benefits of calcium supplementation in terms of reducing the degree of bone demineralization that can accompany weight loss. Bone mineral is lost when weight is reduced through caloric restriction (14). It is unclear whether the degree of bone mineral achieved when dieters reach steady state is less than would be predicted given their new body mass (15). However, given the high rate of osteoporosis in an increasingly older population, any factor that reduces bone mineral mass must be viewed with concern. Recent guidelines for obesity treatment state that "During weight loss, attention should be given to maintaining an adequate intake of vitamins and minerals. Maintenance of the recommended calcium intakes of 1,000 to 1,500 mg/day is especially important for women who may be at risk of osteoporosis" (2). High-calcium diets or calcium supplementation on the order of 1 g/day during weight reduction can reduce loss of bone mineral or markers of bone resorption (16). Therefore, if adequate levels of calcium such as these are not achieved on reducing diets from food sources alone, a calcium supplement may be appropriate (17).

Safety considerations differ somewhat for the different types of dietary supplements. Those containing vitamins and minerals at or below RDA/AI/daily value levels have a long history of use in supplementing low-calorie diets for weight reduction, and more is known about their effects than about botanical or hormonal supplements. Nevertheless, some safety concerns do exist concerning vitamin and mineral preparations. Excessive intakes of nutrient-providing dietary supplements may pose safety risks. To minimize risks of excessive intakes, total nutrient amounts from all sources, including dietary supplements, should not greatly exceed 100% of the RDA/AI and definitely should be below the tolerable upper intake levels (10-18). For individuals who are already consuming the RDA or AI for most nutrients from food sources, there is no recognized health benefit from consuming higher

levels, and they may be at risk of excessive intake, particularly if they exceed the upper intake levels. (Upper intake level values are available online at the National Academies Web site, www.nas.org).

DIETARY SUPPLEMENTS FOR STIMULATING WEIGHT LOSS

The remainder of this article discusses several popular or controversial dietary supplements that have been widely advocated for purposes of stimulating weight loss over the past 5 years. Dietary supplements have been proposed as being useful for stimulating or enhancing weight loss for those on low-calorie diets by altering body functions. The supposed mechanisms of action vary, depending on the ingredient. Some are claimed to have anorectic effects and decrease food intake, whereas others are claimed to bring about metabolic changes that increase energy output and cause weight loss.

Adequate scientific evidence for substantiating claims regarding the efficacy of dietary supplements in enhancing weight-reduction efforts is sparse at present. In addition, for some dietary supplement ingredients and products that make these claims, there are safety concerns.

Dietary supplements are regulated as foods, and, hence, the law generally assumes that they are safe unless proven otherwise. Manufacturers are responsible for ensuring that a dietary supplement is safe for its intended use before marketing. Manufacturers do not need to register with the FDA nor get FDA approval before producing or selling dietary supplements. Safety concerns have led the FDA to issue warnings regarding serious adverse events and other problems associated with some dietary supplements used in weight reduction. These are summarized below. Some products have also been banned in other countries for safety reasons. However, because some are still available for sale in stores and over the Internet, consumers need to be alerted to their hazards.

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Recent studies and observations suggest that some dietary supplements may interact with other over-the-counter and prescription drugs that individuals may be taking for weight reduction and thereby alter drug effectiveness (19). In addition, these dietary supplements may interact with foods and other supplements, and reliable sources should be consulted when providing advice on low-calorie diets and VLCDs (Natural Medicines Database <http://www.naturaldatabase.com>).

Another concern in the case of many botanical and other dietary supplements for weight loss is that the active ingredients are unknown or uncharacterized. Recently developed adverse reaction tracking systems have some information on potential adverse interactions, but such data may be incomplete, and they may not be sensitive enough to pick up potential problems with a par-

ticular supplement product or ingredient. Many of these supplements contain several ingredients that have often not been adequately tested either alone or in combination. Some of these combinations may be contaminated. This was the case with *Aristolochia* contamination of a weight-loss formula that was associated with kidney failure and carcinogenicity and led to an FDA warning issued in April 2001 (<http://www.Cfsan.fda.gov/~dms/ds-bot.html>). Moreover, traditional uses of botanical and other supplements usually did not include weight loss, so history of safe use for this intended function is frequently lacking. More information on the characterization, pharmacology, history of use, and safety of such products is needed. Systematic literature reviews on their effects and safety are being developed and should be consulted concerning ingredient composition, safety, and interactions (18,20-24). Given the present lack of knowledge on safety, it would be prudent to avoid such dietary supplements during pregnancy, lactation, or immediately before surgery. Health professionals and consumers need to be aware that the adverse effects may outweigh the benefits of agents used for stimulating weight loss.

Ephedra (*Ma huang*): Short-term efficacy demonstrated; long-term (beyond 6 month) efficacy untested. Adverse events (nausea, vomiting, psychiatric symptoms, autonomic hyperactivity, palpitations) documented. Concerns regarding serious adverse events (seizures, stroke, deaths) have been raised. Sale prohibited in the United States since April 2004. Ephedra (or *Ma huang*) is the common name for an herbal product used in traditional Chinese medicine (TCM), although its use for weight reduction is not a part of TCM practice. Ephedra-containing dietary supplements, either with or without caffeine, were widely used from the mid-1990s through 2004 for stimulating weight loss. A recent, thorough, systematic review of the safety and efficacy of ephedra, sponsored by the NIH and conducted by the Agency for Healthcare Research and Quality's Evidence-Based Practice Center at Southern California (23) concluded that their use was associated with a modest but statistically significant increase in weight loss over a relatively short time (less than or equal to 6 months). In terms of magnitude, the weight lost by those taking ephedrine and caffeine in combination exceeded that offered by prescription medications for weight loss in two head-to-head, randomized, double-blind, clinical trials (25,26). No studies have assessed their long-term effects (greater than 6 months). Also in controlled trials, these substances were associated with two to three times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and change in mood, autonomic hyperactivity, and palpitations when compared with placebo. In the controlled clinical trials, adverse events, but no serious adverse events (SAEs), were defined as specified by FDA criteria. SAEs were reported to the FDA, and adverse event reports from a manufacturer of ephedra-containing dietary supplements were also evaluated in the RAND/Southern California review. These SAE reports, along with already-published adverse event reports, raised concerns regarding the safety of dietary supplements containing ephedra, although most of those case reports were not documented sufficiently to support an informed judgment regarding the relationship between the use of ephedra-containing dietary supplements and the adverse event in question.

However, the number of deaths, myocardial infarctions, cerebrovascular accidents, seizures, and serious psychiatric illnesses in young adults were judged to be sufficient to warrant further evaluation (23). The FDA has concluded that ephedra-containing products should not be recommended for weight loss because they present an unreasonable risk of illness or injury. The sale of dietary supplements containing ephedra (*Ma huang*) has been prohibited in the United States since April 2004 (27).

Bitter orange: No adequate evidence for efficacy. Safety concerns have been raised, but few data are available. Bitter orange (*Citrus aurantium*) is a plant that has been claimed to stimulate weight loss and to be an "ephedra substitute." It is also known as Seville orange, sour orange, green orange, neroli oil, and kijitsu. The botanical name does not always appear on the label, and its presence is sometimes noted simply as natural flavorings. The active ingredients include various alkaloids with selective α - and β -agonist activity, including synephrine and octopamine. Synephrine (oxidrine) is a sympathomimetic amine, structurally similar to epinephrine. Most products contain 10 to 40 mg synephrine per dose. The most recent reviews of clinical trials to date found little evidence that *Citrus aurantium* products were effective in weight loss and suggested that more research is needed (28,29). Although those reviews reported no adverse events, there has been considerable recent discussion concerning potential harms. Citrus oils are generally recognized as safe (GRAS) by the FDA as natural flavorings in food products. However, the amounts used as supplements may be much higher, and, thus, their GRAS status as flavoring agents may not be relevant to their use in dietary supplements. The synephrine in bitter orange products may increase blood pressure, and, therefore, special caution is recommended when it is taken by individuals with hypertension, cardiovascular disease, or narrow-angle glaucoma. Other compounds are sometimes present, such as 6',7' dihydroxybergamottin and bergapten, which may inhibit cytochrome P4503A and increase serum levels of many drugs. However, in one recent clinical study, the *Citrus aurantium* was devoid of the CYP3A4 inhibitor 6',7' dihydroxybergamottin (30). More safety testing to assess hemodynamic effects and drug interactions over the short- and long-term is needed. In summary, larger, longer, and more rigorous trials of *Citrus aurantium* and synephrine alkaloids are needed to assess their efficacy and safety for weight loss.

Chromium picolinate: Little evidence of benefit; few or no adverse events. Chromium picolinate is a compound consisting of trivalent chromium and picolinic acid, a derivative of tryptophan. The most recent meta-analysis of its effects on weight loss suggests small but statistically significant reductions of approximately 0.08 to 0.2 kg per week compared with placebo during 6- to 14-week interventions. Studies that were included enrolled subjects with an average body mass index (BMI) of 28 to 33 who were told not to change their eating habits and to exercise regularly (24). With respect to safety, no adverse events were reported either in these trials or in another with a niacin-bound form of chromium (31).

Conjugated linoleic acid: Little evidence of benefit. Data on the benefits of conjugated linoleic acid (CLA) from human

studies are equivocal and unconvincing. Larsen and colleagues (32) provided a thorough review of both the animal and the human literature and concluded that CLA appears to reduce fat mass and increase lean mass in animal models. However, based on results from 13 randomized, controlled, short-term (<6 months) trials in humans, they concluded that there was little evidence to support the contention that CLA reduces body weight or adiposity in humans. They further remarked on evidence from mouse and human studies that the CLA isomer trans-10, cis-12 may promote liver hypertrophy and insulin resistance, and speculated that CLA may, therefore, actually have adverse effects. At present, data on CLA are limited to some promising animal studies, and benefits have generally not been borne out in human studies. Documentation of weight loss is not yet available nor is the ability of CLA to prevent regain. CLA may slightly reduce body fat but seems to have no effect on body weight or BMI (33). Few data are available on safety.

Chitosan: Little evidence of benefit; some adverse events (gastrointestinal symptoms). Chitin, found in the exoskeleton of lobsters and other shellfish, is used to produce the cationic polysaccharide chitosan. Proponents of its use for weight loss claim that it decreases fat absorption and thereby works to reduce weight. A recent meta-analysis (21) concluded that the evidence was not convincing and that the effectiveness of chitosan has not been established beyond a reasonable doubt. A more recent randomized trial did not result in a clinically significant weight loss compared with controls over a 24-week study (34).

Other dietary supplements: Little evidence of benefit for garcinia cambogia, glucomannan, guar gum, β -hydroxymethylbutyrate, pyruvate, Yerba mate, and Yohimbe. Adverse gastrointestinal events with guar gum; no data to assess adverse events for pyruvate, Yerba mate. Most of these dietary supplements were evaluated as ineffective in producing weight loss in a recent systematic review (21). Adverse events were noted with guar gum (eg, intestinal symptoms); data were not available to assess adverse events for pyruvate or Yerba mate.

Calcium: Evidence of benefit equivocal and limited to small trials; no major concerns regarding adverse events raised to date. Calcium is another nutrient that is claimed to stimulate weight loss in addition to its other functions. The addition of calcium and dairy products to reducing diets has been claimed to speed weight loss in some studies and samples, but not in all studies, leading to lingering questions regarding whether a true association exists. Some animal studies show impressive reductions in adiposity with calcium intake, but, again, others do not. In human trials, there is also inconsistency. In one small study, increasing amounts of dietary calcium (400 to 500 mg dietary calcium plus 800 mg calcium supplement) and high consumption of dairy products augmented weight and fat loss on reducing diets (35). In a larger multicenter study of close to 100 overweight adults on hypocaloric diets by the same group, high calcium intakes of 1,400 mg/day offered no significantly improved effects on weight loss or body composition compared with a lower-calcium diet (600 mg/day), whereas a high-dairy diet with three servings of milk and milk products per day with 1,400 mg calcium augmented weight loss and fat loss (36). In an-

other study by a different group working on this same issue, calcium supplementation did not increase weight loss in a randomized, double-blind, placebo-controlled weight-loss intervention in adult women (37,38), nor did another randomized, controlled trial find an effect on weight loss (39). The positive efficacy data are limited to small studies and, therefore, it is not yet firmly established that either calcium or dairy foods enhance weight loss on low-calorie diets. No safety problems were identified under the conditions of use of calcium in these studies. More clinical trials with larger numbers of subjects are needed to clarify these observations.

CONCLUSIONS

Dietetics professionals can find reliable information concerning dietary supplements and fact sheets for consumers online at the NIH Office of Dietary Supplements Web site: <http://ods.od.nih.gov/>. Nutrient-containing dietary supplements are helpful for achieving nutrient adequacy on hypocaloric diets. Because there is no demonstrated nutritional need for the ingredients in botanical and other supplements that are marketed for weight loss and because their benefits remain largely unproven, dietetics professionals need to be alert to the potential safety concerns associated with their use.

Dietetics professionals should ask clients who are likely to be using dietary supplements in weight reduction about what dietary supplements and other drugs they are taking. Any interactions should be identified and communicated to the physician and the patient.

If adverse events or effects are noted when dietary supplements are used for stimulating weight reduction, dietetics professionals and consumers can report them to the FDA by calling 1-800-FDA-1088 or visiting the Medwatch Web site www.fda.gov/medwatch. The FDA Web site, www.cfsan.fda.gov, provides information on updates and warnings as they become available, and health hazards identified there should be communicated to patients.

FUTURE DIRECTIONS

Evidence-based clinical practice guidelines on dietary supplementation to achieve nutrient adequacy are needed for restrictive and malabsorptive gastric bypass surgery. Evidence-based reviews of the safety, efficacy, and costs of dietary supplements for patients on VLCDs and low-calorie diets are also needed and should be made available to health professionals and to consumers.

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