AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR THE CLINICAL USE OF DIETARY SUPPLEMENTS AND NUTRACEUTICALS

AACE Nutrition Guidelines Task Force

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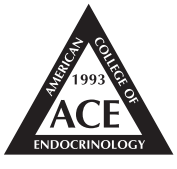

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Abbreviations:
AACE = American Association of Clinical Endocrinologists; **BMD** = bone mineral density; **CHF** = congestive heart failure; **CoA** = coenzyme A; **CoQ10** = coenzyme Q10; **CPT** = carnitine palmitoyltransferase; **DHEAS** = dehydroepiandrosterone sulfate; **DSHEA** = Dietary Supplement Health and Education Act; **DS/N** = dietary supplements and nutraceuticals; **FAs** = fatty acids; **FDA** = US Food and Drug Administration; **HbA1c** = hemoglobin A1c; **HDL** = high-density lipoprotein; **HIV** = human immunodeficiency virus; **IGF** = insulin-like growth factor; **LDL** = low-density lipoprotein; **MUFAs** = monounsaturated fatty acids; **PRCTs** = prospective, randomized, controlled trials; **PUFAs** = polyunsaturated fatty acids

1. FOREWORD

Few topics in medicine are more controversial than the use of alternative care methods and, specifically, the use of dietary supplements and nutraceuticals (DS/N). Because endocrinologists frequently encounter issues involving DS/N, the information in this report should be helpful. Unfortunately, there is a paucity of readily available and unbiased information on DS/N. Moreover, most medical centers do not provide formal and unbiased continuing education suitable for training in this field.

The American Association of Clinical Endocrinologists (AACE) has recognized the importance of nutritional medicine in the practice of endocrinology and metabolism. As a result, AACE has formed a Nutrition Guidelines Task Force. This task force presented preliminary information on nutraceuticals at the 2000 Annual Meeting of AACE in Atlanta (1), and a more detailed discussion on nutraceuticals was included in the AACE Self-Assessment Profile (ASAP) Syllabus published in 2001 (2).

This report will discuss alternative care medicine, introduce DS/N and define their nature, present a strategy for discussing DS/N with patients, provide a list of resources to peruse for further education, and review specific DS/N in detail based on levels of scientific substantiation. These guidelines differ from other extensive reviews on the topic by focusing on hormonal and metabolic agents and by providing consensus recommendations formulated by practicing clinical endocrinologists. This report is not intended to be encyclopedic and complete; rather, it is intended to serve as a resource for endocrinologists and other physicians unfamiliar with the issues surrounding the use of DS/N.

2. SPECIFIC MISSION AND METHODS

The objectives of this report are as follows:

1. Define DS/N
2. Provide appropriate examples of DS/N that physicians may encounter
3. Suggest strategies for physicians to discuss DS/N with their patients
4. Identify resources for physicians to use to learn more about DS/N
5. Discuss potential interactions between DS/N and drugs, nutrients, and other DS/N
6. Outline the rational use of DS/N in adults, within the framework of traditional medicine, based on an established method of grading of the available literature

The following are target audiences for this report:

1. Endocrinologists
2. Physicians specializing in clinical nutrition, nutrition support, and metabolic disorders
3. Health-care practitioners who wish to learn about DS/N in the areas of endocrinology, metabolism, and nutrition

The AACE Nutrition Guidelines Task Force consists of endocrinologists who are experts and practitioners in the field of clinical nutrition. More than 50% of their practice is in the area of nutritional medicine, and they are active members of AACE. Each contributor has published in the field of nutrition and is active in one or more of the major nutrition societies in the United States. Selected DS/N have been reviewed and clinical evidence has been graded by task force members. A separate panel composed of AACE and non-AACE physicians with expertise in nutritional medicine then reviewed the compiled report.

Final recommendations for the DS/N examples represent a consensus among the task force members and have been approved by reviewers, the AACE Publications Committee, and the AACE Board of Directors. Comments and recommendations regarding physician-patient communication are based on expert judgment of task force members.

Guidelines in clinical medicine have shifted from sheer expert opinion to an evidence-based approach (3). Notwithstanding the incompleteness of a purely evidence-based practice of medicine, the inherent flaws in nutrition research, and the paucity of valid data, this task force will rely solely on published scientific clinical evidence when making specific recommendations about DS/N. A summary of the methods used for preparation of these guidelines is presented in Figure 1.

Individual DS/N to be reviewed were selected by individual task force members, on the basis of the relevance to endocrinologists and physician-nutrition specialists, after topic assignment by the task force chairman. Readers should be aware that this compendium of information on DS/N represents only a partial list of DS/N that endocrinologists may encounter (Table 1). Inclusion criteria for use of published material to grade recommendations were that such sources (*1*) must clearly investigate one target agent and not a combination of agents, which could confound data, and (*2*) must be classified within one of the four evidence categories described in Table 2. Occasionally, reports that do not adhere to these criteria have been incorporated in the discussion of the DS/N because they provide theory. The evidence categories were adapted from The Evidence Report on Obesity by the National Institutes of Health (4) and the American Diabetes Association (5) evidence grading system for clinical practice recommendations. For example, a published review of the literature, regardless of how detailed and well written it is, would not contribute to the objective evaluation of the current evidence. References were obtained through computerized searching of the literature, scanning of incoming journals in the medical library, and review of references in pertinent review articles, major textbooks, and syllabi from national meetings, on the subjects of clinical nutrition, natural medicine, alternative medicine, dietary supplements, nutraceuticals, and phytomedicine.

We coded prospective, randomized, controlled trials (PRCTs) with large subject populations, which were highly representative of the target population, as *level 1*. This level also included meta-analyses of PRCTs, multicenter trials, and "all-or-none" data. Providing a nutrient to a patient with a proven nutrient deficiency is an example of an all-or-none indication. These are trivial scenarios and are not included in the discussions to follow, unless some controversial aspect is involved (for example, primary versus secondary carnitine deficiency; hyperglycemia and chromium deficiency). *Level 2* data included individual PRCTs that were limited in subject number or target population representation. *Level 3* data consisted of all other clinical data, including nonrandomized, uncontrolled, and nonexperimental or observational studies, such as well-documented case reports. These studies may be predicated on sound theory, but they require interpretation and, by

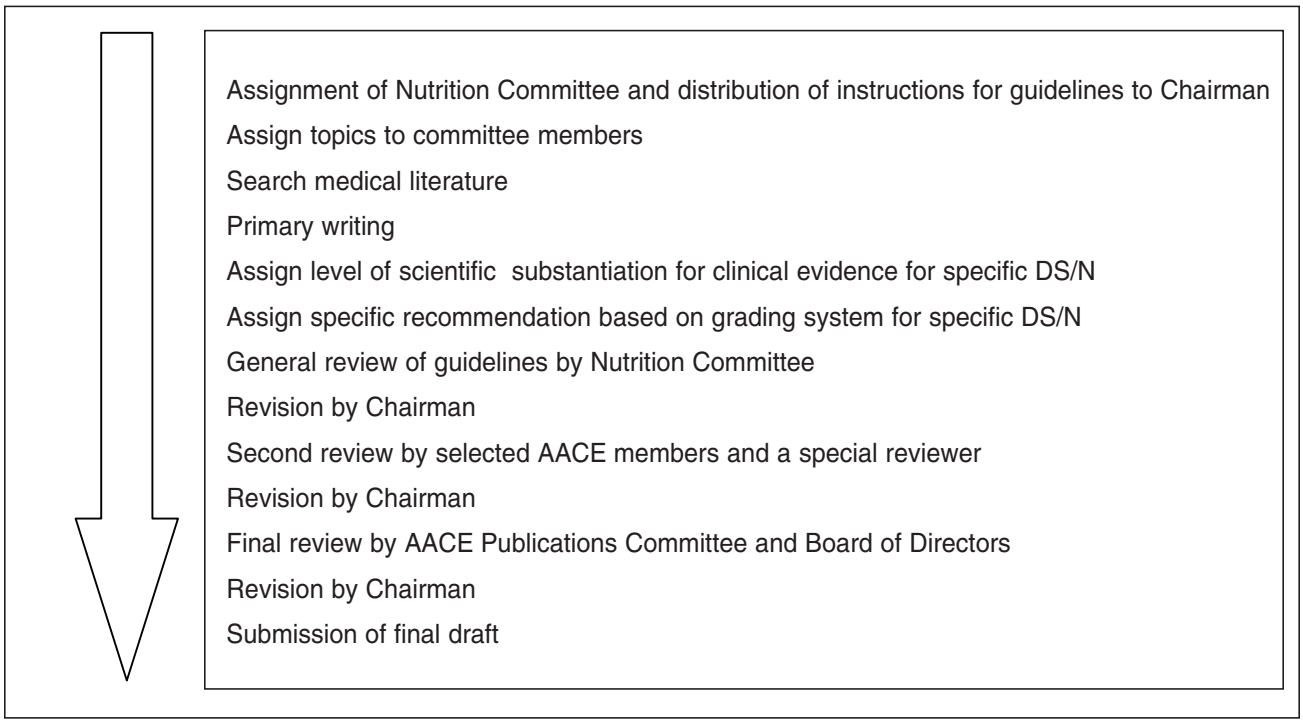

Fig. 1. Methods used for preparation of American Association of Clinical Endocrinologists (*AACE*) guidelines on dietary supplements and nutraceuticals (*DS/N*). See text for further details.

Table 1
Dietary Supplements and Nutraceuticals With Evidence-Based Reviews in These Guidelines

Entity	Guidelines section
Androstenedione	9.14 and 11.14
Carnitine	9.7 and 11.7
Choline	12.2
Chondroitin sulfate	9.9 and 11.9
Chromium	12.1.3
Coenzyme Q10	9.1 and 11.1
Creatine	9.8 and 11.8
Dehydroepiandrosterone sulfate	9.13 and 11.13
Fenugreek	12.1.1.3
Ginkgo biloba	12.1.1.1
Ginseng	12.1.1.2
Glucosamine	9.10 and 11.10
Glutamine	9.5 and 11.5
Gymnema	12.1.1.3
Ipriflavone	9.2 and 11.2
Karela	12.1.1.3
γ-Linolenic acid	12.1.2.2
α-Lipoic acid	12.1.2.1
Melatonin	12.3
Omega-3 fatty acids (fish oils)	9.11 and 11.11
Phytosterols	9.3 and 11.3
Prebiotics and probiotics	9.12 and 11.12
Taurine	9.6 and 11.6
Vanadium	12.1.4
Vitamin E	12.1.2.3

themselves, are not compelling evidence. Problems with proper randomization and control groups or problems with β (type II) error because of a small sample size are typical for this type of evidence. *Level 4* evidence is based solely on anecdote and experience and not substantiated by any scientific data. An example of this level may be exotic testimonial experience from laypersons, published expert opinion, or elegant theory advancing the association between proper nutrition and health. Many of us are familiar with the radio, television, and printed advertisements and articles professing new, miracle cures based on "Nobel Prize-winning research" or "revolutionary techniques." Frequently, an "expert" delivers a highly technical explanation of the agent, attempting to legitimize its use. Alternatively, another form of low-level substantiation is genuine expert opinion that is not based on any scientific evidence. Occasionally, only level 4 data are available.

On the basis of the level of scientific substantiation, a grade recommendation was made (Table 3). Although this recommendation was a subjective process, it was based on evidence and is reproducible. For example, AACE will recommend the "first-line" use of a DS/N shown to have benefit greater than risk on the basis of conclusive level 1 published evidence (grade A). Conclusive level 2 data showing benefit greater than risk will allow the recommendation for "second-line" use of a DS/N if conventional therapy has failed (grade B). Conclusive level 3 data showing benefit greater than risk will allow the use of a DS/N if conventional therapy has failed and adverse effects are negligible (grade C). In addition, if the extant evidence demonstrates no benefit and no risk whatsoever for a particular DS/N, and if the patient is already taking that DS/N, then there may be "no objection" to continuing the use of that DS/N (grade C). At the present time, AACE will not recommend any DS/N (grade D) for (*1*) any indication devoid of scientific evidence of benefit (absence of level 1, 2, or 3 evidence) or (*2*) any situation with conclusive level 1, 2, or 3 evidence demonstrating that the risks exceed the benefits. Clearly, the task force exercises a degree of subjectivity when assigning a grade to published data. For instance, if certain data are subjectively judged as inconclusive, then the grade will reflect the relative merits of conclusive and inconclusive data as well as the quantity of data in one evidence level versus another evidence level.

These methods have the following shortcomings: (*1*) reliance on subjective measures for distinguishing level 1, 2, and 3 data, (*2*) subjective weighing of risks versus benefits, (*3*) requiring only one conclusive study at a certain level to determine the grade (if no mitigating studies are available), (*4*) subjective weighing of positive and negative data at a specific evidence level (if mitigating studies are available), and (*5*) depending on task force primary authors for a complete literature search. Again, the purpose of reviewing the literature on specific DS/N was not to provide a comprehensive review but to demonstrate, by example, the quality and quantity of evidence that exists for certain DS/N and to formulate a limited number of specific recommendations. The task force was impressed by the vastness of the available literature and the variability of extant data on the subject of DS/N. Hence, a list of educational and reference resources is provided for those who wish to explore beyond the scope of this publication (see section 8, "Physician Resources").

3. WHAT IS ALTERNATIVE CARE?

Before formal guidelines on the use of nutraceuticals are presented, a brief discussion of the practice of alternative care medicine should help to gain a perspective on this controversial subject. The general practice of prescribing substances to treat diseases when the US Food and Drug Administration (FDA) has not approved their use, because of insufficient scientific substantiation, is termed "uncon-

Table 2
Levels of Substantiation in Evidence-Based Medicine*

Level	Description	Comments
1	Prospective, randomized, controlled trials—large	Data derived from a substantial number of trials, with adequate power, involving a substantial number of subjects and outcome data Large meta-analyses using raw or pooled data or incorporating quality ratings Well-controlled trial at one or more medical centers Consistent pattern of findings in the population for which the recommendation is made (generalizable data) Compelling nonexperimental, clinically obvious, evidence (for example, use of insulin in diabetic ketoacidosis); "all-or-none" indication
2	Prospective, randomized, controlled trials—limited body of outcome data	Limited number of trials, small population sizes in trials Well-conducted single prospective cohort study Limited but well-conducted meta-analyses Inconsistent findings or results not representative for the target population Well-conducted case-controlled study
3	Other experimental outcome data and nonexperimental data	Nonrandomized, controlled trials Uncontrolled or poorly controlled trials Any randomized clinical trial with one or more major or three or more minor methodologic flaws Retrospective or observational data Case reports or case series Conflicting data with weight of evidence unable to support a final recommendation
4	Expert opinion	Inadequate data for inclusion in above categories; situation necessitates an expert panel's synthesis of the literature and a consensus Experience-based information Theory-driven conclusions

*Levels 1-3 represent a given level of scientific substantiation or proof. Level 4 represents unproven claims.

ventional," "alternative," or, when used in combination with FDA-approved therapies, "complementary" or "integrative." For the purposes of these guidelines and the sake of clarity, the term "unproven" will refer to any intervention with insufficient scientific substantiation to support a specific claim. Obviously, a "gray area" exists between empiric and impressionistic traditional medicine and true alternative medicine. Within these guidelines, we attempt to codify this gray area. One example might be the use of choline. Choline is recommended by the Food and Nutrition Board of the National Academy of Sciences for use by pregnant or breast-feeding women. Choline may also be recommended for use in patients with hyperhomocysteinemia, for total parenteral nutrition-related hepatopathy, or for memory enhancement. In each of these scenarios, the amount of scientific substantiation differs. These guidelines provide an objective basis to evaluate these and similar issues.

The role of integrative medicine was debated by Dr. Arnold Relman, editor-in-chief emeritus of the *New*

Table 3
Grade-Recommendation Protocol Adopted by the AACE Nutrition Task Force*

Grade	Description	Recommendation
A	≥1 conclusive level 1 publications demonstrating benefit >> risk	Recommended for indications reflected by the publications; can be used with other conventional therapy or as **"first-line" therapy**
B	No conclusive level 1 publication ≥1 conclusive level 2 publications demonstrating benefit >> risk	Recommended for indications reflected by the publications *if* the patient refuses or fails to respond to conventional therapy; must monitor for adverse effects, if any; can be recommended as **"second-line" therapy**
C	No conclusive level 1 or 2 publication ≥1 conclusive level 3 publications demonstrating benefit >> risk *or* No risk at all and no benefit at all	Recommended for indications reflected by the publications *if* the patient refuses or fails to respond to conventional therapy, provided there are no significant adverse effects; **"no objection" to recommending their use** *or* **"no objection" to continuing their use**
D	No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk Conclusive level 1, 2, or 3 publications demonstrating risk >> benefit	**Not recommended** Patient is advised to **discontinue use**

*AACE = American Association of Clinical Endocrinologists.

England Journal of Medicine, and Dr. Andrew Weil, a leading proponent of integrative medicine, in the *Archives of Internal Medicine* in 1999 (6). Also in a recent issue of *Thyroid*, Goodman (7) argued that evidence-based medicine may be criticized because of the lack of relevance to practical patient problems, inasmuch as extrapolation from tightly controlled, clinical trials poorly represents actual individual patient scenarios. This philosophical problem becomes even more blurred when the relatively high frequency of adverse events with traditional medicine in comparison with alternative modalities is considered (8-10).

In short, several salient features of alternative care contrast with the traditional "Western" biomedical paradigm. First, traditional medicine relies on the scientific method and proven therapies, whereas lesser degrees of substantiation are typically used to support an alternative care claim. These pseudoscience techniques are sometimes difficult for even the most experienced clinician to recognize but can be very persuasive to the general population. Second, unproven therapies generally are not taught in medical schools in the United States, although this trend seems to be changing. Third, unproven therapies usually target a patient's complaints without requiring a diagnosis as with traditional medicine; common examples are pain, headache, abdominal discomfort, fatigue, and hair loss.

Currently, an undeniable emphasis is placed on preventive medicine and the attainment of "good health." A growing segment of the American population prefers "natural" remedies over "drugs." As a result, expenditures for alternative-medicine professional services increased 45% from 1990 to 1997, totaling $21 billion in 1997, $12 billion of which was paid out-of-pocket by the patients (11). An alarming 72% of patients availing themselves of alternative care fail to disclose this fact to their physicians (12).

What events have contributed to this explosive use of DS/N? This task force is impressed with many of the extraneous political, economic, and self-serving pressures that have resulted in the widespread use of DS/N. We are concerned about the potential harmful effects of DS/N and the disadvantaged posture of the traditional medical profession and the FDA in confronting the issues of alternative medical care in general and of DS/N in particular. Nevertheless, many well-designed and significant scientific studies involving DS/N are emerging in the traditional medicine literature. Therefore, by prioritizing the Western biomedical paradigm over alternative approaches, we can develop scientific and evidence-based guidelines for the use of DS/N.

4. WHAT ARE DS/N?

In 1994, the US Congress passed the Dietary Supplement Health and Education Act (DSHEA) to promote and increase the use of DS/N on the basis of their presumed safety and efficacy in self-healing. The intent was to achieve substantial cost savings for the nation in light of enormous and ever-increasing health-care expenses. The DSHEA has also resulted in greater funding for the Office of Alternative Medicine at the National Institutes of Health and has increased investigations of DS/N by the Cochrane Controlled Trials Register.

Dietary supplements are defined by DSHEA as (*1*) a vitamin or mineral, (*2*) an herb or other phytochemical, (*3*) an amino acid, (*4*) a dietary substance to supplement the diet by increasing the total dietary intake (for example, enzymes or tissues from organs or glands), or (*5*) a concentrate, metabolite, constituent, or extract of any of the foregoing. As a result of this definition, dietary supplements are not limited to the commonly perceived nutritional agents. Dietary supplements are not foods in their natural form or meal substitutes such as Ensure, Boost, or Sustacal.

The DSHEA allows three types of claims on labels of dietary supplements: (*1*) nutrient content (such as "high in calcium"), (*2*) "structure-function" or nutrition support (for example, "vitamin C prevents scurvy" or "calcium builds strong bones"), and (*3*) disease claims. Only this last claim requires FDA authorization based on a review of scientific evidence and substantiation (Table 4). Otherwise, the product label must contain the following wording: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, mitigate, or prevent any disease." Even the definition of "disease" is controversial. Claims that address common symptoms associated with life stages such as pregnancy (morning sickness), menopause (hot flashes), or general aging (hair loss or wrinkling) may be subject to intense scrutiny because whether these life stages represent a disease state is debatable.

Shortcomings of the DSHEA are the inability to address the (*1*) absence of scientifically based information regarding safety, (*2*) observed potential to cause harm, (*3*) lack of adequate scientific substantiation of clinical benefit, and (*4*) DS/N manufacturing process. Patients must be alert to the possibility of fraudulent products. Such products are often identified by pseudomedical jargon ("detoxify," "purify," "energize") or claims of a "secret" "miracle" "cure" or "new discovery." Moreover, economic fraud can occur by substitution of an inferior, less expensive ingredient. The FDA may issue warnings about reports of adverse events associated with DS/N (Table 5). Importantly, for placement of a DS/N on the market, the DSHEA does not require proof of efficacy or safety (although manufacturers are expected to be able to provide data), and no regulatory process exists for quality control—that is, no procedures verify that the correct amount or even the correct ingredient has been manufactured. Consequently, a problem must be reported in order for the FDA to intervene and regulate a DS/N.

Nutraceuticals are dietary supplements that contain a concentrated form of a presumed bioactive substance originally derived from a food, but now present in a nonfood matrix, and used to enhance health in dosages exceeding those obtainable from normal foods (13). For instance, soy protein is a dietary supplement, but ipriflavone, a synthetic derivative of the isoflavone daidzein found in soy protein, is a nutraceutical. One might not be able to ingest sufficient soy protein to provide the amounts of ipriflavone necessary to have effects on bone health. Another example is ingestion of concentrated omega-3 fatty acid (fish oil) capsules in comparison with eating the pounds of fish necessary for a cardioprotective effect.

Dietary supplements may be purchased without a prescription, and their use is governed by the DSHEA. Some investigators have argued that nutraceuticals, by

Table 4
FDA-Approved Disease Claims of Dietary Supplements, Based on Strong (Level 1) Evidence*†

Supplement	Disease claim
Calcium	Decreased risk of osteoporosis
Fiber	Decreased risk of cancer and coronary artery disease
Folic acid	Decreased risk of neural tube defect
Psyllium seed husk	Decreased risk of coronary artery disease
Soy protein	Decreased risk of coronary artery disease

*FDA = US Food and Drug Administration.
†See Table 2 for levels of substantiation of data.
Adapted from Mechanick et al (2).

Table 5
FDA Alerts Regarding Adverse Effects of Certain Nutraceuticals*

Ingredient	Adverse effect	Note
γ-Hydroxybutyric acid γ-Butyrolactone γ-1,4-Butanediol	Coma, seizure, death	Any product containing one of these unapproved ingredients is an unapproved drug
Chomper herbal laxative	Fatal heart block	Found in poisonous plants
Herbal "fen-phen" (may contain *Ephedra*, L-tryptophan, ma huang)	Amphetamine effect on CNS or heart	FDA considers these as unapproved drugs because the name reflects an antiobesity intent
5-Hydroxy-L-tryptophan	Sedative	Impurity "peak X" found in 1 case of eosinophilia-myalgia syndrome in 1991
Plantain (mistakenly contained *Digitalis lanata*)	Myocardial infarct	Intended as laxative; unrelated to tropical banana plant
Sleeping Buddha (contains estazolam for insomnia)	Fetal damage	Unlabeled prescription drug

*CNS = central nervous system; FDA = US Food and Drug Administration.
From Mechanick et al (2).

virtue of their druglike actions, should be regulated more tightly, not by prescription (because they are technically not drugs) but perhaps as over-the-counter medicines by the FDA (13). Clearly, a spectrum of agents can be used to affect health and disease; this array includes foods, meal replacements, dietary supplements, nutraceuticals, over-the-counter drugs, and prescription drugs (Fig. 2). Sometimes, however, the distinct labels become blurred. For instance, calcium can be considered a DS/N with a disease indication, an over-the-counter drug (calcium carbonate with or without vitamin D), or a prescription drug (calcium glubionate [NeoCalglucon]). For the purpose of clarity, dietary supplements and nutraceuticals will be considered together in the forthcoming discussions.

Several other factors regarding the ingestion of therapeutic substances should be considered. Is the substance adequately absorbed? Does it actually affect the targeted tissue? A classic example involving digestion is the early attempt to treat diabetes mellitus by the ingestion of powdered pancreas. Although unappreciated by the proponents of this "rational" therapy, the insulin was inactivated by proteolytic enzymes. An example involving problems with absorption is heparin. This naturally occurring substance found in animal lung tissue has a strong positive charge that prevents its absorption. An example involving problems with utilization is collagen. Approximately a third of this building block of connective tissue is hydroxyproline. This hydroxyproline, however, has no biologic value because it is incorporated as proline and then hydroxylated in situ. Hence, collagen and hydroxyproline, which are intuitively thought to rebuild damaged soft tissue, are actually useless for this purpose when ingested.

Nutritional medicine is faced with a dilemma. With the ever-growing demand for information about diet, health, and disease, the demand for DS/N by the general public to promote better health, and the contamination of the medical literature with nonscientific data, at what level of substantiation should a particular DS/N be recommended by a physician?

5. "FUNCTIONAL MEDICINE" APPROACH TO ENDOCRINE AND METABOLIC DISORDERS

Physicians should remain abreast of not only advances in traditional medicine but also evolving alternative medical practices. Sorting through the seemingly endless lexicon that is articulated by alternative care practitioners is particularly challenging. Long scientific words and technical phraseology are commonplace. Nonetheless, analysis of alternative opinions may yield advantages.

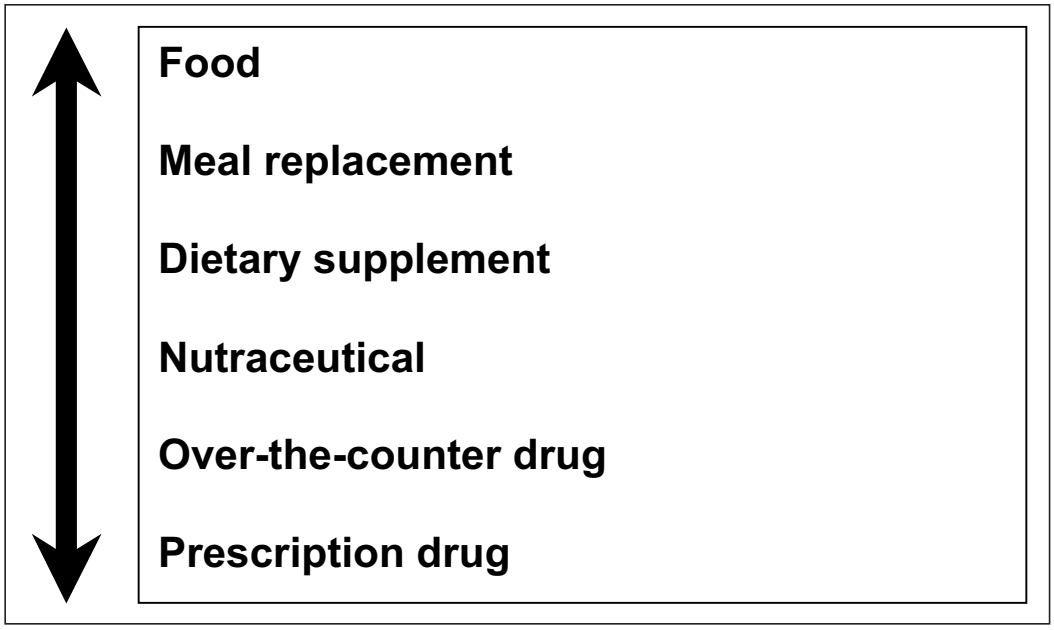

Fig. 2. Spectrum of therapeutic interventions that can affect health and disease.

First, such studies can be highly informative and lead to "lateral thinking" and innovative applications of proven therapies. Second, they can stimulate new ideas for the design of scientific medical research. Third, they can assist discussions with patients contemplating such therapies. Finally, they may eventually lead to proven therapies with DS/N.

One alternative practice that is gaining popularity is "functional medicine." This term is used by some healthcare practitioners to describe a clinical approach emphasizing (*1*) the physiologic and biochemical uniqueness of each patient, (*2*) the ability of laboratory testing to detect such uniqueness, and (*3*) the importance of minor symptoms to guide prevention of and therapy for suboptimal health, degenerative disease, and chronic illness. The overarching teleologic principle is that individualized nutrition, based on a person's unique genotype and phenotype, can produce a state of optimal health. "Functional foods" are defined as foods that contain, in adequate concentrations, one or more substances that have a positive physiologic effect.

In functional medicine, complex theories involving the psycho-immune-neuroendocrine axis are blueprints for natural interventions (14). Data from scientific and nonscientific studies are applied to buttress an argument against polypharmacy with traditional medicines and to favor lifestyle changes and the use of a wide variety of DS/N. "Nutrigenomic" and "nutriproteomic" therapies are nutritional interventions directed at genomic and cellular mechanisms of disease. An example would be genomic screening of children early in life (perhaps in utero) for methylenetetrahydrofolate reductase polymorphisms. A potential treatment would be to increase the dietary intake of folate or the nutraceutical 5-methyltetrahydrofolate. This approach would theoretically prevent pediatric leukemia, which has been linked to altered folate metabolism (15).

Adaptogens are substances derived from therapeutic botanicals and are used in functional medicine. They are complex mixtures that "resist" stressors and "normalize" endocrine function and the stress response. A summary of various DS/N used in functional medicine is presented in Table 6. At present, no conclusive level 1 or 2 data are available to support the role of these agents. Level 3 data exist but are inconclusive. A more detailed review of functional medicine is beyond the scope of these guidelines.

6. INTERACTIONS OF DS/N WITH DRUGS, NUTRIENTS, AND OTHER DS/N

Numerous issues face physicians who encounter patients taking, requesting, or inquiring about use of DS/N. In addition to philosophic and controversial questions regarding the use of unproven therapies, or therapies with weak scientific substantiation, a pragmatic issue is whether the DS/N in question will interfere with conventional medications, various nutrients, or even other DS/N the patient may be taking. Some of the major potential drug-DS/N interactions are summarized in Table 7. Patients should be strongly cautioned against taking any DS/N that may interact with any current or potentially needed medication. Furthermore, the study of drug-DS/N, nutrient-DS/N, or DS/N-DS/N interactions is not required by the FDA, as are drug-drug interactions. This makes it unlikely that many such interactions with DS/N have been discovered or that they will be adequately studied.

Table 6
Dietary Supplements and Nutraceuticals Used in Functional Medicine*

Action or scenario	Dietary supplements and nutraceuticals
Adrenal function	Dehydroepiandrosterone sulfate
	Glycyrrhiza glabra (licorice root)
	5-Methyltetrahydrofolate
	Ocimum sanctum (holy basil leaf)
	Pregnenolone
	Probiotics
	Vitamin B_5
	Vitamin B_6
	Vitamin B_{12}
	Vitamin C
Antioxidants	B-complex vitamins
	Coenzyme Q10
	Lipoic acid
	Quercetin
	Vitamin C
	Vitamin E
Functional hypothyroidism (biochemically normal)	Carnosic acid
	Commiphora molmol (myrrh)
	Desiccated animal thyroid extract
	Linoleic acid
	Omega-3 fatty acids
	Organic iodide
	Selenium methionine
	Tiratricol (TRIAC; 3,5,3′-triiodothyroacetic acid)
	Tyrosine
	Vitamin A
	Vitamin D
	Vitamin E
	Withania somnifera
	Zinc glycinate
Hypercholesterolemia	Coenzyme Q10
	Policosanol
	Red yeast rice
Insulin and glucose control	Chromium
	Magnesium
	Omega-3 fatty acids
	Vitamin E
	Zinc
Menopause	*Acorus calamus*
	Bacopa monniera
	Centella asiatica (Gotu Kola)
	Cimicifuga racemosa (black cohosh)
	Enterolactone and enterodiol
	Hypericum perforatum (St. John's wort flowering tops)
	Indole-3-carbinol
	Lavandula angustifolia (lavender flower)
	Linum usitatissimum (flax)
	Matricaria recutita (chamomile flower)
	Panax ginseng
	Pueraria lobata (kudzu vine root)
	Soy isoflavones
	Trifolium pratense (red clover)
	Vitamin B_{12}, vitamin B_6, folic acid, betaine, 5-methyltetrahydrofolate
	Vitex agnus-castus (chasteberry)
	Withania somnifera
Polycystic ovary syndrome	D-*chiro*-Inositol
	Chromium
	Magnesium
	Omega-3 fatty acids
	Vitamin E
Prostate health	Quercetin
	Saw palmetto
	Soy isoflavones
	Vitamin E
Stress adaptogens	*Cordyceps sinensis* (caterpillar fungus)
	Eleutherococcus senticosus (Siberian ginseng)
	Panax ginseng (Asian ginseng root)
	Rhodiola crenulata (Arctic root; goldenroot)
	Withania somnifera (ashwagandha; Indian ginseng)

*The dietary supplements and nutraceuticals used in functional medicine have not been graded by the American Association of Clinical Endocrinologists Nutrition Task Force.
From Bland (14).

Table 7
Potential Interactions Between Various Dietary Supplements and Nutraceuticals and Some Common Conventional Medications*

Medication	Dietary supplements and nutraceuticals
Anticonvulsants	Borage oil, evening primrose oil, shankapulshpi, biotin, folate, vitamins B_6 and D
Barbiturates	Valerian
Benzodiazepines	Valerian, kava root, grapefruit juice
Bisphosphonates	Bonemeal, calcium, ipriflavone, iron, magnesium
Corticosteroids	*Aloe* latex, buckthorn bark and berry, cascara, fenugreek, licorice root, *Ephedra*, *Echinacea*, zinc
Cyclosporine	St. John's wort
Digoxin	Digitalis, *Ephedra*, guar gum, hawthorn, licorice root, pectin, psyllium, kyushin, plantain, uzara root, ginseng, St. John's wort
Estrogens	Androstenedione, grapefruit juice, chasteberry, fenugreek, licorice root, *Panax ginseng*, saw palmetto, Siberian ginseng
Glitazones	Inositol, niacin
Heparin	Goldenseal
Insulin	Chromium, ginseng
Iron	St. John's wort, saw palmetto
Lithium	Caffeine, coffee, guarana, psyllium
Metoclopramide	Chasteberry
Oral contraceptives	St. John's wort
Oral hypoglycemics	α-Lipoic acid, devil's claw, *Ephedra*, fenugreek, feverfew, garlic, ginger, Gotu Kola, guar gum, horse chestnut seed, licorice root, *Panax ginseng*, psyllium, Siberian ginseng, stinging nettle, karela, inositol, niacin
Proton pump inhibitors	Bonemeal, calcium, indole-3-carbinol, iron, vitamin B_{12}
Spironolactone	Licorice
SSRIs†	St. John's wort
Statins	Red yeast (*Monascus*), grapefruit juice, pectin, coenzyme Q10, vitamin C
Tetracycline	Calcium, iron, manganese, magnesium, pectin
Theophylline	Ipriflavone, vitamin B_6
Thiazides	*Ginkgo biloba*
Thyroid hormone	Bugleweed, red yeast, kelp, calcium, iron, bonemeal
Warfarin	Garlic, *Ginkgo biloba*, devil's claw, dong quai, *Panax ginseng*, vitamin E, feverfew, vitamin K, borage oil, *Chlorella*, coenzyme Q10, curcuminoids, evening primrose oil, flaxseed oil, tocopherols, hemp seed oil, inositol, iodine, niacin, psyllium, tiratricol, wheat and barley grass, chondroitin

*References: Jellin JM, ed. *Natural Medicines Comprehensive Database*. Stockton, CA: Therapeutic Research Faculty, 1999. (209) 472-2244; www.naturaldatabase.com. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med*. 1998;158:2200-2211. Hendler SS, Rorvik D, eds. *PDR for Nutritional Supplements*. Montvale, NJ: Medical Economics, Thomson Healthcare, 2001. Markowitz JS, DeVane CL. The emerging recognition of herb-drug interactions with a focus on St. John's wort (*Hypericum perforatum*). *Psychopharmacol Bull.* 2001;35:53-64.

†SSRIs = selective serotonin reuptake inhibitors.

7. PHYSICIAN-PATIENT COMMUNICATION SKILLS

Issues about unproven therapies may arise in several clinical scenarios (Table 8). The success of the physician-patient interaction may depend on the manner in which these topics are addressed. The interaction can be optimized by the physician becoming knowledgeable about DS/N, alternative care practices, and methods of scientific substantiation. This task force recognizes that physicians themselves have varied backgrounds, cultural preferences, knowledge bases, and opinions. It is always hoped that the physician and patient are comfortable discussing the use of DS/N. If, however, the physician remains adamantly opposed to any treatment modality not incorporated in traditional medicine, this opinion should be stated at the outset to avoid an argumentative encounter. In accordance with the DSHEA, physicians may state to their patient that the DS/N product "has not been evaluated by the FDA, and it is not intended to diagnose, treat, cure, mitigate, or prevent any disease." Physicians should also discuss the potential adverse effects of DS/N.

Table 8
Potential Physician-Patient Scenarios
Involving the Use of Dietary Supplements and Nutraceuticals*

Problem	Approach
Routine office consultation or follow-up	Inquire about any nonprescribed medications or remedies Examine the actual supplement labels if available If not available, have patient fax list and labels after office visit Look up any substances that are not familiar to you Address any concerns you have about risks If any DS/N the patient is taking has not been approved by the FDA, inform the patient about that status and that many potential risks are unknown State your recommendations based on the level of available evidence
Second opinion regarding unproven DS/N use	See above State personal opinions regarding unproven therapy Review data in layperson's terms and according to the strength of evidence and provide appropriate recommendation Review risks and interactions with other medications in detail
Incidental discovery of DS/N use (not initially volunteered by patient), nonconfrontational	See above In a nonconfrontational manner, discuss the risks and benefits of DS/N from the standpoint of scientific substantiation Address any specific deleterious effects of the particular DS/N
Belligerent patient, strongly in favor of alternative medicine and against traditional medicine; confrontational	Clearly state your position and the extent you incorporate DS/N in your practice; allow the patient the option of terminating the consultation if the discussion is not anticipated to be helpful If the consultation continues, convey central importance of science over anecdote May concede imperfections in traditional medicine, but stress "track record" of the scientific method, its objectivity, and its relative safety, including addressing any specific deleterious effects of the particular DS/N Once a suitable dialogue is reached, the specific DS/N may be discussed with respect to the level of evidence If a suitable dialogue cannot be reached, the consultation should conclude

*DS/N = dietary supplements and nutraceuticals; FDA = US Food and Drug Administration.

In these guidelines, we recommend the following procedure for evaluating an issue concerning DS/N in a particular patient. First, formally assess the patient with respect to history and physical findings, as in any clinical encounter. Second, evaluate each DS/N being considered relative to its scientific evidence or level of substantiation. Third, convey one of four recommendations (as outlined in Table 3) to the patient in a sincere and caring manner. For example, you are consulted to evaluate the condition of a patient in the intensive-care unit, and a family member of the patient provides a list of 20 DS/N suggested by an alternative care practitioner for your consideration. Initially obtain a formal history, examine the patient, and then formulate a diagnosis and plan. On review of the DS/N and their respective levels of scientific substantiation, you may conclude that (*1*) multivitamins may be given in traditional doses but not "megadoses" (grade C), (*2*) vitamin B_{12} may also be given subcutaneously (grade C), and (*3*) DHEA, creatine, and large intravenous doses of magnesium are unproven therapies in this setting (grade D).

Four scenarios are reviewed in which physicians may encounter patients who are already taking or are considering taking one or more DS/N.

7.1. Scenario 1: The Routine Office Visit

Physicians must always ask about *all* medications, not just those that are prescribed. In addition, specific mention should be made of over-the-counter agents, prescribed and nonprescribed DS/N, and other alternative substances because only about 50% of patients will volunteer that they are taking dietary supplements, even when specifically asked by written questionnaire (16). If the patient brought in the DS/N, the labels should be reviewed. If not, then the patient should be instructed to fax or mail copies of the labels, or written information, regarding all DS/N and nonprescribed medications. These guidelines maintain that all health-care interventions should be classified in terms of "proven" and "unproven," effects, rather than using emotionally charged terms, such as "alternative," "complementary," "integrative," "nontraditional," and "unconventional." If any agents are judged to be risky or have potential detrimental interactions with other agents, then the patient should be dissuaded from continuing their use; again, the basis for this opinion should be the lack of scientific substantiation and not arbitrary bias. In fact, physicians can readily cite many DS/N that are "proven" effective and part of standard medical practice (Table 1). Mention can also be made of other DS/N that many physicians frequently recommend in the absence of conclusive level 1 data, such as fish oil, glucosamine, and chondroitin sulfate.

7.2. Scenario 2: The Incidental Discovery of DS/N Use

Another type of clinical encounter results when, after the initial interview fails to disclose use of DS/N, it becomes apparent that the patient actually has been taking one or many DS/N. Sometimes, this is an inadvertent omission by the patient, who did not realize that DS/N are forms of medication. At other times, it is a deliberate omission stemming from embarrassment or deception. Consistent with this, such patients may be amenable to an open and frank discussion about unproven therapies, whereas others are so passionately attached to the practice of alternative care that any attempt to present a cogent opinion will be met with anger, avoidance, or questioning of your knowledge and competence as a physician. The physician must (*1*) judge the potential psychologic barriers to an open discussion of this topic and (*2*) judge how relevant and important it is to resolve these issues with respect to the purpose of the consultation and the patient's overall health risks. If a decision is made to proceed with an open discussion, the same principles apply as in the aforementioned scenarios for routine office visits.

7.3. Scenario 3: The Second Opinion (Nonconfrontational)

Occasionally, patients present to the physician for a second opinion about a specific DS/N or group of DS/N. Generally, the patient is nonconfrontational in this setting. Again, the physician should declare a personal position on the subject of unproven therapies, including certain biases and experiences, if they exist. Then, the specific DS/N issue should be addressed within the context of the individual patient's problem. The physician should discuss the evidence at a level commensurate with the patient's ability to comprehend scientific data and theory. Scientific evidence (levels 1, 2, and 3) should take priority over anecdote and opinion (level 4). A thorough discussion of nutrient-drug interactions should also follow. A specific recommendation based on the grading schema in these guidelines (Table 3) is suggested.

7.4. Scenario 4: The Confrontational Encounter

Finally, a patient may overtly schedule an appointment to discuss alternative care strategies. Popular examples would be about taking (*1*) thyroid extract for fatigue, hypothermia, or weight gain, (*2*) preandrogens or aromatase inhibitors for bodybuilding, (*3*) herbs to treat diabetes mellitus *instead* of taking proven therapies, (*4*) "natural" agents for hormone replacement therapy in women, (*5*) DS/N to lose weight, or (*6*) performance enhancers as part of sports nutrition. Physicians should formulate their own opinions about unproven therapies so that their response to such patients can be organized, clear, and unemotional. Overall, AACE recommends that only proven therapies (grades A, B, and C in Table 3) be used to treat medical conditions. A patient's uncertainty may be clarified by helping the patient to understand the different levels of provability and scientific substantiation. Furthermore, the clinical evidence can guide therapeutic recommendations for a specific diagnosis. If the patient becomes argumentative, and simply cannot prioritize scientific substantiation over testimonial data or excessive risk, then the encounter should end. No doubt, the patient will then seek, and eventually find, another health-care provider who will participate in requested alternative care strategies.

8. PHYSICIAN RESOURCES

Physicians must become more knowledgeable about DS/N as they grow in popularity. Formal education is not routinely provided in medical schools or postgraduate medical training programs. Fortunately, various websites, societies and organizations, and comprehensive publications offer well-balanced information on DS/N (Table 9). The *Natural Medicines Comprehensive Database, PDR for Herbal Medicines*, and *PDR for Nutritional Supplements* offer reviews of DS/N. In a study by Walker (17), seven herbal resources were evaluated on the basis of their ability to answer questions generated by academic and institutional drug information centers. The *Natural Medicines Comprehensive Database* provided direct answers to 61% of questions, in comparison with 49% for the *AltMedDex*, 44% for the *Natural Pharmacist*, 24% for the *Lawrence Review of Natural Products*, 21% for the *PDR for Herbal Medicines*, 11% for the *Complete German Commission E Monographs*, and 9% for *Tyler's Honest Herbal*.

Of importance, websites are not subjected to any level of verification or substantiation. Many sites frequented by professionals and the general public purport to provide "objective" information but in actuality provide information that may be biased or fraudulent.

9. EXECUTIVE SUMMARY OF RECOMMENDATIONS FOR SPECIFIC DS/N

In this section, various DS/N are evaluated with respect to their levels of scientific substantiation, as outlined by grades shown in Table 3. These conclusions are summarized in Table 10. Readers are directed to the Appendix material for a detailed and referenced discussion of the theoretical foundations and scientific data concerning DS/N.

9.1. Coenzyme Q10

Coenzyme Q10 (CoQ10) has beneficial effects for mitochondrial disorders, congestive heart failure (CHF), and ischemia-reperfusion injury (grade C). For these indications, physicians may recommend it in situations in which the patient has not gained sufficient improvement from conventional therapy, providing there is no reasonable anticipation of adverse effects. No persuasive data compel this task force to endorse the use of CoQ10 in a wide variety of other claimed benefits, including performance enhancement, retardation of the aging process, immune system enhancement, diabetes mellitus, hypertension, or cancer (grade D).

9.2. Flavonoids, Isoflavones, and Ipriflavone

Glazier and Bowman (18), who reviewed more than 1,000 articles on phytoestrogens for a 30-year period, found 74 relevant studies to examine in detail. These authors concluded that insufficient evidence was available to recommend phytoestrogens instead of traditional hormone replacement therapy or to endorse any specific recommendations about particular phytoestrogen products. We agree with this conclusion (grade D).

Nevertheless, it would be prudent to recommend a diet high in legumes and cereals to women who are at risk for cardiovascular disease or estrogen-dependent malignant lesions or who are perimenopausal (grade A). In particular, ample conclusive level 1 and 2 data support the beneficial effect of soy protein in patients at risk for cardiovascular disease (grade A). There are also conclusive level 2 and 3 data concerning isoflavones or ipriflavone and osteoporosis (grade B). Overall, increasing the dietary consumption of fruit, vegetables, and certain beverages containing flavonoids (tea and red wine) seems prudent as part of a healthful diet. Currently, however, specific quantitative recommendations cannot be made for the general population.

9.3. Phytosterols

The use of phytosterols has been investigated in patients with hypercholesterolemia and found to reduce low-density lipoprotein (LDL) cholesterol levels. Conclusive level 1 data have accrued because of the numerous PRCTs that have been conducted. AACE, in agreement with the American Heart Association Nutrition Committee, recommends the use of phytosterols in patients with hypercholesterolemia and in patients requiring secondary prevention after an atherosclerotic event (grade A). All treated patients must be monitored for sitosterolemia in case they are heterozygotes. Patients with normal cholesterol levels may also take phytosterols if they, and their physicians, are aware of the potential risks of sitosterolemia (grade C). AACE does not recommend the use of phytosterols for the treatment or prevention of malignant disease, inasmuch as only inconclusive level 3 data exist for this indication (grade D).

9.4. Saw Palmetto

Only two strong studies support the use of saw palmetto extract in patients with benign prostatic hypertrophy. Clinical toxicities related to the use of this product seem to be minimal. Therefore, with conclusive level 2 data available, saw palmetto extract may be recommended for patients with benign prostatic hypertrophy who refuse conventional therapy or in whom conventional therapy fails (grade B). AACE does not support the proactive (first-line) recommendation of saw palmetto extract in any patient who has prostate cancer or prostate enlargement or who simply requests prevention of either of these two conditions by use of this approach rather than conventional therapy.

9.5. Glutamine

Glutamine is a nontoxic, physiologically important agent that is beneficial in critical illness (grade A). Glutamine may protect the gastrointestinal mucosa in the setting of acute stress and surgical treatment (grade B). This effect is most prominent in low-birth-weight

Table 9
Educational Resources on Dietary Supplements and Nutraceuticals

Resource	Further details
Websites	
American Botanical Council	http://www.herbalgram.org
American Nutraceutical Association	http://www.americanutra.com
The Cochrane Library	http://www.update-software.com/cochrane/
ConsumerLab.com	http://www.consumerlab.com
FDA Overview of Dietary Supplements	http://www.cfsan.fda.gov/~dms/ds-oview.html
HerbMed	http://www.herbmed.org/
The Institute for Functional Medicine	http://www.functionalmedicine.org
MD Anderson Complementary/Integrative Medicine	http://www.mdanderson.org/departments/cimer/
National Center for Complementary and Alternative Medicine	http://nccam.nih.gov/
Natural Database	http://www.naturaldatabase.com
Office of Cancer Complementary Alternative Medicine	http://www3.cancer.gov/occam/
Phytochemical and Ethnobotanical Databases	http://www.ars-grin.gov/duke/
Quackwatch	http://www.quackwatch.com/
Books	
Dictionary of Nutraceuticals and Functional Foods	Eskin NAM, Snait T. Boca Raton, FL: CRC Press, 2003
Essentials of Complementary and Alternative Medicine	Jonas WB, Levin JS. Hagerstown, MD: Lippincott Williams & Wilkins, 2003
The 5-Minute Herb and Dietary Supplement Consult	Fugh-Berman A. Hagerstown, MD: Lippincott Williams & Wilkins, 2003
Functional Foods	Gibson GR, Williams CM. Boca Raton, FL: CRC Press, 2000
Handbook of Nutraceuticals and Functional Foods	Wildman REC. Boca Raton, FL: CRC Press, 2000
Herbal Medicine, Expanded Commission E Monographs	Blumenthal M, Goldberg A, Brinckmann J. Newton, MA: Integrative Medicine Communications, 2000
Natural Medicines Comprehensive Database	Jellin JM, ed. Stockton, CA: Therapeutic Research Faculty, 1999
Nutraceuticals	Roberts AJ, O'Brien ME, Subak-Sharpe G. New York, NY: Penguin-Putnam, Inc, 2001
Nutraceuticals in Health and Disease Prevention	Kramer K, Hoppe P-P, Packer L. New York, NY: Marcel Dekker, Inc, 2001
Nutrition and the Strength Athlete	Jackson CR. Boca Raton, FL: CRC Press, 2000
PDR for Herbal Medicines	Greenwald J, Brendler T, Jaenicke C, eds. Montvale, NJ: Medical Economics, 2000
PDR for Nutritional Supplements	Hendler SS, Rorvik D, eds. Montvale, NJ: Medical Economics, Thomson Healthcare, 2001
Rational Phytotherapy	Schulz V, Hansel R, Tyler VE. Berlin: Springer-Verlag, 1998
Sports Drinks	Maughan RJ, Murray R. Boca Raton, FL: CRC Press, 2000
Stedman's Alternative Medicine Words	Hagerstown, MD: Lippincott Williams & Wilkins, 2003
The Review of Natural Products	DerMarderosian A, ed. St. Louis, MO: Facts and Comparisons Publishing Group, 1996

Table 10
Summary of Evidence-Based Indications for Dietary Supplements and Nutraceuticals Reviewed in These Guidelines*

DS/N	Grade A	Grade B	Grade C	Grade D
Androstenedione	…	…	…	Performance Body composition
Carnitine	Primary deficiency	…	2° deficiency Performance Cardiac Renal Valproate use	…
Choline	Pregnancy Breast-feeding	…	Hyperhomocysteinemia TPN-induced hepatopathy	Memory
Chondroitin	…	Osteoarthritis	…	Cognition Cardiovascular Renal stones
Coenzyme Q10	…	…	Mitochondrial disorder Congestive heart failure Ischemia-reperfusion injury	Performance Antiaging Immunity Diabetes mellitus Hypertension Cancer
Creatine	…	…	Ergogenic McArdle's disease	Congestive heart failure
DHEAS	…	…	…	Androgen replacement Performance Antiaging Libido Immunity Body composition
Glucosamine	…	Osteoarthritis	…	…
Glutamine	Critical illness	…	Stomatitis	Crohn's disease Immunity Cancer Performance
Melatonin	…	…	Sleep/jet lag Menopause (mood)	Cancer
Omega-3 fatty acids	Cardiovascular	High triglycerides	IBD	Immunity HIV Hypertension Behavior Asthma Rheumatoid arthritis Psoriasis Chronic fatigue syndrome
Phytosterols	High cholesterol 2° prevention of atherosclerosis	…	…	Normal cholesterol Cancer Chronic disease
Probiotics	…	Chronic pouchitis	Antibiotic-related diarrhea *C. difficile* colitis	…
Saw palmetto	…	BPH	…	…
Flavonoids	CAD risk reduction	Osteoporosis	…	Hormone replacement Hot flashes Cognitive therapy Antiaging
Taurine	…	Chronic alcoholism	TPN-induced hepatopathy	Congestive heart failure Diabetes mellitus Dyslipidemia
Antidiabetic indications				
α-Lipoic acid	…	Neuropathy	…	…
American ginseng	…	…	…	Glycemic control
Chromium	Chromium deficiency	…	…	Glycemic control Dyslipidemia Obesity
γ-Linolenic acid	…	Neuropathy	…	…
Ginkgo biloba	…	…	…	Peripheral neuropathy Erectile dysfunction Intermittent claudication
Momordica charantia	…	…	…	Glycemic control
Vanadium	…	…	…	Glycemic control
Vitamin E	…	…	…	Cardiovascular risk

*BPH = benign prostatic hypertrophy; CAD = coronary artery disease; DHEAS = dehydroepiandrosterone sulfate; DS/N = dietary supplements and nutraceuticals; HIV = human immunodeficiency virus; IBD = inflammatory bowel disease; TPN = total parenteral nutrition; 2° = secondary.

neonates receiving parenteral nutrition support. Glutamine also seems to be effective in the treatment of oral mucositis and stomatitis associated with both localized radiation therapy and systemic chemotherapy (grade C) and in the decrease of occurrence of peripheral neuropathy after paclitaxel therapy (grade C).

Other effects attributed to glutamine supplementation are not clearly defined. Data supporting enhancement of the immune system are weak and inconclusive at best (grade D). Glutamine seems to have no benefit as an energy-providing performance-enhancing agent (grade D). Use of glutamine in patients with liver disease and impaired ureagenesis is associated with hyperammonemia. Otherwise, published reports have provided no clear evidence of major toxic effects associated with either enteral or parenteral supplementation with glutamine.

9.6. Taurine

A derivative form of taurine, *N*-acetylhomotaurine, has demonstrated effectiveness in the treatment of alcohol abuse (grade B). Emerging clinical data support the addition of taurine to parenteral nutrition when hepatopathy cannot be explained by any other mechanism (grade C). No published data clearly support any other beneficial or therapeutic activity of supplemental taurine in healthy adults or pathologic states (grade D). In neonates, taurine appears to be an essential amino acid during stress ("conditionally essential") (grade C).

9.7. Carnitine

In the rare cases of primary carnitine deficiency, carnitine therapy is effective (grade A). In secondary carnitine deficiency, carnitine therapy has limited proven value (grade C). Level 2 and 3 data regarding carnitine as a performance-enhancing or ergogenic (energy-providing) agent are available, but not all studies show conclusive evidence of benefit (grade C). Trials of carnitine used in the treatment of CHF are emerging and appear encouraging (grade C). Similar results have been noted in the treatment of cardiac and peripheral vascular ischemic disease (grade C), as well as for the use of carnitine in patients with anemia associated with chronic renal disease who are receiving hemodialysis (grade C). Finally, carnitine therapy may be useful in patients treated with valproic acid for seizure disorders (grade C). No clear evidence has shown appreciable toxic effects associated with use of carnitine.

9.8. Creatine

Contradictory level 1, 2, and 3 evidence of a proenergy effect, reflected by improved performance, exists for creatine for any type of exertion, although the weight of evidence favors a beneficial effect (grade C). Claims for efficacy in the treatment of CHF are inconclusive (grade D). Limited data indicate that careful dosing of creatine may diminish symptoms associated with McArdle's disease (glycogen storage disease type V) (grade C).

9.9. Chondroitin

Chondroitin sulfate, administered for a long-term period, probably has some beneficial action in restoring cartilage damaged by osteoarthritis (grade B). Additional data investigating the combination of chondroitin sulfate and glucosamine in the management of osteoarthritis are reviewed in the subsequent section and do not affect this recommendation.

9.10. Glucosamine

Glucosamine may be an effective treatment for osteoarthritis. Several large metareviews have demonstrated such benefit but have failed to meet level 1 criteria. In addition, several level 2 and 3 studies of glucosamine demonstrate benefit in the treatment of osteoarthritis (grade B). Therefore, glucosamine may be recommended for those patients refusing, or not responding to, conventional therapy for acute osteoarthritis, administered alone or in combination with chondroitin sulfate.

9.11. Omega-3 Fatty Acids, Including Fish Oils

Polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs) appear to be useful in the treatment of hypertriglyceridemia and the prevention of cardiovascular events (grade A). Efficacy in inflammatory bowel disease is supported by level 3 evidence (grade C). Adverse effects may be noted at dosages larger than 3 g/day.

9.12. Probiotics

Probiotics may be used safely in patients with antibiotic-associated diarrhea and recurrent *Clostridium difficile* colitis. The level 1, 2, and 3 data are inconclusive, with the weight of evidence favoring demonstrable benefit (grade C). Chronic pouchitis flare-ups apparently are prevented by a mixed-organism probiotic, as reported in recent, conclusive level 2 studies (grade B).

9.13. Dehydroepiandrosterone Sulfate

Although many level 3 scientific reports have focused on dehydroepiandrosterone sulfate (DHEAS), the data are insufficient to support the use of DHEAS in healthy adults in any circumstance at the current time (grade D). In 1999, Oelkers (19) argued in an editorial that DHEAS may be used as part of replacement therapy in women with adrenal insufficiency; however, as intuitive as this application seems, confirmation of efficacy with level 1 data is necessary (grade D).

9.14. Androstenedione

The available data do not support the use of androstenedione or androstenediol for performance-enhancing effects (grade D). In fact, deleterious effects on the lipid profile are suggested by the data. The addition of other herbal compounds with unproven efficacy seems to be a marketing ploy to entice purchase of these DS/N. Any agent that directly or indirectly increases androgen levels

should be avoided in men with prostate cancer until clinical trials demonstrate its safety.

10. CONCLUSIONS

The AACE Nutrition Guidelines Task Force has organized a subset of DS/N that may be of particular interest to clinical endocrinologists. These DS/N have been evaluated with use of an evidence-based rating system, similar to those previously used for the evaluation of therapies for obesity and diabetes mellitus. Many popular remedies and self-treatment strategies with use of various DS/N have been found to be unproven scientifically (grade D), and AACE does not recommend their use. Nevertheless, this task force has been impressed with the scientific evidence (grades A, B, or C) pertaining to certain DS/N that may be recommended for some medical conditions. Specifically, DS/N may be recommended in accordance with the guidelines outlined in Table 3. In time, many DS/N may eventually be incorporated into the standard of care for these conditions.

11. APPENDIX 1: DETAILED DESCRIPTION OF THEORETICAL FOUNDATIONS AND SCIENTIFIC DATA FOR CERTAIN DS/N

11.1. Coenzyme Q10

11.1.1. General Discussion of Underlying Physiology and Biochemistry

CoQ10 occurs in virtually all cells—hence the formal name "ubiquinone." It functions in mitochondria to facilitate electron transport in the oxidative phosphorylation pathway (nicotinamide adenine dinucleotide and flavin adenine dinucleotide oxidation). It is normally synthesized in situ and, unlike vitamins, has not been identified as an essential nutrient. The "Q10" refers to the number of isoprenoid units associated with the root quinone structure. Functional coenzymes with differing numbers of isoprenoid moieties have been identified, and 10 is the most common. CoQ10 is present not only in mitochondria but also in the Golgi complex, plasma membranes, and lysosomes. The role in these nonmitochondrial organelles is not clear but probably involves an electron transport chain that promotes proton translocation across membranes.

When administered orally, CoQ10 has complex pharmacokinetics (20). Deuterium-labeled studies on plasma levels of CoQ10 after ingestion define a dual peak: an initial peak at 6.5 hours and a second peak at 24 hours. The terminal elimination half-life is approximately 33 hours. These data are thought to reflect initial hepatic uptake, transfer to very-low-density lipoproteins, and then redistribution to the systemic circulation. No published report has provided evidence of notable toxic effects of CoQ10.

11.1.2. Claimed Benefits and Controlled Clinical Trial Data

In the literature, orally administered CoQ10 has been claimed to be effective in the treatment of mitochondrial energy function diseases: mitochondrial myopathies such as Kearns-Sayre syndrome, CHF and other heart failure syndromes, vascular ischemic-reperfusion injury syndromes, neurologic disorders such as Huntington's and Parkinson's diseases, periodontal disease, type 2 diabetes mellitus, thyroid disease, abnormal spermatogenesis, and general aging.

Because CoQ10 is primarily a mitochondrial coenzyme, it is clearly rational that CoQ10 should have a beneficial role in the management of mitochondrial myopathies and neuropathies: Kearns-Sayre syndrome, cytochrome oxidase deficiency, succinate dehydrogenase (complex III) deficiency, Leigh disease, familial progressive external ophthalmoplegia syndrome, myoclonic epilepsy, and ragged red fibers syndrome. These studies have been relatively small and heterogeneous, and they present level 2 and 3 data (21-25).

Several controlled trials of CoQ10 have been performed for the indication of CHF, and the results have been highly variable. A randomized double-blind trial measuring the effect of orally administered CoQ10 on peak oxygen consumption, exercise duration, and ejection fraction showed no effect of CoQ10 on any of these variables (26). Other studies have confirmed only a marginal beneficial effect of CoQ10 in CHF (27). A relatively small (N = 17), open-label study demonstrated improvement in subjective physiologic factors and suggested a positive inotropic effect and vasodilation with CoQ10 in patients with CHF (28). Several other studies have also supported a salutary effect of CoQ10 in the management of CHF (29-32). Significantly, Ghirlanda et al (33) and Watts et al (34) reported plasma CoQ10 depletion, by as much as 54%, with statin therapy for dyslipidemia. CoQ10 and cholesterol share common biosynthetic pathways (35), but CoQ10 therapy does not interfere with the cholesterol-lowering effects of the statins (36).

CoQ10 has also been suggested as beneficial in the ischemia-reperfusion syndrome seen after cardiopulmonary bypass. Several studies have suggested that preoperative treatment with CoQ10 improves the tolerance of cardiac tissue to ischemia (37-40). Although some studies have had contradictory results, the preponderance of available level 2 and 3 data suggests a small beneficial effect (41).

Other therapeutic claims attributed to CoQ10 involve hypertension, impaired immune status, breast cancer, and various neurologic disorders including Huntington's disease and Parkinson's disease. No outcome data of level 1, 2, or 3 describing clinical benefit from CoQ10 could be found in the literature for these conditions.

In the general population, there is an implicit assumption that because CoQ10 is integral for the production of metabolic energy, it must be useful as a performance-enhancing agent. Several investigators have studied this issue and found no benefit on aerobic training in athletic or nonathletic populations (42-46). In a double-blind study, however, Folders and Yamamura (47) reported that administration of 100 mg of CoQ10 for 7 days improved endurance time, speed, and treadmill performance in healthy male runners.

11.2. Flavonoids, Isoflavones, and Ipriflavone

11.2.1. General Discussion of Underlying Physiology and Biochemistry

Flavonoids are substances with a phenolic structure found in a variety of plant sources (48) (Table 11). They have several mechanisms of action that have appealed to the general public interested in self-healing. Antioxidant effects are a result of (*1*) direct free-radical scavenging, attributable to the high reactivity of their hydroxyl group, and inhibition of LDL oxidation in vitro (49), (*2*) interference with inducible nitric oxide synthase activity and reduction of ischemia-reperfusion injury (50), (*3*) inhibition of xanthine oxidase activity, which decreases oxidative injury (50), (*4*) modulation of receptor-mediated calcium channels, serum complement reduction, decreased leukocyte immobilization, and, as a result, decreased neutrophil degranulation with reperfusion injury (51,52), and (*5*) direct inhibition of lipid peroxidation, α_1-antitrypsin activation, and arachidonic acid metabolism (53-55). As a result, various clinical effects have been postulated for flavonoids, including antiatherosclerotic, anti-inflammatory, antitumor, antithrombogenic, antiosteoporotic, and antiviral actions.

Table 11
Categorization of Natural Flavonoids

Group	Flavonoid	Major food sources
Flavones	Apigenin	Parsley
	Chrysin	Thyme
	Luteolin	Celery
	Rutin	Sweet red pepper
	Sibelin	
Isoflavones	Genistein	Soybeans
	Daidzein	Legumes
Flavonols	Kaempferol	Onions
	Myricetin	Kale
	Quercetin	Broccoli
		Apples
		Cherries
		Fennel
		Sorrel
		Berries
		Tea
Flavanones	Fisetin	Citrus foods
	Hesperetin	Prunes
	Narigin	
	Naringenin	
	Taxifolin	
Catechins	Catechin	Tea
	Epicatechin	Apples
	Epigallocatechin gallate	Cocoa
Anthocyanins	Cyaniding	Cherries
	Delphinidin	Grapes
	Malvidin	
	Pelargonidin	
	Peonidin	
	Petunidin	

Adapted from Nijveldt et al (48).

The overwhelming interest in a "natural" method of managing menopausal symptoms has incited scientific investigations involving phytoestrogens, soy proteins, and isoflavones. Lignans, the first detected phytoestrogen in humans (in 1979), are phenolic compounds structurally similar to steroids and are believed to have a protective effect against cancer. Lignans are found in cereal grains, flaxseed (linseed), many oilseeds, legumes, seaweed, fruits, and vegetables. Soy protein is derived from foods composed of, or derived from, soybeans or processed soy protein ingredients. Other soy products are isoflavones, fiber, and saponins. Isoflavones are a class of phytoestrogens found in legumes and beans, with soybeans being a particularly rich source (56) (Table 12). The isoflavones daidzein and genistein act as estrogen agonists and antagonists and are termed "natural selective estrogen receptor modulators." There are also non-soy phytoestrogens such as ginsenoside Rg1, derived from the ginseng root, which have cardioprotective, anticarcinogenic, neuromodulatory, and immunomodulatory actions (57).

Soy isoflavones are heterocyclic phenols with structural similarity to 17β-estradiol; the phenolic ring confers binding activity to the β- > α-estrogen receptors. Antagonism occurs with high circulating 17β-estradiol levels (premenopausal women), and agonism occurs with low circulating 17β-estradiol levels (postmenopausal women). Additional actions of soy isoflavones include antioxidation independent of receptor activation, inhibition of estrogen biosynthetic enzymes (for example, 17β-hydroxysteroid dehydrogenase), inhibition of 5α-reductase and aromatase, stimulation of sex hormone-binding globulin, reduction of bioavailable sex steroids, and inhibition of intracellular signaling protein kinases (58-61). Of note, flavones inhibit aromatase better than isoflavones; in the former, rings A and C mimic rings D and C of the androgen substrate (62). Genistein can act to decrease platelet aggregation through protein tyrosine kinase inhibition (63).

Ipriflavone is a synthetic flavonoid devoid of estrogenic activity. It directly inhibits osteoclasts and possibly stimulates osteoblasts (64,65). Hagiwara et al (66) found that acceleration of osteoblastic differentiation by ipriflavone results from down-regulation of endothelin receptors. Ipriflavone also stimulates expression of bone sialoprotein, decorin, and type I collagen and facilitates the deposition of mineralized matrix; thus, the biomechanical properties of bones are improved (67).

Individuals may vary in their ability to metabolize isoflavones (68). Metabolism is increased with a diet rich in carbohydrates, which increases intestinal bacterial fermentation and biotransformation of isoflavones; metabolism is decreased with antibiotics that alter intestinal flora (69).

11.2.2. Claimed Benefits and Controlled Clinical Trial Data

In 1999, the FDA authorized the use of food labels stating that soy protein was associated with reduction of risk of coronary artery disease. This FDA approval resulted from a favorable review of the scientific evidence (level 1 data and a grade A recommendation) and provides an example of a particular type of DS/N having a role in traditional medicine. Several studies investigated a daily intake of 25 g of soy protein, which resulted in clinically demonstrable reductions in levels of total cholesterol and LDL cholesterol. With soy intake, LDL cholesterol was less susceptible to oxidation in comparison with consumption of soy-free diets (70). In a meta-analysis of 38 controlled human clinical trials, an average soy protein consumption of 47 g/day was associated with decreased total

Table 12
Isoflavone Content of Certain Foods*

Food	Daidzein (μg/100 g dry wt)	Genistein (μg/100 g dry wt)
Cauliflower	5	9
Broccoli	6	8
Lentil	3-10	7-19
Barley	14	7.7
Peanut	58	64
Alfalfa	62	5
Chickpea	11-192	69-214
Clover seed	178	323
Soybean	10,500-85,000	26,800-120,500

*Wt = weight.
Adapted from Mazur (56).

serum cholesterol, LDL cholesterol, and triglyceride levels (71). In 3 other randomized, controlled studies, soy protein at levels as low as 20 g/day exerted lowering effects on total and LDL cholesterol levels similar to estrogen replacement therapy, without increasing high-density lipoprotein (HDL) cholesterol or triglyceride levels (72-74).

In contrast to dietary soy protein, purified isoflavones in pill form do not have this extent of salutary effects on lipoproteins (75). In a randomized, crossover trial of 18 postmenopausal women during three 93-day periods, the LDL cholesterol level was lowered 6.5% ($P<0.02$) and the ratio of LDL to HDL cholesterol was lowered 7.7% with daily consumption of 132 ± 22 mg of isoflavones in comparison with a control diet (76). There were no effects on levels of total cholesterol, HDL cholesterol, triglycerides, apolipoproteins A-I and B, and lipoprotein(a) or on LDL peak particle diameter (76). In postmenopausal and perimenopausal women, daily ingestion of 80 mg of isoflavones increased systemic arterial compliance 26%, similar to that observed with estrogen—a result possibly accounting for the reduction of cardiovascular risk (77).

Furthermore, in epidemiologic studies of East Asian countries where soy protein is a dietary staple, the incidence of hormone-dependent disease such as breast and ovarian cancer and coronary artery disease is lower than that in the West (78). Zheng et al (79) found an association between dietary soy intake and a decreased risk of breast cancer in a population-based, case-control study in Shanghai, China. Nevertheless, extrapolation of these epidemiologic data is confounded by genetic and other salient differences in diet and lifestyle between Asian and American populations. The antiproliferative effects of genistein in breast cancer may be due to (*1*) tyrosine kinase inhibition, (*2*) topoisomerase I and II inhibition, and (*3*) inhibition of endothelial cell proliferation and angiogenesis (80,81). Hormonal effects of isoflavones include (*1*) decreased serum endogenous estrone and estradiol, (*2*) reduction of luteal phase progesterone, (*3*) increased length of the menstrual cycle, and (*4*) suppression of gonadotropin surges (82-84). In a short-term study of only 2 weeks, however, soy supplementation to premenopausal women exerted a weak estrogenic effect (85).

Because the beneficial role of estrogen replacement therapy on bone mineral density (BMD) in postmenopausal women is well established (86,87), it is not surprising that in vitro studies and animal studies have supported such an effect of isoflavones (88,89). Most clinical studies to date involving isoflavones and BMD have been limited by the treatment duration and sample size. Potter et al (73) found that administration of doses of 90 mg, but not of 55.6 mg, of soy isoflavone for 6 months was associated with an increase in BMD. Similar benefit was demonstrated in a randomized, controlled trial by Alekel et al (90) in perimenopausal women treated with soy isoflavone (80.4 mg/day). These results, however, are challenged in a report by Wangen et al (91) in which 2 randomized, crossover studies involved 14 premenopausal and 17 postmenopausal women, who received low (control; 0.13 mg/kg per day), medium (1.0 mg/kg per day), and high (2.01 mg/kg per day) doses of isoflavone for more than 3 months. Although biochemical markers were consistent with decreased bone resorption, the magnitude was deemed too small to translate into a clinically relevant effect. In a study of 650 southern Chinese women, Mei et al (92) confirmed these results by finding that in postmenopausal women with habitually high dietary isoflavone intakes, parathyroid hormone, osteocalcin, and N-telopeptide levels were lower, without any improvements in BMD, in comparison with postmenopausal women who had low dietary isoflavone intakes. In contrast, Scheiber et al (93) found that, in 42 postmenopausal women, dietary use of 60 mg of isoflavone daily for 12 weeks was associated with an increase in serum osteocalcin levels and a decrease in N-telopeptide excretion rate. Lastly, Chiechi et al (94) reported that a soy-rich diet stimulated bone osteoblastic activity (increased osteocalcin levels) and prevented the decreased BMD observed in control subjects, in a randomized, controlled trial of 187 healthy asymptomatic postmenopausal women who were 39 to 60 years old. These beneficial effects were comparable to those observed in the hormone replacement therapy group (94).

In a PRCT of postmenopausal women, ipriflavone (600 mg/day), with or without hormone replacement therapy, decreased the rate of loss of BMD in the spine during a period of 12 months (95). Another randomized controlled trial involving 134 postmenopausal women in 6 Italian medical centers, use of ipriflavone, 200 mg orally three times a day, resulted in decreased biochemical indices of bone turnover and increased BMD of the spine after 2 years (96). In yet another randomized, controlled study of 56 women within 5 years of menopause, use of ipriflavone decreased rapid bone loss in the spine and reduced bone turnover (97). When used in combination with conjugated equine estrogen shortly after oophorectomy, ipriflavone (600 mg/day) inhibited loss of BMD in the spine more effectively than did conjugated equine estrogen or ipriflavone alone (98). This synergistic effect of ipriflavone in conjunction with estrogen may be due to the beneficial influence of ipriflavone on bone formation (with increased osteocalcin levels) in addition to its inhibitory actions on bone resorption (with decreased urinary pyridinoline excretion) (98). Ipriflavone also prevented rapid bone loss after medical menopause induced by gonadotropin-releasing hormone agonists (99). Furthermore, in two multicenter randomized, controlled 2-year trials, ipriflavone, 200 mg orally three times a day with meals, prevented both axial bone loss and spinal bone loss in postmenopausal women (100).

A metareview by Agnusdei and Bufalino (101) of 2,769 patients (3,132 patient-years) in 60 clinical studies in Italy, Japan, and Hungary showed that ipriflavone is safe and may increase BMD and possibly prevent fractures in elderly patients with established osteoporosis. Another later metareview by Scheiber and Rebar (102) supported the use of ipriflavone as a safe alternative to hormone replacement therapy for osteoporosis in postmenopausal

women. Finally, in a 4-year European multicenter PRCT of 474 postmenopausal women, no benefit was noted from ipriflavone therapy, and subclinical lymphopenia developed in 13.2% of treated subjects (103).

Similarly, published reports have described conflicting findings regarding the effect of soy protein on hot flashes. In a multicenter PRCT, Albertazzi et al (104) demonstrated a substantial reduction in the frequency of hot flashes in 104 postmenopausal women with the use of 60 mg of soy daily. Knight et al (105), however, failed to demonstrate any relief from menopausal symptoms by using powdered energy drinks that contained isoflavones, although there was a high withdrawal rate among study participants. Brzezinski et al (106) were also unable to demonstrate any alleviation of hot flashes in 75 postmenopausal women. Finally, Quella et al (107) were likewise unable to demonstrate any reduction in hot flashes with soy isoflavones in a controlled study of breast cancer survivors, 68% of whom were receiving tamoxifen.

Other miscellaneous effects of isoflavones have been supported by in vitro studies and animal studies, but insufficient clinical trials have been conducted. These effects include (*1*) improvement of cognitive function by means of increased choline acetyltransferase and nerve growth factor gene expression (108) and (*2*) decreased photoaging of the skin through antioxidation (109).

Other than subclinical lymphopenia mentioned in the foregoing material, no serious adverse effects have been associated with short-term or long-term use of soy proteins in humans (110). Theoretically, because isoflavones are a potential substrate for thyroid peroxidase, an excess of isoflavones could induce an iodine deficiency state and hypothyroidism (111). Moreover, absorption of orally administered levothyroxine is decreased with concomitant ingestion of soy protein supplements (112). Duncan et al (113) found that soy isoflavones did not have significant effects on vaginal cytology or endometrium. Lastly, the controversial findings surrounding hormone replacement therapy in the Women's Health Initiative randomized controlled trial (114) will undoubtedly add to the complexity involving the use of phytoestrogens.

11.3. Phytosterols

11.3.1. General Discussion of Underlying Physiology and Biochemistry

Plant sterols have a chemical structure similar to cholesterol and can be isolated from various vegetable oils, seeds, nuts, and fruits (115) (Table 13). They constitute 0.1% of adult human intake, amount to 180 mg of the daily dietary intake in Americans compared with 400 mg in Japanese, and consist of sitosterol (65%), campesterol (30%), stigmasterol, and others (116-119). Because only 5% of ingested plant sterols are absorbed, plasma levels are low, except in patients with sitosterolemia (120). In this rare genetic disease, affected children have tendinous xanthomas and normal to high LDL cholesterol levels. Once absorbed, phytosterols circulate in lipoproteins and then may be used as precursors for steroid hormones because they accumulate in the liver, adrenal glands, ovaries, and testes (121).

Plant sterols have been credited with cholesterol lowering, particularly in children with heterozygous familial hypercholesterolemia (122-124) and in management of atherosclerosis. Sitostanol is a fully saturated plant sterol and, like other phytosterols, is a potent inhibitor of intestinal absorption of cholesterol. Phytosterols also increase de novo hepatic cholesterol synthesis and secretion, decrease hepatic and lipoprotein lipase activities, and increase serum lecithin:cholesterol acyltransferase activity (125-127).

11.3.2. Claimed Benefits and Controlled Clinical Trial Data

In a review of the literature, Moghadasian and Frohlich (128) found a 13% reduction of LDL cholesterol level and a 10% reduction of total cholesterol level with use of dietary physterols among 590 study patients. Specifically, the review included 11 randomized, double-blind studies with sample sizes ranging from 7 to 102 (129-136), 5 uncontrolled or nonrandomized studies with sample sizes ranging from 8 to 100 (122,137-140), and 3 studies in which the experimental design was not stated and sample sizes ranged from 7 to 33 (123,124,141 [the only negative study in the metareview]).

In another study, consumption of olive oil (50 g/day) increased the sitosterol content of LDL cholesterol, and this finding was associated with antiatherogenic effects: a notable reduction of in vitro lipid peroxidation and macrophage uptake (142). Blair et al (143) found that the

Table 13
Phytosterol Content of Certain Foods

Food	Phytosterol content (mg/100 g food)
Corn oil	952
Sunflower oil	725
Safflower oil	444
Soybean oil	221
Olive oil	176
Almonds	143
Beans	76
Corn	70
Wheat	69
Palm oil	49
Lettuce	38
Banana	16
Apple	12
Tomato	7

Adapted from Ostlund (115).

addition of 1 pat of canola-oil-based, stanol-containing margarine three times a day (5.1 g/day; 162 kcal/day; $25.00/mo) to statin therapy reduced serum total and LDL cholesterol levels, without any changes in HDL cholesterol or serum triglyceride concentration. Overall, ingestion of 2 to 3 g of plant stanol esters daily reduces LDL cholesterol levels by 10 to 15% without side effects (144). In fact, a "designer" DS/N targeting cardiovascular disease containing plant sterols, niacin, omega-3 fatty acids (FAs), folic acid, and vitamins B_6 and B_{12} is used at the Arizona Heart Hospital (145).

Phytosterols have also been found to have benefit in certain malignant conditions and chronic diseases, but the data have been primarily from animal and epidemiologic studies. Clinical studies have been limited, and results are equivocal (146,147). Adverse effects are generally limited to patients homozygous for sitosterolemia, in whom sitosterol is hyperabsorbed and hypercholesterolemia and xanthomas may actually develop. Data regarding sitosterolemia heterozygotes are not available. Erythrocyte membrane fragility and hepatopathy may also be found in rare patients. Phytosterols may also have deleterious effects on the status of fat-soluble vitamins—α- and β-carotene, α-tocopherol, and lycopene. Overall, the Nutrition Committee of the American Heart Association advises that stanols and sterol esters not be recommended as a preventive measure to the general population with normal cholesterol levels, in light of limited data regarding potential risks. They may be used, however, for adults with hypercholesterolemia or adults requiring secondary prevention after an atherosclerotic event (148).

11.4. Saw Palmetto

11.4.1. General Discussion of Underlying Physiology and Biochemistry

Preparations and extracts from the berries of saw palmetto (*Serenoa repens*) have been used to alleviate symptoms in patients with benign prostatic hypertrophy. The berries contain FAs, fatty alcohols, flavonoids (isoquercitron, kaempferol-3-O-glucosides, and rhoifolin), and sterols (β-sitosterols). The pharmacologic action is believed to be due to its inhibition of 5α-reductase activity, responsible for the conversion of testosterone into dihydrotestosterone (149-151), inhibition of dihydrotestosterone binding to androgen receptors (152,153), anti-inflammatory activity (154), and relaxation of smooth muscle (155). Moreover, inhibition of basic fibroblast growth factor-induced prostate cell proliferation was mediated by the saw palmetto extracts lupenone, hexacosanol, and another unsaponified fraction (156).

11.4.2. Claimed Benefits and Controlled Clinical Trial Data

Several clinical trials have examined the effects of saw palmetto extract on hormone levels and prostate function. Casarosa et al (157) found no effect of 320 mg of a liposterolic saw palmetto extract on testosterone, luteinizing hormone, or follicle-stimulating hormone levels in 20 men. Rhodes et al (158) (in 32 patients) and Strauch et al (159) (in 32 patients) found no effect of use of 320 mg of saw palmetto extract (Permixon) for 1 week on dihydrotestosterone, whereas both testosterone and dihydrotestosterone decreased with administration of finasteride (Proscar). In contrast, longer durations of treatment with 320 to 480 mg of saw palmetto extract, but with small numbers of study patients, were associated with decreased levels of dihydrotestosterone and androgen receptor activity (160,161). Furthermore, in larger, multicenter, double-blind, placebo-controlled studies involving 177 patients (162) and 200 patients (163), β-sitosterol-based saw palmetto extract improved urinary flow in patients with benign prostatic hypertrophy.

11.5. Glutamine

11.5.1. General Discussion of Underlying Physiology and Biochemistry

Glutamine is the most abundant amino acid in the body that is incorporated into protein. It is used by rapidly dividing cells (enterocytes and leukocytes). Glutamine supports nucleotide biosynthesis and provides high energy during periods of stress. It is generally considered nonessential but becomes conditionally essential during stress and in the presence of gastrointestinal tract disease. It functions not only as a nontoxic nitrogen donor but also as an important glucose precursor in the tricarboxylic acid cycle and stimulates muscle glycogen storage and gluconeogenesis. During times of stress, glutamine is provided by free intracellular stores, muscle catabolism, and glutamine synthesis (164-166). High rates of glutamine utilization by immune system cells furnish sufficient intracellular biosynthetic intermediates for nucleotide and protein synthesis (167). During strenuous exercise, serum glutamine levels decrease, and this situation is purported to contribute to the subsequent relative immune suppression and risk of infection (167). In 2001, a symposium on glutamine was published as a supplement to *The Journal of Nutrition* (168).

11.5.2. Claimed Benefits and Controlled Clinical Trial Data

Glutamine supplementation, both orally and parenterally, is claimed to improve the function and integrity of the gastrointestinal tract, including the buccal mucosa. Additionally, it is claimed to improve immune function. In a PRCT, Powell-Tuck et al (169) were unable to demonstrate any benefit of addition of 20 g of glutamine to parenteral nutrition in 85 patients, in comparison with 83 control patients. Nevertheless, studies of length of hospital stay, hospital cost, and 6-month survival support the generalized efficacy of glutamine supplementation (170). In a metareview of 550 titles, 14 randomized trials that used glutamine in surgical and critically ill patients were identified (171). Glutamine use was associated with a reduction in infection-related complication rates and in hospital stay, without increased mortality, in surgical patients (171). In critically ill patients, glutamine use was

associated with decreased mortality and complications. These effects were most pronounced when high-dose, parenterally administered glutamine was used (171).

Extrapolation of data from low-birth-weight and critically ill infants to adults, either sick or essentially well, who take supplements is difficult. Nonetheless, much of the available information supporting the benefits of glutamine was suggested by pediatric studies. The increased metabolic demands of sepsis and organ failure are particularly devastating in this patient population. In such a patient population, glutamine was first assessed as a conditionally essential amino acid. Several studies that have assessed complication rates, survival, and even decreased hospitalization costs have confirmed the decreased morbidity and mortality associated with glutamine supplementation in premature infants (172-174).

Although published data support a beneficial effect of glutamine supplementation for the maintenance of gastrointestinal mucosal function postoperatively and at times of other physiologic stress, the data for other specific disorders, such as Crohn's disease, are less compelling (175,176). Much of the data indicating a beneficial effect of glutamine on bowel integrity is based primarily on intensive-care and postoperative studies in which patients have been maintained on total parenteral nutrition for prolonged periods. Specific variables, other than survival, are difficult to assess, and many of the studies supporting the use of glutamine rely on indirect measures, such as hormone and amino acid profiles (177-179).

Glutamine has also been used in conjunction with other agents, particularly growth hormone, in the treatment of small-bowel disease and short-bowel syndrome. In this setting, however, no clear pattern has emerged, and ascertaining whether glutamine, growth hormone, or a modified diet was the determining factor is difficult (180,181).

Because glutamine degradation is associated with both lymphocyte activation and leukocyte degranulation, glutamine supplementation has also been suggested as beneficial at times of immunologic stress and after immunosuppression, particularly after bone marrow transplantation (167,182). Here, too, the data are equivocal at best (183-185). In other states associated with altered immune function, particularly exercise and overtraining syndromes, glutamine has been proposed as beneficial. Because glutamine is an energy source and plasma glutamine levels decline after exercise, supplementation with glutamine was thought to be potentially a performance-enhancing measure; however, supplemental glutamine has not been shown to enhance performance (186). In the overtraining syndrome, there is a measurable increase in circulating neutrophils with degranulation, which does not change with glutamine supplementation (187,188).

In a study of 151 athletes randomized to drinking a glutamine-based supplement or placebo, immediately and 2 hours after exercise, more infections occurred in the control group (51%) in comparison with the glutamine group (29%) within 7 days after the exercise (189). Symptoms of overtraining (fatigue, muscle soreness, and frequent infections) associated with prolonged glutamine depletion may be attenuated by postexercise ingestion of a glucose-glutamine-based drink, which was demonstrated to promote muscle glycogen resynthesis and whole-body carbohydrate storage (190).

An interesting area for which good documentation indicates a benefit for glutamine use is in stomatitis and mucositis after both radiation therapy and chemotherapy for malignant conditions. Orally administered glutamine as a "swish and swallow" has been used with good results in stomatitis associated both with irradiation of the head and neck and with systemic chemotherapy. The mechanism for this action is unknown (191,192). In another study that was not a placebo-controlled trial, Vahdat et al (193) found that glutamine, 10 g orally four times daily for 4 days, reduced the severity of peripheral neuropathy associated with high-dose paclitaxel therapy.

11.6. Taurine

11.6.1. General Discussion of Underlying Physiology and Biochemistry

Taurine is an end product amino acid of cysteine catabolism and is found in many tissues, particularly the liver, retina, and central nervous system. It is the most abundant amino acid in the body but is not incorporated into proteins (as mentioned previously, glutamine is the most abundant amino acid that is incorporated into protein). Hepatic taurine and glycine combine with bile acids to form bile salts—specifically, glycolic acid, taurocholic acid, glycochenodeoxycholic acid, and taurochenodeoxycholic acid. Bile salts are essential for the emulsification of dietary fats. There is a continuous enterohepatic circulation of bile acids and bile salts.

Taurine is considered a conditionally essential amino acid, primarily because of its necessity in low-birth-weight newborns. Levels of taurine are reduced in patients with trauma-induced injuries and patients receiving parenteral nutrition, which typically lacks taurine in the amino acid solution (194). In both children and adults, taurine functions as a modulator of intracellular osmolarity (cell volume regulation) and, possibly, as a neuroactive amino acid. Whether this neuronal effect is on glial cell tonicity, which then affects neuronal cells, or whether taurine is directly inhibitory to neuronal tissue is unclear (195,196). In the renal medulla, taurine participates in an adaptive mechanism to modulate intracellular osmolarity in the face of rapid and large changes in the interstitial fluids bathing the tubular cells (197-200). A similar function seems to be subserved in the brain of adults as well as neonates (201). No clear evidence of severe toxicity has been associated with oral intake of taurine.

11.6.2. Claimed Benefits and Controlled Clinical Trial Data

Taurine has been claimed to be of benefit in the treatment of CHF, diabetes mellitus, hypertension, and epilepsy. Because taurine is a conjugate for bile acids, it has been postulated to have salutary effects in lipid disorders.

On the basis of data in premature infants, taurine has been suggested to benefit several retinal disorders (202).

In infants, particularly those receiving nutritional support, taurine synthesis may be inadequate, and renal resorption is insufficient. Hence, these children are at increased risk of taurine depletion. In this population, and particularly in infants and children with cystic fibrosis, taurine is important for fat absorption, presumably because taurine-conjugated bile acids are better emulsifiers than glycine-conjugated bile acids.

Taurine deficiency in neonates has been noted to result in failure to granulate the retina and in electroencephalographic changes, which may be the result of an inability to adapt to osmotic changes in the brain (203,204). The implication is that addition of taurine will ameliorate these changes related to the deficiency. No firm data show a benefit for taurine in such patients.

An acetylated form of taurine, *N*-acetylhomotaurine, which is marketed as acamprosate, has been developed as a therapeutic intervention for substance abuse disorders. Several well-controlled trials have indicated the safety and efficacy of acamprosate as adjuvant therapy in chronic alcoholism (205-207); however, no data support taurine supplementation by itself for this indication.

In CHF, few studies have demonstrated benefit with use of taurine. Taurine improves ejection fraction compared with CoQ10, but no placebo-control group has been studied (208). Additional theoretical advantages of taurine therapy for CHF have been proposed, but experimental evidence is clearly lacking (209,210).

Only one study has demonstrated efficacy for taurine in treating patients with diabetes mellitus. Administration of taurine was associated with decreased platelet aggregation in insulin-treated patients with diabetes compared with control subjects without diabetes (211). These data may be extrapolated to an effect on diabetes-related complications; however, no clinical data support such an outcome effect. Although experimental rat models of diabetes mellitus have suggested a role for taurine in the development of CHF (212), no published studies in humans have tested this hypothesis.

Data supporting the proposed beneficial effect of taurine on lipid metabolism are equivocal. In one study, oral administration of taurine in normal male volunteers on a high-cholesterol diet demonstrated a lesser increase in the total, LDL, and very-low-density lipoprotein cholesterol and triglyceride levels than in the control-treated group also receiving a high-cholesterol diet (213). In children with fatty liver due to obesity, oral taurine supplementation decreased enzyme elevations, and computed tomographic data suggested some decrease in the hepatic fat without regard to the effectiveness of weight control (214). In children treated with parenteral nutrition, particularly those with short-bowel syndrome, taurine supplementation may prevent parenteral nutrition-related hepatopathy (215).

11.7. Carnitine

11.7.1. General Discussion of Underlying Physiology and Biochemistry

Tissue carnitine stores are derived from dietary sources (meat and dairy) or endogenous biosynthesis from a combination of the essential amino acids lysine and methionine in the liver and kidney. Carnitine functions in the transfer of long-chain FAs from the cytosol into the mitochondrion ("carnitine shuttle") and then mitochondrial oxidation of long-chain FAs through β-oxidation and acylation-deacylation of coenzyme A (CoA). Long-chain FAs are a major oxidative energy source for cardiac tissue, which functions in a continuous aerobic energy cycle. In fact, carnitine palmitoyltransferase (CPT) II activity, determined by cardiac muscle biopsy, is reduced by 21% in patients with chronic CHF (216).

Carnitine also facilitates the oxidation of pyruvate and branched-chain amino acids. Pyruvate dehydrogenase is the rate-limiting step in carbohydrate oxidation and is modulated by the acyl CoA:CoA ratio (during starvation, acyl CoA from increased FA oxidation inhibits pyruvate dehydrogenase activity which, in turn, leads to decreased carbohydrate oxidation). When pyruvate dehydrogenase is active, acyl groups are transferred from acyl CoA to carnitine to form acylcarnitine, a reaction catalyzed by carnitine acyltransferase. Carnitine is also essential in the development of hepatic ketone synthesis, which inhibits oxidation of both glucose and lactate; thus, these substrates are spared for biosynthetic functions (217).

Primary carnitine deficiency results from a lack of active carnitine transport across plasmalemmal membranes. There are at least two types of CPT. CPT type 1 (CPT1) is located at the outer mitochondrial membrane, and CPT type 2 (CPT2) is localized at the inner mitochondrial membrane. Two isoforms of CPT1 have been identified. Patients with genetic deficiency of L-CPT1 (hepatic form; 13 families identified) present with hypoketotic hypoglycemia, whereas patients with M-CPT1 deficiency (myopathic form) have not yet been identified. CPT2 deficiency (more than 150 families identified) manifests with a variable picture, including rhabdomyolysis provoked by exercise, hypoketotic hypoglycemia, and brain and kidney dysgenesis (218-220).

Secondary carnitine deficiencies are associated with medical conditions, such as renal, hepatic, and gastrointestinal disease. These disorders are attributable to reduced exogenous carnitine absorption or reduced endogenous production in the kidney and liver (or both factors). Carnitine deficiency is best diagnosed by determining tissue levels on biopsy material. Serum levels of carnitine, however, can suggest a carnitine deficiency when either (*1*) free carnitine levels are abnormally low or (*2*) the ([total − free]/free) carnitine levels are >0.4. A presumptive diagnosis of secondary carnitine deficiency is suggested by the presence of unexplained hypoglycemia,

hypertriglyceridemia, hyperammonemia, myopathy, or hepatopathy. Other conditions associated with secondary carnitine deficiency are critical illness, human immunodeficiency virus (HIV) infection, chronic fatigue syndrome, long-term use of total parenteral nutrition, and use of certain drugs such as valproic acid.

11.7.2. Claimed Benefits and Controlled Clinical Trial Data

In cases of CPT deficiency, benefit has been associated with dietary supplementation of carnitine, dietary fat restriction in conjunction with medium-chain FA supplementation, and exercise restriction. In neonates receiving parenteral nutrition, a carnitine deficiency can develop; this outcome supports the role of carnitine as a conditionally essential nutrient in this population. Neonates receiving breast milk and most infant formulas do not seem to be at risk for carnitine deficiency.

In primary carnitine deficiency, orally administered carnitine is an extremely effective treatment. In secondary carnitine deficiencies, carnitine replacement is less clearly defined (218,221,222). Because carnitine and its derivative propionyl-L-carnitine have a central role in carbohydrate energy generation and in the reduction of intracellular metabolites in ischemia, carnitine or its esters have been suggested as beneficial in CHF and peripheral ischemic disease, predominantly claudication.

Several studies investigating the efficacy of carnitine in CHF have yielded mixed results. Ferrari and De Giuli (223), who conducted a randomized study of 50 patients with mild CHF, found that propionyl-L-carnitine increased the maximal exercise time, reduced the production of lactate, and improved the left ventricular ejection fraction. In a phase 2, parallel, single-blind, randomized and placebo-controlled study of short-term (30 mg/kg intravenous bolus) and long-term (1.5 mg/day for 1 month) administration of propionyl-L-carnitine to 30 patients with chronic CHF (New York Heart Association Class II and III), the results were increased exercise capacity and reduced ventricular size, without effects on hemodynamics or neurohormone levels (224). Long-term studies were undertaken in the multicenter Carnitine Ecocardiografia Digitalizzata Infarto Miocardico Trial in patients who had had acute myocardial infarction. This investigation showed some attenuation of the left ventricular dilatation following myocardial infarction after 1 year of treatment with carnitine. No differences were noted in ejection fraction or in the combined incidence of death or CHF (225). A randomized, double-blind placebo-controlled trial in the United States in a similar population demonstrated no change in end-systolic volume, end-diastolic volume, or ejection fraction after a 3-month treatment period with carnitine (226). Another study produced more variable results (227). In a more recent double-blind, randomized, placebo-controlled study of 155 patients with severe claudication, Hiatt et al (228) found that carnitine, 2 g/day for 6 months, improved treadmill exercise performance and functional status.

In rats, carnitine therapy attenuates sarcolemmal membrane defects in CHF after myocardial infarction (229). There are few studies of carnitine treatment in patients with angina and acute myocardial infarction. In one study, administration of carnitine to 50 patients who had had a myocardial infarction was associated with a decreased infarct size in comparison with the placebo-treated group after 28 days (230). Left ventricular hypertrophy, ventricular enlargement, and total arrhythmias were also decreased in the treatment group; these findings suggest that carnitine may be useful in the reduction of acute necrosis and complications in the acute phase of myocardial infarct (230). Additional suggestive, but inconclusive, data obtained in patients who underwent cardiac surgical procedures indicated some benefit in limited populations (231). Similarly, marginal data have been obtained in patients with ischemic angina (232).

In renal failure, carnitine has been suggested as beneficial for the maintenance of muscle mass and erythrocyte mass in patients receiving long-term hemodialysis. Carnitine deficiency may increase resistance to human recombinant erythropoietin in patients with anemia receiving hemodialysis (233,234). In a double-blind, randomized trial investigating the effect of carnitine on erythropoietin-treated dialysis patients, half of the treated patients demonstrated an increased erythrocyte survival time and a decreased erythrocyte requirement (235). Other authors have postulated that carnitine deficiency is associated with poor leukocyte function in patients receiving dialysis. A double-blind, randomized study in patients receiving long-term dialysis demonstrated no beneficial effects on phagocytic function or viability (236).

Patients, especially children, taking valproic acid for seizure disorders have decreased total and free serum carnitine levels and are at increased risk of hyperammonemia and hepatotoxicity. Carnitine supplementation has been thought to ameliorate the hepatotoxic effects associated with this treatment, particularly in neonates and children younger than 2 years (237-239). A few well-controlled trials have demonstrated a beneficial effect of carnitine supplementation and improvement in ammonia levels with valproic acid (240). The overall effect on patient health, however, is not clear.

Carnitine has been proposed as a performance-enhancing agent for athletes and as an aid in weight loss because of its role in energy production from FAs. In PRCTs, improvements in athletic performance with L-carnitine have been demonstrated in rowers, kayakers, swimmers, and long-distance runners (241,242). In a single-blind study of six untrained subjects, L-carnitine had protective effects against pain and damage from eccentric exercise, mainly attributable to vasodilatation (243). In addition, L-carnitine has been shown to induce loss of weight and fat in a placebo-controlled study (244) and, in conjunction with chromium therapy, to induce these body composition changes along with an increase in resting metabolic rate (245).

In other studies of exercise performance, carnitine has not been demonstrated to have a significant effect on performance in double-blind, crossover and double-blind, parallel studies in endurance trained athletes during their runs or recoveries (246-248). In a study of overweight women, carnitine supplementation in addition to aerobic exercise had no effect on exercise tolerance or weight loss (249). In a randomized, double-blind, placebo-controlled 6-month study of 50 women, Benvenga et al (250) found improvements in bone mineralization and a decrease in thyrotoxic symptoms with oral administration of carnitine, 2 to 4 g/day, in patients with iatrogenic hyperthyroidism. This outcome supports animal and uncontrolled clinical studies implicating carnitine as a peripheral antagonist of thyroid hormone action.

11.8. Creatine

11.8.1. General Discussion of Underlying Physiology and Biochemistry

Creatine phosphate is a phosphorylated derivative of creatine that can rapidly and reversibly donate its phosphate group to adenosine diphosphate to form the higher energy phosphate bond in adenosine triphosphate. Creatine is synthesized in the liver, kidney, and pancreas and is found in higher quantities in muscle tissue. It is synthesized intracellularly from glycine, a guanidino group from arginine, and a methyl group from *S*-adenosylmethionine. It is metabolized at a constant rate to creatinine, which is an end product excreted in the urine. Published reports have presented no clear evidence of any notable toxic effects of creatine when taken as an oral supplement.

11.8.2. Claimed Benefits and Controlled Clinical Trial Data

Oral administration of creatine, usually as the monohydrate, is proposed both as an energy- and performance-enhancing agent and as a muscle mass-increasing agent for athletes. Review articles in sports medicine claim that creatine is "beyond doubt the best-documented aid to exercise performance" based on its ability to provide up to 30 times the working energy for muscle, to increase muscle creatine content by up to 50%, and to enhance the lactic acid buffering capacity; thus, the anaerobic working capacity of muscle is extended (251-253). In addition, benefits as a therapeutic agent in CHF have been claimed.

There is good evidence that orally administered creatine is absorbed and incorporated in the intracellular muscle compartment. The general underlying principle is that oral creatine can be "loaded" into the muscle mass and incorporated into phosphocreatine. In the phosphorylated form as phosphocreatine, resynthesis of high-energy adenosine triphosphate from adenosine diphosphate is augmented. Whether the ingested creatine is well incorporated as phosphocreatine, however, is unclear (254,255).

In a retrospective review based on computerized literature searching, Juhn and Tarnopolsky (256) concluded that short-term supplementation with creatine had insignificant beneficial effects on ergogenic mass-dependent activities, such as running and swimming, probably because of increased water retention. With weight lifting, however, strength may be increased because of augmentation of myofibrillar protein synthesis. In a 28-day placebo-controlled trial involving 8 weight lifters, 20 g of creatine daily produced increased strength, body weight, and lean body mass (257). In another short-term study, creatine supplementation led to an increase in body weight, attributable to fluid retention (258). In a PRCT of 20 healthy men, use of 0.3 g/kg of creatine daily for 7 days improved sprint cycle performance in the heat (37°C, 80% relative humidity) without altering thermoregulatory responses (259). In a summary of 31 studies, oral administration of creatine (20 g/day for 5 to 7 days) improved repetitive, short-duration (<30 seconds), high-intensity performance, mainly in the laboratory but not in the field setting (260). Of note, most reports on the use of creatine have involved durations shorter than 3 months.

In many well-controlled studies of standardized energy output in elite trained athletes, significant improvement has been documented in exercise performance, particularly repetitive high-energy-output exercise, with use of creatine supplementation (261-267). In some cases, magnetic resonance spectroscopic studies of phosphate energy production and regeneration were also performed, but the results were variable. Several other studies using similar procedures and athletes have demonstrated no real effect (268-272). In a study of 328 high school athletes, 27 (8.2%) were taking creatine; however, 12 of 22 respondents (55%) did not know how much creatinine they were taking (273).

In 19 sedentary women, Vandenberghe et al (274) found that longer term creatine supplementation (20 g/day for 10 weeks of resistance training for 3 hours daily) enhanced the progress of muscle strength in comparison with placebo. Other studies in essentially normal, nonelite athletes have not demonstrated benefit after either short-term or long-term oral supplementation with creatine (275,276). Some experts claim that creatine exerts its salutary effects during hard resistance training; this relationship explains the lack of appreciable effect in nonathletes. Of interest, at least two published studies suggest that caffeine can reverse the claimed beneficial effects of orally administered creatine (277,278).

The data regarding the putative therapeutic effects of creatine in CHF are equivocal and much less voluminous than the data for exercise enhancement (279-281). We found data on only one other specific metabolic disease for which creatine was clearly beneficial. Creatine, 60 to 150 mg/kg daily, has been shown to be an effective treatment for McArdle's disease, in which there is a muscle phosphorylase deficiency (282), but symptoms were worse with higher dosages of creatine (283).

Both short-term and long-term studies have noted little toxicity associated with administration of creatine. These studies, however, were designed to detect only gross pathologic changes (284,285). Anecdotal creatine-associated adverse events that have been reported to the FDA include rash, dyspnea, vomiting, diarrhea, nervous-

ness, anxiety, fatigue, migraine, myopathy, polymyositis, cramping, seizure, and atrial fibrillation (286).

11.9. Chondroitin

11.9.1. General Discussion of Underlying Physiology and Biochemistry

Chondroitin is a member of the proteoglycans, which is a subgroup of the glycosaminoglycan group. Chondroitin is usually found in the sulfated form as chondroitin sulfate. Essentially, proteoglycans are repeating disaccharide structures (acidic sugar—amino sugar—acidic sugar—amino sugar, and so forth) that incorporate an amino group as a replacement for a hydroxyl group as a side chain. Chondroitin 4-sulfate and chondroitin 6-sulfate are disaccharides of *N*-acetylgalactosamine and glucuronic acid with a sulfate bound to the 4 and 6 carbon positions. These disaccharide units then form long repeating unit chain aggregates that bind to proteins. Unlike many of the other substances in this review, these are essentially extracellular compounds that are used as structural members rather than metabolically active agents. In cartilage, they bind collagen and hold the fibers in a tight, strong network. Chondroitin 6-sulfate seems to be the major form in synovial fluid, and the C6S:C4S ratio decreases with advancing age and with the severity of chronic osteoarthritis (287).

Aggrecan is a compound composed of chondroitin sulfate and hyaluronic acid. Aggrecan confers shock-absorbing properties to articular cartilage. Viscotherapy with intra-articular administration of hyaluronic acid increases joint lubrication and is approved by the FDA. Orally administered chondroitin sulfate is thought to be absorbed and eventually able to influence intra-articular viscosity. Specifically, chondroitin sulfate increases intra-articular hyaluronic concentration and the intrinsic viscosity, while also decreasing intra-articular collagenolytic activity and phospholipase A_2 and *N*-acetylglucosaminidase activity (288).

Physiologically, apart from their role in cartilage, chondroitin sulfate proteoglycans may have a central role in cell adhesion and as a structural matrix in the central nervous system (289,290). Therapeutically, specific proteoglycans containing chondroitin have been used as anticoagulants and antithrombotic agents and are similar to heparin (291).

11.9.2. Claimed Benefits and Controlled Clinical Trial Data

Orally administered chondroitin sulfate is claimed to diminish the symptoms of degenerative joint disease (osteoarthritis), to lower the cholesterol level, to reduce the progression of atherosclerosis, and to decrease the incidence of kidney stones.

The most commonly suggested benefit for supplemental chondroitin sulfate is as a treatment for osteoarthritis. Short-term benefit (<12 months) has been demonstrated by several level 2 studies. In a 1-year PRCT by Uebelhart et al (292), chondroitin 4- and 6-sulfate, 800 mg/day, reduced pain and increased overall mobility capacity in 42 patients with knee osteoarthritis. In a multicenter PRCT, chondroitin sulfate, 1,200 mg/day, administered in a single or divided doses, decreased clinical symptoms of knee osteoarthritis in 127 patients (293). Similar alleviation of symptoms was demonstrated by Morreale et al (294), Verbruggen et al (295), Bucsi and Poor (296), and McAlindon et al (297).

Little information from controlled studies was found to support the claims of benefit for chondroitin as an anticholesterol or antiatherosclerosis agent. One study was found to support the role of glycosaminoglycans as inhibitors of renal stone formation (298). Although no specific claims have been made for chondroitin sulfate in Alzheimer's disease, some recent data suggest that chondroitin sulfate proteoglycans, such as amyloid precursor protein (appican), NG2 proteoglycan, decorin, or testican, may have a role in the development of this process (299,300). Lastly, chondroitin sulfate by intra-articular injection is approved by the FDA for use with hyaluronic acid as a viscoelastic agent in the surgical treatment of cataracts, but it is not a DS/N in this capacity.

No clear evidence of major toxicity has been reported for chondroitin sulfate taken in its simple form. If taken as part of a proteoglycan, it may exert the effects associated with that structure. Bleeding is a potential adverse effect, and commercial preparations of various glycosaminoglycans have been used as anticoagulants—for example, in cases of heparin-induced thrombocytopenia, in which heparin is contraindicated (301).

11.10. Glucosamine

11.10.1. General Discussion of Underlying Physiology and Biochemistry

Glucosamine is an integral part of glycosaminoglycans and consists of repeating disaccharide units of an acidic sugar and an amino sugar. Either glucosamine or galactosamine can act as the amino sugar. Glucosamine stimulates production of proteoglycans, which are the ground substance of articular cartilage, as well hyaluronic acid, which is responsible for the lubricating and shock-absorbing properties of synovial fluid (302).

11.10.2. Claimed Benefits and Controlled Clinical Trial Data

Supplemental glucosamine is claimed to be effective in the treatment of osteoarthritis. Frequently, glucosamine in combination with chondroitin sulfate has been suggested for osteoarthritis therapy.

Some data support glucosamine as an effective agent in the short-term treatment of osteoarthritis. In two recent placebo-controlled trials of glucosamine for the symptomatic treatment of knee osteoarthritis, glucosamine was no more effective than the placebo (303,304). Other studies support glucosamine as about as effective as a nonsteroidal anti-inflammatory drug (305). For a period of 3 years, Reginster et al (306) studied 212 patients with osteoarthritis, given 1,500 mg of glucosamine versus

placebo, and found a statistically significant reduction in osteoarthritis pain with glucosamine. Unfortunately, many of these studies have design flaws that limit their applicability (307-309).

Combined treatments with glucosamine and chondroitin sulfate have been found to prevent progression of osteoarthritis in animal studies (310) and in small clinical studies (292,295,311). In two randomized, double-blind, placebo-controlled clinical trials, a beneficial effect of combination therapy was demonstrated for knee osteoarthritis: Das and Hammad (312) conducted a follow-up study of 93 patients for 6 months and Leffler et al (313) studied 34 men in a 16-week crossover trial. McAlindon et al (297) performed a metareview of 15 randomized, double-blind, placebo-controlled, clinical studies of glucosamine, chondroitin sulfate, or both, for at least 4 weeks, and concluded that treatment may yield moderate to large beneficial effects, although these effects are exaggerated by publication biases.

The costs of using glucosamine and chondroitin sulfate in the treatment of osteoarthritis are in the range of $30 to $45 per month and may exceed the costs of using conventional nonsteroidal anti-inflammatory drugs (314). Potential concerns with use of glucosamine are exacerbation of insulin resistance, through impairment of glucosamine-6-phosphate synthase activity (315) and modulation of phosphatidylinositol 3-kinase activity (316), and allergic reactions in patients with shellfish allergy. The generally recommended dosage is 500 mg orally three times a day for 12 weeks.

11.11. Omega-3 Fatty Acids, Including Fish Oils

11.11.1. General Discussion of Underlying Physiology and Biochemistry

FAs are hydrocarbon chains with a terminal hydroxyl group and are transported physiologically as lipoproteins. Unsaturated FAs can be in a *cis* configuration, in which the unsaturated site is "kinked," or in a *trans* configuration, which is more linear. Naturally occurring unsaturated FAs are almost always in the *cis* configuration. When unsaturated FAs, which are liquid at room temperature, are modified to change their physicochemical properties by the saturation of unsaturated bonds (hydrogenation), the result is almost always a *trans* configuration. The atherogenicity of FAs depends on the degree of unsaturation (saturated, monounsaturated [MUFA], polyunsaturated [PUFA], and *cis* or *trans* configurations). There are two essential FAs in humans: linoleic (an omega-6 FA) and linolenic (an omega-3 FA). The number refers to the number of carbon atoms from the methyl terminal end of the molecule at which the first double bond occurs. Arachidonic acid becomes essential if its precursor, linolenic acid, is absent in the diet.

Supplements taken as nutraceuticals are most often in the form of eicosapentaenoic acid and docosahexaenoic acid. These are the omega-3 FAs that are preponderant in cold-water fish (salmon, mackerel, cod, and others). Commercially available nutraceutical-enriched cheese contains 112 mg of omega-3 FAs per ounce. Flaxseed-enriched bread contains 1,728 mg of omega-3 FAs in 2 slices (Omega Rich, Nutrasur, Ontario; *New York Times*. August 8, 2001:F5). This content compares with 1,800 mg of omega-3 FAs in 3.5 oz of fresh salmon or 1,600 mg of omega-3 FAs in 3.5 oz of fresh bluefin tuna. Most clinical studies support a beneficial role of 1 to 3 g/day of omega-3 FAs.

Potential mechanisms of action are related to (*1*) direct effects on myocardial tissue to stabilize membranes and prolong the relative refractory period (317), (*2*) diversion of intermediaries away from proinflammatory prostaglandins (318), (*3*) alteration of metabolism of lipoproteins (319), and (*4*) modulation of metabolism of nitric oxide (320).

11.11.2. Claimed Benefits and Controlled Clinical Trial Data

Omega-3 FAs have been used for inflammatory bowel disease, autoimmune disease, peripheral vascular disease, adult respiratory distress syndrome and critical illness, and psychosis. These agents are proposed to provide benefit by attenuating the immune or inflammatory response.

A large volume of literature is available regarding PUFA and MUFA requirements in premature and term infants. Breast milk contains adequate amounts of these substances, but infant milk formulas may not. Despite several controlled and blinded studies, extrapolation of clinical results of such supplementation on growth and neurologic development in the general population is difficult (321-323). Although the evidence suggests no effect on growth, visual and neurologic development may be delayed with a marginal deficiency in essential FAs that may occur with formula feeding (324-326).

Inflammatory bowel disease has been reported to be ameliorated by the oral administration of omega-3 FAs. Whether this result is attributable to a general effect on the immune response or an effect specific to these disorders is not clear. Omega-3 FAs have been postulated to alter colonic epithelial cell proliferation, but these data have not been confirmed (327,328). In distal proctocolitis, benefits from eicosapentaenoic and docosahexaenoic acids have been demonstrated with a postulated inhibition of natural cytotoxic suppression (329). Other studies of patients with Crohn's disease and ulcerative colitis have shown no benefit from essential FA supplementation (330,331).

The relationship between omega-3 FAs and the immune response is not clear. Several studies suggest that the addition of PUFAs and MUFAs may increase cell-mediated immune responses through the action of prostaglandins (332-334). The inhibitory effects of FAs on immune function seem to be mediated by changes in surface adhesion on leukocytes and lymphocytes (335,336). Patients with HIV infection seem to have no response to omega-3 FAs (337,338).

Modulation of serum lipids, and the implied effect on cardiovascular disease, has been postulated. This has been accomplished by a variety of approaches, some quite

novel, including the feeding of PUFAs and MUFAs to chickens to alter the lipid content of eggs as well as to hogs to alter the composition of pork fat (339,340). The addition of PUFAs and MUFAs to the diet, with or without hydroxymethylglutaryl-CoA reductase inhibitors, is associated with the reduction in levels of lipids, primarily triglycerides, and cardiovascular events (341-344). Whether these effects are independent or causally related is not clear (345).

The relationship to coronary artery disease is a complex one. Clearly, reduced levels of cholesterol and oxidized LDL are beneficial for the reduction of atherosclerotic disease. Several studies that have analyzed the relationship between PUFAs and MUFAs and cardiovascular disease have reported varied results. Some studies have been unable to demonstrate an effect on coronary circulation or disease progression (345-347), whereas others suggest a modest benefit (348-350).

The Diet and Reinfarction Trial (DART), an uncontrolled multicenter secondary prevention study, demonstrated benefit of omega-3 FAs in 2,033 post-myocardial infarction patients at 2 years (351) but not during the subsequent 3 years (352) (level 3). The randomized, controlled Indian Experiment of Infarct Survival, performed by Singh et al (353), was relatively small and short in duration but demonstrated clinical outcome benefit of omega-3 FAs (level 2). The GISSI Prevenzione Trial (350) is the largest PRCT to date examining the cardiovascular effects of omega-3 FAs. In this study of 11,324 myocardial infarction survivors, long-term use of 1 g/day of omega-3 FAs, but not vitamin E, improved survival (level 1). Overall, extensive and consistent epidemiologic data demonstrate that consumption of as little as 1 to 2 servings of fish per week is associated with reduction of risk of sudden death.

Hypertension is another cardiovascular disease in which omega-3 FAs have been evaluated for therapeutic efficacy. The mechanism of action is unknown, but vascular elasticity changes and effects on vasoconstrictors have been postulated (354). When hypertension of pregnancy is used as the test variable, most of the studies show no effect of omega-3 FAs on blood pressure (355,356). In nonpregnant persons, the results are variable, possibly because of the differing effects of eicosapentaenoic acid and docosapentaenoic acid (357-359).

The effect of omega-3 FAs on behavior is an interesting area of investigation. Bipolar disorders, dysmenorrhea, aggression, and depression have all been reported to improve with administration of omega-3 FAs (360-362). Overall, there is no clear mechanism, either postulated or based on evidence, to support these claims.

Finally, evidence for and against the effectiveness of treatment with omega-3 FAs, omega-6 FAs, and MUFAs has been presented for a wide variety of disorders. There are data for and against efficacy in asthma (363,364) and rheumatoid arthritis (365,366). Intravenous administration of omega-3 FAs has been proposed as a treatment for chronic plaque psoriasis (367). In one study, chronic fatigue syndrome was not responsive to essential FA treatment (368).

Use of omega-3 FAs is associated with three major adverse effects: increased LDL cholesterol levels (<5 to 10% or up to 30% in patients with hypertriglyceridemia [369,370]), excessive bleeding, and deterioration of glycemic control in patients with type 2 diabetes mellitus. The FDA has concluded that omega-3 FAs are "generally recognized as safe" in dosages of less than 3 g/day, on the basis of metareview of more than 2,600 clinical studies (level 1) (371).

11.12. Probiotics

11.12.1. General Discussion of Underlying Physiology and Biochemistry

The term "probiotic" refers to microorganism supplements intended to improve health or treat a specific disease. To be classified as a probiotic, the organism must have scientifically proven beneficial physiologic effects, must be safe for human consumption, must be stable in bile and acid, and must be able to adhere to the intestinal mucosa (372). "Prebiotics" are metabolic substrates for probiotic agents, such as various dietary fibers, inulin, and oligofructosaccharides. The term "synbiotics" refers to the administration of a mixture of probiotics and prebiotics.

Probiotics protect the intestinal mucosa by competing with pathogens for attachment sites. Probiotics also upregulate a specific glycosyltransferase enzyme (373). This enzyme affects the glycoconjugate receptor on glycolipid and protein microvillus membrane surface molecules (373). Moreover, probiotics strengthen tight junctions and improve mucosal immunity through crosstalk with epithelial cells (373). Probiotics also provide maturational signals for gut-associated lymphoid tissues. These signals continually prime gut inflammatory responses (374). Some probiotic strains induce proinflammatory cytokine release, such as tumor necrosis factor-α and interleukin-6 (375). Some lactic acid bacteria prevent carcinogenesis in animals by abrogating the effects of carcinogens on proto-oncogene activation or tumor-suppressor gene inactivation (376).

Colonic anaerobic microflora salvage energy by means of bacterial fermentation of undigested carbohydrate and protein into short-chain FAs, which are trophic to colonocyte physiology. Beneficial genera are *Bifidobacterium* and *Lactobacillus*, and detrimental species are *Clostridium perfringens* and *Escherichia coli*. Abnormal gut flora results from overgrowth of various enteric pathogens, such as *Clostridium difficile*, which, in turn, results in disturbance of colonic salt and water resorption, nutrient absorption, and gas formation. *Lactobacillus* GG can survive the digestive process, is not killed by gastric pH or bile (377), and can persist in the colon for more than a week (378).

11.12.2. Claimed Benefits and Controlled Clinical Trial Data

With a 15-g daily dose of oligofructosaccharide or inulin, *Bifidobacterium* becomes the dominant genus in feces (379). Several small experimental studies have yielded positive and negative results of probiotics on

antibiotic-associated diarrhea (380-386). *Lactobacillus* GG treatment has been used successfully for the management of recurrent *Clostridium difficile* colitis (387). Recently, however, this result has been challenged in a randomized, placebo-controlled trial involving 267 adult hospitalized patients in whom *Lactobacillus* GG failed to decrease the rate of antibiotic-associated diarrhea (388). Vanderhoof et al (389) found a significant decrease in antibiotic-associated diarrhea with use of *Lactobacillus* GG in a randomized, placebo-controlled study of 188 children. Symptoms resulting from secondary lactose intolerance in adults may also be alleviated after correction of gut dysbiosis, slowing of gastric emptying, and partial fermentation of lactose after probiotic use (374).

Both *Lactobacillus rhamnosus* strain GG and *Lactobacillus acidophilus* strain La1 enhance phagocytosis in humans (390,391). Besides stabilizing indigenous gut microflora, probiotics also reduce the duration of rotavirus shedding (386), reduce the increased gut permeability resulting from rotavirus infection (392), and increase IgA-secreting cells in response to rotavirus (393,394). Moreover, probiotics can reduce the generation of local gut cytokines and reverse immunologic abnormalities found with food allergies (395), rheumatoid arthritis (396), and atopic eczema (392).

In two controlled studies by Malin et al (396,397) of 14 children with Crohn's disease and 9 children with juvenile chronic arthritis, *Lactobacillus* GG therapy for 10 days was associated with an increased gut IgA immune response. In a double-blind, randomized, placebo-controlled study of 40 patients with ulcerative colitis, a mixed-organism probiotic (VSL-3: 4 strains of lactobacilli, 3 strains of bifidobacteria, and 1 strain of *Streptococcus salivarius*) prevented flare-ups of chronic pouchitis (398). This effect is thought to be due to the ability of antibiotic and probiotic treatment to increase tissue interleukin-10 levels and to decrease proinflammatory cytokines, inducible nitric oxide synthase, and matrix metalloproteinase activity (399).

Probiotics have also been found to reduce atopy by (*1*) modifying the structure of potentially harmful antigens and thus decreasing their immunogenicity, (*2*) controlling excess formation of IgE and development of helper T cell subtype 2-skewed immune responsiveness, and (*3*) reducing interleukin-4 elaboration (392,393,400).

In a recent metareview of 143 human clinical trials involving more than 7,500 subjects between 1961 and 1998, no adverse events were associated with probiotic use, generally at doses of 10^6 to 10^9 colony-forming units daily for up to 1 year (401). In rare cases of *Lactobacillus* bacteremia, the source has not been identified as food or translocation of native colonic flora (402).

11.13. Dehydroepiandrosterone Sulfate

11.13.1. General Discussion of Underlying Physiology and Biochemistry

DHEAS is a steroid hormone produced mainly by the adrenal gland. It is the most abundant steroid in human plasma and is a precursor for both estrogens and androgens. DHEAS has been touted as a life-prolonging agent because of the following observations: (*1*) plasma levels decline to 10 to 20% of peak levels by age 80 years (403), (*2*) lower levels correlate with loss of bone and muscle mass, increase in fat mass, and increased risk of type 2 diabetes mellitus and atherosclerosis in humans (404), and (*3*) multiple studies in rodents support an antiaging, antioxidant, antitumoral, and immunomodulatory role (405-407). In fact, Zwain and Yen (408) demonstrated that rat astrocytes express P-450c17, produce DHEA, and can metabolize DHEA into testosterone and estradiol. Extrapolation of findings in rodent studies to humans, however, is invalid because of considerable differences in steroid biochemistry, production rates, and sources (409).

11.13.2. Claimed Benefits and Controlled Clinical Trial Data

DHEA was a prescription medicine in the United States until 1996; currently, it is not approved by the FDA for the treatment of any disease. The marketing of DHEA is now governed by the Dietary Supplement Health and Education Act. This arrangement is based on the circuitous rationale that DHEA is a concentrate of a chemical that might be ingested as part of a foodstuff (organ meat or gland). This same rationale would apply for other steroid compounds, such as androstenedione (see next section). In an observational study for 8 years in 290 male and female patients, there was a global decrease of DHEA levels of 2.3% yearly for men and 3.9% yearly for women, in conjunction with an increase in about 30% of patients consistent with the heterogeneity of the population (410). In addition, this study reported the following findings: (*1*) no association between DHEA levels and mortality in women, (*2*) an increased relative risk of death with lower DHEA levels in men, and (*3*) a higher relative risk of death in smokers with a low level of DHEA in comparison with nonsmokers with a high DHEA level. In another observational study, Feldman et al (411) also found that low DHEA and DHEAS levels predicted the presence of ischemic heart disease in a random sample of 1,709 men who were 40 to 70 years old.

Many level 3 studies have been performed investigating DHEA therapy. The published results have not been conclusive. In a PRCT of 11 patients, 3 weeks of DHEA therapy increased natural killer cell activity; thus, a theoretical framework for an antioncogenic effect for this steroid was provided (412). Morales et al (413) performed a PRCT in 30 subjects, with ages ranging from 40 to 70 years, who received 50 mg of DHEA daily for 6 months in a crossover design. Restoration of DHEA to young adult levels induced an increase in bioavailable insulin-like growth factor (IGF)-I, in association with improved psychologic well-being but no change in libido. In premenopausal women, Casson et al (414) found that 300-mg oral doses of micronized DHEA or 150-mg vaginal doses of DHEA diminished bioconversion into testosterone, compared with the same oral doses of crystalline preparations. In a small, placebo-controlled study, Khorram et al

(415) found that DHEA, 50 mg daily for 20 weeks, resulted in a 20% increase in IGF-I, a 32% increase in the ratio of IGF-I to IGF binding protein-1, and an augmentation of both cellular and humoral immunity factors. In 120 male and female patients, ranging in age from 15 to 75 years and with inflammatory and immunologically mediated diseases, Straub et al (416) found that DHEA, DHEAS, and androstenedione levels inversely correlated with interleukin-6 levels. Another study of indices of body composition, involving only five men, claimed beneficial effects of DHEA on lean mass and a potential role for insulin as a physiologic regulator of DHEA (417). In a controlled, double-blind study of 23 women with systemic lupus erythematosus who received 50 mg of DHEA daily, only a weak effect on outcome was noted with an optimal serum DHEA level of 1,000 μg/dL (418).

In a 9-month double-blind, crossover, randomized study of 39 healthy older men, 100 mg of DHEA daily for 3 months produced no changes in body composition, urologic variables, or sense of well-being, no improvement in sexual function, and no lasting changes in levels of blood urea nitrogen, creatinine, alanine transaminase, total cholesterol, HDL cholesterol, or potassium (although transient biochemical changes were noted in these analytes) (419). Arlt et al (420) did not observe any benefit of DHEA therapy (50 mg/day for 4 months) in a double-blind, crossover study of 22 healthy male volunteers with physiologic declines in DHEAS levels. In a PRCT by Arlt et al (421), 24 women with adrenal insufficiency received 50 mg of DHEA orally each morning for 4 months. This therapy resulted in improved well-being, less depression and anxiety, and increased frequency of sexual thoughts, interest, and satisfaction. In a double-blind, placebo-controlled trial, use of DHEA, 50 mg/day for 4 months, was also found to improve mental function in 32 patients with advanced HIV disease (422). In a study by Legrain et al (423), administration of 25 or 50 mg of DHEA to 24 healthy men and women was safe and resulted in (*1*) a terminal half-life of 20 hours, equivalent to endogenous serum DHEAS, attributable to back-hydrolysis into DHEAS, (*2*) increased conversion of DHEAS to DHEA in women, and (*3*) no accumulation of steroid metabolites.

Villareal et al (424) studied 18 elderly patients (10 women and 8 men; mean age, 73 ± 1 years) in a nonrandomized, prospective 6-month trial of orally administered DHEA, 50 mg daily, and compared the results with findings in an untreated control group. They found that, in the elderly women, DHEA replacement partially reversed age-related changed in fat mass, lean mass, and BMD. IGF-I and testosterone were postulated as mediators of these changes because these levels increased with DHEA treatment. In a randomized, controlled study of 61 young women with anorexia nervosa, use of DHEA, 50 mg/day, was associated with increased markers of bone formation (bone-specific alkaline phosphatase and osteocalcin), a decreased marker of bone resorption (N-telopeptide), and anabolic effects (weight gain) (425). After accounting for weight gain, however, no increase in spine or hip BMD was noted.

Adverse effects of DHEA therapy include various androgenic symptoms in women. Metabolism of DHEA into androgens may increase the risk of prostate cancer in men, and metabolism of DHEA into estrogens may increase the risk of growth of breast cancer and endometrial cancer in women (426). These theoretical risks, however, have been challenged by Labrie et al (427) in a discussion of the benefits of locally derived androgens and estrogens resulting from DHEA replacement therapy. In fact, a new field of endocrinology, termed "intracrinology," has been designated to describe these phenomena (427).

11.14. Androstenedione

11.14.1. General Discussion of Underlying Physiology and Biochemistry

Androstenedione is an androgen produced by the gonads and adrenal glands. It has been used in Europe in nasal spray form to enhance athletic performance and is available in the United States in tablet form. Because it is a direct precursor of testosterone, it is presumed to induce the anabolic effects of supraphysiologic doses of testosterone—increased nitrogen retention, strength, and muscle mass. Little clinical data are available regarding outcome measures.

11.14.2. Claimed Benefits and Controlled Clinical Trial Data

In a study of 10 men undergoing resistance training, androstenedione (200 mg for 2 days in a double-blind, crossover design) was associated with an increase in estrogen but no increase in testosterone levels; thus, it was deemed unlikely to induce an anabolic effect (428). In another controlled study of eight patients taking the supplement ANDRO-6 (which contains 300 mg of androstenedione, 150 mg of DHEA, 750 mg of *Tribulus terrestris* [an herbal source of steroidal sapogenins purported to mimic testosterone action and to increase levels of serum testosterone and luteinizing hormone] [429], 625 mg of chrysin [5,7-dihydroxyflavone, a flavonoid from *Passiflora caerulea* that inhibits aromatase activity] [430], 300 mg of indole-3-carbinol [an antiestrogen phytochemical] [431], and 540 mg of saw palmetto [an inhibitor of 5α-reductase activity]), testosterone levels were unaffected, estradiol and estrone levels were increased, and adaptations to resistance training were not augmented (432). In addition to chrysin, other flavonoids with significant antiaromatase activity being investigated for cancer chemoprevention are apigenin, hesperetin, 7,8-benzoflavone, flavone, flavanone, and quercetin (430,433). Finally, Broeder et al (434) performed a randomized, double-blind, placebo-controlled trial of 50 men, 35 to 65 years old, participating in high-intensity resistance training. They found that treatment with androstenedione or androstenediol for 12 weeks was associated with (*1*) a significant increase in the aromatization products estrone and estradiol, (*2*) a transient increase in testosterone, which normalized by 12 weeks because of aromatization and

luteinizing hormone suppression (18 to 33%) in the androstenedione group, and (*3*) adverse effects on lipid status, despite the absence of any adaptation in body composition or muscle strength.

12. APPENDIX 2: DS/N USED FOR SPECIFIC ENDOCRINE AND METABOLIC DISORDERS

12.1. Diabetes Mellitus

Patients with diabetes often seek unproven therapies as an alternative to traditional pharmacologic and dietary interventions. In a survey performed by Ryan et al (435), 78% of patients with diabetes were taking prescribed medications, 44% of patients with diabetes were taking over-the-counter supplements, and 31% of patients with diabetes were taking alternative medications. This distribution was essentially the same for respondents without diabetes (435). For all subjects interviewed, the amount of money spent on alternative medications and nonprescription supplements almost equaled that spent on prescription medications (435). Many of these products are consumed by patients with diabetes in addition to their conventional medications and diabetic diets to facilitate optimal glycemic control. Patients should be encouraged to disclose consumption of these products to their physician, as well as the consistency with which they take them, so that the physician can regulate medication properly. Recommendation grades for DS/N used as antidiabetic therapies are included in summary Table 10.

12.1.1. Phytochemicals

12.1.1.1. *Ginkgo biloba.*—*Ginkgo biloba*** has been unproved but used in the treatment of peripheral neuropathy and erectile dysfunction. A meta-analysis of randomized trials involving *Ginkgo biloba* extract demonstrated superiority over placebo in the treatment of intermittent claudication (436). This botanical contains flavonoids and terpene trilactones, including bilobalide and ginkgolide; ginkgolide B inhibits platelet-aggregating factor (437). Other reported actions of this phytochemical are release of nitric oxide, increased free-radical scavenging, decreased erythrocyte aggregation, decreased blood viscosity, and increased transcutaneous partial pressure of oxygen (438,439). Ingestion of *Ginkgo biloba* has also possibly been associated with an increase in the metabolic clearance rate of insulin and oral hypoglycemic agents, leading to hyperglycemia (440). No compelling data support the recommendation of *Ginkgo biloba* for the treatment of diabetes (grade D).

12.1.1.2. *Panax quinquefolius.*—*Panax quinquefolius*** (American ginseng) also has antidiabetic effects and was found to decrease postprandial glycemia significantly in a small placebo-controlled randomized study of 10 patients with type 2 diabetes (441) as well as in a randomized study with a crossover design of 12 healthy subjects (442). In another double-blind, placebo-controlled study of 36 patients with type 2 diabetes, 200 mg of American ginseng administered orally every day for 8 weeks improved hemoglobin A1c (HbA1c) levels and reduced fasting blood glucose concentration (443). Moreover, Vuksan et al (444) found that a 3-g dose of American ginseng lowered blood glucose levels in normoglycemic subjects if taken 40 minutes before a meal but did not affect blood glucose if taken with a meal; decreased levels of blood glucose were observed in patients with type 2 diabetes regardless of timing relative to a meal. In a metareview by Vogler et al (445) of 16 PRCTs, however, a definitive benefit of ginseng root extract in patients with diabetes could not be established. Nevertheless, no compelling data support the use of *Panax quinquefolius* in patients with diabetes (grade D).

12.1.1.3. Other Botanicals Used in Diabetes Mellitus.—*Momordica charantia* (karela; bitter lemon, orange, melon) exhibits hypocholesterolemic, hypotriglyceridemic, and antidiabetic effects in experimental animal models (446) (grade D). *Trigonella foenumgraecum* (fenugreek) is rich in steroid saponins and has beneficial effects on glycemic control and lipid status (total cholesterol, LDL cholesterol, and very-low-density lipoprotein cholesterol but not HDL cholesterol) in clinical studies (447,448). In a double-blind, placebo-controlled study of 25 patients, performed in India, the area under the curve for glucose and insulin was lower after an oral glucose tolerance test with fenugreek extract (449). Because of the lack of any conclusive clinical outcome studies, however, the use of fenugreek in diabetes mellitus remains unproven (grade D). Saponins and other chemicals from *Gymnema sylvestre* (GS4) and *inodorum* extracts are associated with (*1*) decreased intestinal glucose absorption independent of α-glycosidase activity and (*2*) increased insulin release due to increased cell permeability but not exocytosis (450-455) (grade D).

Additional plant extracts with hypoglycemic effects are *Allium cepa*, *Allium sativum*, *Aloe vera*, *Azadirachta indica*, *Brassica juncea*, *Caesalpinia bonducella*, *Canjanus cajan*, *Catharanthus roseus*, *Coccinia indica*, *Eugenia jambolana*, *Ficus bengalenesis*, *Jiangtangkang* (chrysanthemum), Konjac-mannan, *Mucuna pruriens*, *Murraya koeingii*, *Nopalea* (prickly pear cactus), *Ocimum sanctum*, *Opuntia*, *Pterocarpus marsupium*, *Swertia chirayita*, *Syzygium cumini*, *Tecoma,* and *Tinospora cordifolia* (456,457). Furthermore, the following culinary agents were also found to have insulin-sensitizing effects with use of a rat epididymal adipocyte assay: cinnamon > witch hazel, green and black teas, allspice, bay leaves, nutmeg, cloves, sage, mushrooms, brewer's yeast > flaxseed meal, and basil (458). No compelling data support the recommendation of use of these miscellaneous botanicals in patients with diabetes (grade D).

12.1.2. Antioxidants

Various antioxidants have been studied in clinical trials. In a randomized, prospective trial of 595 surgical critically ill patients, administration of vitamins C and E was associated with a decrease in organ failure and a shorter

intensive-care unit stay (459). In Germany, antioxidant therapy represents the standard of care for managing diabetes-related complications, such as peripheral neuropathy, that are thought to be due, at least in part, to oxidative stress and injury (460).

12.1.2.1. α-Lipoic Acid.—α-Lipoic acid is believed to exert beneficial antioxidant effects on neuropathy through metal chelation, regenerating vitamins C and E, increasing intracellular glutathione and CoQ10 (461), increasing microcirculation of the vasa nervorum (462), generation of nitric oxide, activation of heat shock protein protective systems (463), and decreasing nuclear factor-kappa B-binding activity (464). In addition, α-lipoic acid increases insulin action in type 2 diabetes (465). In a PRCT by Kahler et al (466), 600 mg of α-lipoic (thioctic) acid (N = 20), 100 μg of selenium (N = 20), or 1,200 IU of D-α-tocopherol (N = 20) used for 3 months demonstrated significant reductions in urinary albumin excretion and symptoms of peripheral neuropathy. In a large multicenter PRCT of 260 patients with type 2 diabetes who had peripheral neuropathy, 600 mg of α-lipoic acid administered intravenously for 3 weeks significantly decreased neuropathic symptoms (467). In addition, another multicenter PRCT demonstrated a neutral to small beneficial effect of α-lipoic acid (800 mg orally daily for 4 months) on cardiac autonomic neuropathy (468). These beneficial effects of α-lipoic acid on neuropathy, as well as glycemic control, were confirmed in several subsequent studies; some of these were large multicenter controlled trials, but others had relatively small sample size or limited study durations (or both) (469-478). Collectively, these clinical data include three large multicenter trials in Germany (Alpha-Lipoic Acid in Diabetic Neuropathy [ALADIN I, II, and III]) as well as several controlled studies with various design shortcomings. The effects are not entirely consistent but highly suggestive that a beneficial effect exists for α-lipoic acid on diabetic neuropathy (grade B).

12.1.2.2. Linoleic Acid.—Linoleic acid is an essential omega-6 FA. Its conversion into γ-linolenic acid is inadequate in patients with diabetes (479). This disorder contributes to microvascular and hemorheologic abnormalities leading to ischemia and neuronal hypoxia, oxidative endothelial injury, axonal dysfunction, and eventually diabetic neuropathy (479). Jamal and Carmichael (480) found that 360 mg of γ-linolenic acid decreased the symptoms of neuropathy and improved neuronal function in 12 patients with diabetes, in comparison with 10 control subjects receiving placebo. Evening primrose oil is a DS/N; a single capsule contains 45 mg of γ-linolenic acid and 360 mg of linoleic acid. Arisaka et al (481) found that use of 2 capsules of evening primrose oil for 4 months, and then 4 capsules a day for 4 months, reduced abnormal FA levels in 11 children with diabetes, in comparison with control subjects taking a placebo. Lastly, Keen et al (482) performed a multicenter randomized, double-blind, placebo-controlled study of 111 patients taking γ-linolenic acid, 480 mg daily. They demonstrated benefit on the course of mild diabetic neuropathy, which was more pronounced in patients with well-controlled, compared with poorly controlled, diabetes (482). Overall, the data concerning γ-linolenic acid merit a B grade because of the presence of level 2 studies that have demonstrated benefit.

12.1.2.3. Vitamin E.—Vitamin E is an essential, fat-soluble nutrient with antioxidant properties. Vitamin E deficiency states are associated with neurologic abnormalities. Vitamin E and omega-3 FAs (fish oils) promote the action of diacylglycerol kinase and inhibit phosphatidate phosphohydrolase (483). These actions reduce diacylglycerol, which can inhibit the action of protein kinase C (483). This, in turn, diminishes the adverse effect of free FAs on muscle insulin sensitivity (483). Although several controlled studies have demonstrated benefit of vitamin E with regard to cardiovascular risk, the recent Heart Outcomes Prevention Evaluation (HOPE) Study failed to detect any benefit on cardiovascular or cerebrovascular risk of vitamin E at a 400-IU daily dose (484). These negative results were confirmed in subsequent studies by de Gaetano and the Collaborative Group of the Primary Prevention Project (485) and the SECURE trial (Study to Evaluate Carotid Ultrasound Changes in Patients Treated With Ramipril and Vitamin E) (486). The cumulative data on use of vitamin E in patients with diabetes are similarly equivocal.

In a PRCT of 50 patients with type 2 diabetes, 600 mg/day of vitamin E (versus placebo) decreased HbA1c and insulin levels and improved cardiac sympathetic and parasympathetic tone (487). This effect was thought to be due to a decline in oxidative stress, and a later study by Park and Choi (488) supported the antioxidant role of vitamin E in type 2 diabetes. Vitamin E can also lower plasminogen activator inhibitor type 1 levels implicated in vascular complications (489,490). In type 2 diabetes, this effect does not seem to be related to improvement in glycemic status or antioxidant activity (489,490). When administered with vitamin C (1,250 mg daily), vitamin E (680 IU daily) is associated with decreased urinary albumin excretion in type 2 diabetes (491). Nevertheless, when these weak positive data are considered in conjunction with the strong negative data cited in the previous paragraph, the use of vitamin E in patients with diabetes is not supported (grade D).

12.1.3. Chromium

Chromium is taken orally by individuals in attempts to control diabetes (type 1 and type 2), to induce weight loss and lowering of lipid levels, and to enhance athletic performance. Moreover, chromium is part of several standard multiple trace element intravenous preparations used in parenteral nutrition, and additional intravenously administered chromium may be prescribed when large doses of insulin are required to control severe hyperglycemia with parenteral nutrition. Chromium is contained in "glucose tolerance factor," which increases insulin sensitivity. Low-molecular-weight chromium-binding substance (chromodulin), which functions in a manner similar

to calmodulin (a calcium-binding protein), is maintained as an apo-oligopeptide that binds four chromic ions in response to a chromium flux (492). The resulting holoprotein then activates insulin receptor tyrosine kinase activity and improves insulin action (493). Chromium picolinate is purported to sensitize central nervous system glucoceptors to insulin; the results are appetite suppression, activation of the sympathetic nervous system and thermogenesis, and down-regulation of insulin secretion.

Because insulin has also been found to promote collagen synthesis by osteoblasts, raise levels of DHEAS which is thought to preserve postmenopausal bone density, and antagonize parathyroid hormone-mediated bone resorption, chromium has been used in metabolic bone disease (494). Nevertheless, clinical data are lacking regarding this indication for use of chromium (grade D).

The upper limit of the estimated safe and adequate daily dietary intake for chromium is 50 to 200 μg. Most Western diets provide less than this amount. Common doses recommended by manufacturers for use in diabetes are in the range of 200 μg orally one to three times a day. With use of daily doses of 1.2 to 2.4 mg, anemia, thrombocytopenia, hemolysis, hepatic dysfunction, and renal failure can develop. Vitamin C and zinc can augment chromium absorption, and niacin can potentiate the effects of chromium on glucose tolerance.

In a placebo-controlled trial, use of 200 μg of chromium daily reduced insulin, sulfonylurea, and metformin requirements, and greater effects were noted in type 2, compared with type 1, diabetes and in women with either type of diabetes in comparison with men (495). In another placebo-controlled trial of 76 patients with atherosclerosis, 250 μg of chromium daily for 7 to 16 months lowered serum triglyceride levels and increased HDL cholesterol levels (496). These results were confirmed by Lee and Reasner (497). Uusitupa et al (498), however, demonstrated that a daily dose of 160 μg of chromium failed to improve glycemic or lipid status in elderly patients with impaired glucose tolerance. In two studies by Anderson et al (499,500) of 3 groups of 60 Chinese subjects each, 500 μg of chromium administered orally twice a day improved glycemic control and cholesterol levels in comparison with 100 μg orally twice a day or placebo. High-dose biotin, 3 mg orally three times a day, enhances glucokinase gene expression and suppresses phosphoenolpyruvate carboxykinase activity, to achieve a net improvement in insulin sensitivity (501). For this reason, biotin has been thought to potentiate the effects of chromium (501).

In contrast, Thomas and Gropper (502) failed to detect any benefit of chromium (200 μg orally daily), complexed with nicotinic acid, on insulin, glucose, or lipid concentrations. Moreover, in obese women who did not exercise, chromium supplementation (400 μg orally daily) was associated with weight gain (503). A combination of zinc (30 mg/day orally) and chromium (400 μg/day orally) administered for 6 months also failed to improve HbA1c levels, even though antioxidant activity could be demonstrated (504). An uncontrolled pilot study by Trow et al (505) likewise failed to demonstrate beneficial effects of chromium, 100 μg orally daily for 8 weeks, on insulin and lipoprotein levels.

Collectively, the presence of inconclusive level 1 to 3 data, and ample level 4 opinion and theory pertaining to the benefit of chromium in diabetes, results in a grade D. This body of literature represents a good example of a DS/N with available clinical data, but because the results are inconclusive, chromium has unproven effectiveness and cannot be recommended. This assertion is principally influenced by the meta-analysis by Althuis et al (506), in which data from 15 randomized, controlled trials involving 618 participants with and without diabetes failed to demonstrate any conclusive beneficial effect of chromium on glucose, insulin, or HbA1c levels.

In patients with manifestations of chromium deficiency (hyperglycemia, hyperlipidemia, peripheral neuropathy, and low chromium levels), however, the use of enteral or parenteral chromium therapy is clinically obvious (all-or-none indication: level 1; grade A).

12.1.4. Vanadium

Another trace element often used by individuals for the management of diabetes is vanadium. This element is also used for self-treatment of hypoglycemia, hypercholesterolemia, heart disease, edema, and cancer as well as for enhancing athletic performance. Limited clinical data demonstrate an effect of vanadium on bone growth, cardiac inotropy, diuresis, and natriuresis. Vanadium can also mimic insulin by phosphorylating insulin-sensitive receptors; thus, carbohydrate oxidation and glycogen synthesis are stimulated, and hepatic gluconeogenesis and lipolysis are inhibited.

One of the first described cellular actions of vanadium was inhibition of the sodium-potassium adenosinetriphosphatase enzyme. Recently, however, investigations have shown that vanadyl, the reduced form of vanadium, also modifies certain metabolic steps integral to early insulin signaling, such as insulin receptor activity and substrate tyrosine phosphorylation (507). Vanadium does not modify the action of insulin to stimulate glycogen synthesis (507).

Adverse effects include mutagenesis, carcinogenesis, and interference with mitosis and chromosomal distribution. Vanadium can also cause gastrointestinal, renal, and neurologic symptoms. Usual intakes range from 10 to 60 μg daily (508). Toxic effects, including death, occur with doses exceeding 20 mg daily. At 60 to 120 mg daily, vanadium can be lethal. Food sources rich in vanadium are skim milk, seafood (lobster), oils, cereals, grains, and vegetables. One 10-mg tablet of vanadyl sulfate contains 3.1 mg of elemental vandium.

In a randomized, double-blind, placebo-controlled study, diet plus exercise plus use of a nutritional supplement containing vanadium for 4 weeks resulted in greater loss of body fat in 56 subjects compared with 67 control subjects (509). In contrast, however, Fawcett et al (510) studied the effects of daily oral administration of 0.5

mg/kg of vanadyl sulfate on body composition and performance in a 12-week, double-blind, placebo-controlled trial in 31 athletes and failed to detect any significant difference.

Vanadyl has pro-oxidant activities on lipoproteins in patients with diabetes. With use of euglycemic hyperinsulinemic clamps and oral glucose tolerance testing, vanadyl sulfate, 100 mg/day for 3 weeks, was found to improve hepatic and peripheral insulin sensitivity, through enhancement of insulin inhibition of lipolysis, in patients with type 2 diabetes but not in normoglycemic subjects (511,512). Similar results were found by Boden et al (513), who administered smaller doses (50 mg orally twice a day) of vanadyl sulfate for 4 weeks in eight patients. In a later study by Goldfine et al (507), higher doses of vanadyl sulfate (150 and 300 mg daily for 6 weeks) improved glucose metabolism (assessed by euglycemic insulin clamp, fasting blood glucose values, and HbA1c levels), whereas no improvements were seen with lower doses (75 mg daily). Adverse gastrointestinal symptoms were associated with the higher doses without tissue oxidative stress (507). New organically chelated compounds of vanadium that are more potent and less toxic have been developed (514). Lastly, in a study of 11 patients with type 2 diabetes, vanadyl sulfate, 150 mg/day for 6 weeks, was found to improve hepatic and muscle insulin sensitivity (515). This outcome correlated with endogenous glucose production but not insulin-mediated glucose disposal (515). These results support the liver, and not muscle, as the principal site of action of vanadyl sulfate. Overall, because of the lack of conclusive level 1 and 2 data and the narrow therapeutic window, and excessive risk with long-term exposure, the use of vanadyl sulfate in type 2 diabetes mellitus merits a grade D.

12.2. Choline and Hyperhomocysteinemia

Choline is a required nutrient for humans. In addition to deficiencies in vitamin B_{12}, vitamin B_6, and folic acid, hyperhomocysteinemia can result from inadequate dietary choline. Eggs are a particularly rich source of choline. Adequate choline intake ensures structural and functional integrity of cell membranes, normal cellular and nerve signaling, and efficient lipid transport and metabolism (516). Choline is a major source of methyl groups, and its metabolite, betaine, participates in the methylation of homocysteine to form methionine. Deficiencies in taurine and betaine are also associated with hyperhomocysteinemia, and "B-complex" supplements containing these agents are commercially available. Betaine can increase levels of *S*-adenosylmethionine, which can decrease hepatic steatosis (517). When added to folic acid, vitamin B_{12}, and vitamin B_6, choline—with or without betaine and taurine supplementation—can prevent the development of hyperhomocysteinemia due to minor genetic defects (518) (grade C). If choline is excluded from a total parenteral nutrition admixture in patients receiving this treatment on a long-term basis, choline deficiency and hepatopathy may ensue. Liver function abnormalities can then be reversed with choline supplementation (519) (grade C). Increased choline intake is also recommended by the Food and Nutrition Board of the National Academy of Sciences for pregnant and breast-feeding women, to support fetal brain development (516,520) (grade A).

12.3. Melatonin

Melatonin is produced by the pineal gland during darkness and regulates circadian rhythms and sleep. It also participates in the timing of puberty, regulation of body temperature, cardiovascular-autonomic function, immune function, tumorigenesis, and free-radical scavenging. People use this agent for insomnia, tardive dyskinesia, shift-work disorders, immune enhancement, tinnitus, depression, antiaging, contraception, and adjunctive cancer therapy. Menopause is thought to be associated with desynchronized pineal circadian rhythmicity and deranged pineal-hypothalamic controlled ovarian cyclicity. In a randomized, double-blind, placebo-controlled study, melatonin, 3 mg orally every day a bedtime, was found to be a mood enhancer and antidepressant during the perimenopausal period (521). Melatonin, however, can worsen depression, can interact with sedative-hypnotics, atenolol, verapamil, and immunosuppressants, and can reduce glucose tolerance and insulin sensitivity in postmenopausal women (522-524).

In a randomized, double-blind, placebo-controlled, crossover trial involving 22 patients, melatonin, given in a daily dose of 5 mg for 4 weeks, improved subjective and objective measures of "delayed sleep phase syndrome" (525). With a mean daily dose of 5.4 mg, melatonin was also found to improve the quality of sleep in a randomized, double-blind, placebo-controlled study of 33 medically ill patients (526). At a lower daily dose of 3.6 mg of sustained-release melatonin, taken 30 minutes before daytime sleep, night workers experienced improved sleep, but this effect diminished with dosing on consecutive days (527). At still lower, physiologic doses of 0.3 mg of melatonin daily, sleep efficiency was also restored in geriatric patients with low nocturnal melatonin levels (528). The chronobiologic efficacy of melatonin or melatonin agonists with time shifts (jet lag) has been demonstrated with level 3 data (529,530).

Pineal indolamines also modulate interleukin-2- and interleukin-12-dependent anticancer immunity (531). In phase 2 studies involving solid tumors and hematologic malignant conditions, melatonin, 20 mg/day, amplified the efficacy of cytokine therapy (531,532). Melatonin has also been found to control tumor growth by acting as an antiangiogenic molecule through lowering of vascular endothelial growth factor levels (533).

Overall, several conclusive level 3 studies have demonstrated the benefit of melatonin on sleep (grade C); however, these effects are dependent on the dose, and adverse effects and tolerance occur at higher doses. One level 3 study links beneficial melatonin use with behavior in the perimenopausal period (grade C). The theories linking melatonin with anticancer therapy are attractive but devoid of conclusive evidence (grade D).

12.4. Obesity

Many DS/N and nonprescription products have been studied as potential remedies for obesity. Among 14,679 adults randomly surveyed by telephone from 1996 to 1998, 7% reported overall use of nonprescription weight loss products, with 2% using phenylpropanolamine (which has since been withdrawn from any use in the United States by the FDA) and 1% using *Ephedra* (534). Allison et al (535) reviewed 18 alternative-care treatments and, despite "plausible mechanisms of action" and "encouraging preliminary data," found that none was demonstrated to be safe and effective by more than one PRCT in a peer-reviewed journal.

Many antiobesity DS/N are collectively contained in various patented combinations and therefore violate the a priori methods for evidence-based recommendations in these guidelines, namely, that DS/N evidence should be gleaned from studies that use a single agent at a time. In a retrospective, nonrandomized study by Sindler (536), the use of two combination herbal supplements, one without prescribed medication and the other with phentermine, was associated with weight loss (79% and 87% of the patients lost >0.5 lb/wk, respectively; level 3 data). As pointed out in an editorial in the same issue of *Endocrine Practice* (537), however, this result corresponded to an average of only 5 to 6% weight loss, which is comparable to the placebo group studied by Weintraub et al (538). Other studies have examined the antiobesity effects of other single DS/N: medium-chain triglycerides (levels 2 and 3) (539,540), linoleic acid (levels 2 and 3) (541,542), and certain combinations, such as ma huang-guarana (*Ephedra*-caffeine) (levels 1 and 2) (543-545) and antioxidants-lipotropic nutrients (level 2) (509). These studies are limited by design flaws, short-term observation periods (less than 1 year), small sample sizes, or a demonstrable benefit that does not outweigh the demonstrable risks (particularly with *Ephedra*; grade D). Examples of antiobesity DS/N are presented in Table 14.

Because the principle of "do no harm" cannot be guaranteed in light of (*1*) the multiplicity and complexity of DS/N-food-medication interactions and (*2*) the lack of sufficient scientific substantiation to outweigh potential risks, AACE cannot recommend the use of any DS/N or nonprescription product for obesity management (grade D). Lifestyle changes, including diet and exercise, along with approved, proven medical therapies remain the mainstay of antiobesity therapy.

12.5. Hypothyroidism

Three broad categories of DS/N are marketed as enhancing thyroid function. The first are products containing iodine that are purported to increase thyroid function.

Table 14
Dietary Supplements and Nutraceuticals and Nonprescription Products Used as Antiobesity Agents

Alisma root	Gymnemic acid
Angelica dahuricae root	Hawthorn berry
Angelica sinensis root	Hibiscus acid
Arabinose	Hydroxycitrate (*Garcinia cambogia*)
Arginine	Inulin
Benzocaine	Jujube seed
Caffeine (guarana)	Leucine
Capsicum	Magnesium
Carnitine	Niacin
Chitosan	*Nomame herba*
Chromium picolinate	Notoginseng
Codonopsis root	Phenylalanine
Ephedrine (ma huang)	Phenylpropanolamine
Eucommia bark	Prebiotics and probiotics
Folic acid	Pyridoxine
Garlic	Rehmannia root
Ginkgo biloba	Riboflavin
Ginseng	Schizandrae berry
Glycine	St. John's wort
Green tea (catechins)	Thiamine
Griffonia seed extract (L-5-hydroxytryptophan)	Vanadyl sulfate
	Vitamin B_{12}

The most popular among these products is kelp. Potential adverse effects include hyperthyroidism (546) and allergic reactions. No data support the role of iodine in enhancing thyroid function (grade D). The effects of iodine on thyroid hormone release and synthesis are well established in hyperthyroidism.

The second category of DS/N used as thyroid function enhancers contains tyrosine. This application is based on the claim that tyrosine is a substrate for the biosynthesis of thyroid hormone. No published data, however, support the claim that ingestion of tyrosine increases the production of thyroid hormone (grade D).

The third category of DS/N used as thyroid hormone enhancers are thyroid hormone extracts or analogues. The unregulated availability and distribution of desiccated porcine or bovine thyroid through health food stores, mail order catalogues, and the Internet are associated with undertreatment or overtreatment of true hypothyroidism or with hyperthyroidism in persons with normal thyroid function (547). Tiratricol, or TRIAC (3,5,3′-triiodothyroacetic acid), is a metabolite of levothyroxine with intrinsic thyromimetic activity. At low doses, tiratricol can inhibit pituitary secretion of thyroid-stimulating hormone (thyrotropin) and has been used as a treatment for selective pituitary resistance and thyrotropin-dependent hyperthyroidism (548). At higher doses, however, significant metabolic stimulation, symptoms of hyperthyroidism, and frank thyrotoxicosis can occur (549). Hence, tiratricol is marketed not only as a regulator of thyroid function but also as a "fat burner." Nevertheless, no available data support an effect of tiratricol on fat catabolism (grade D). Sherman et al (550) studied 24 athyreotic patients randomized to treatment, titrated to suppress thyrotropin to less than 0.1 mU/L, with levothyroxine (1.9 μg/kg daily) or tiratricol (24 μg/kg twice a day). After 2 months of treatment, similar effects were noted on cardiovascular function, resting metabolic rate, body weight, urinary urea nitrogen excretion, and the thyrotoxicosis symptom score in both groups (550). The tiratricol-treated patients, however, had augmented hepatic and skeletal effects in comparison with the levothyroxine-treated patients (550). A pituitary-specific effect of tiratricol was not supported by this study. The FDA banned several tiratricol-containing products, but others are still available to the public. AACE does not recommend the use of any desiccated thyroid product or thyroid analogue as a "regulator" or "enhancer" of thyroid function (grade D).

ACKNOWLEDGMENT

AACE wishes to thank Coram, Inc., for providing an unrestricted educational grant in support the publication and distribution of this educational resource.

DISCLAIMER

AACE Medical Guidelines for Clinical Practice are systematically developed statements to assist health-care professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflect the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information on conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

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