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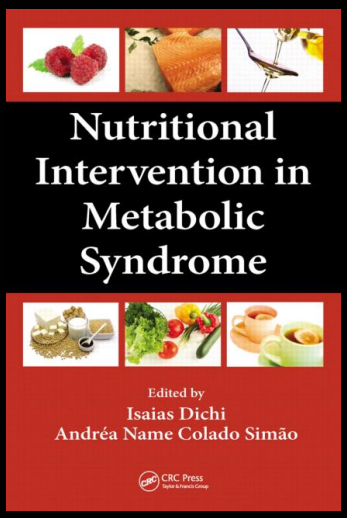

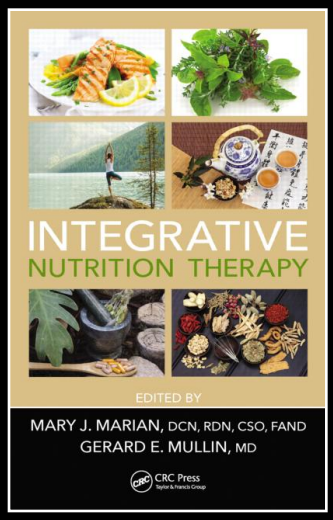

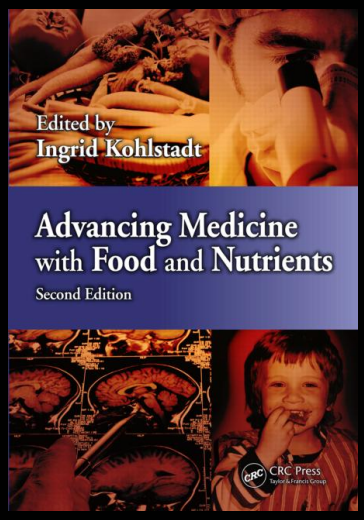

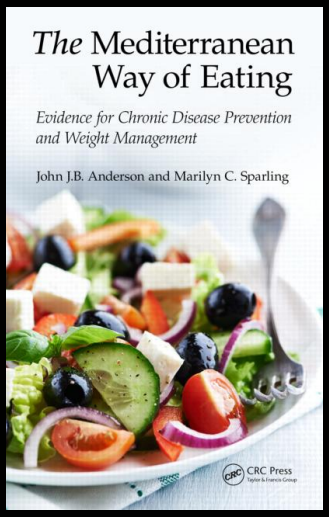

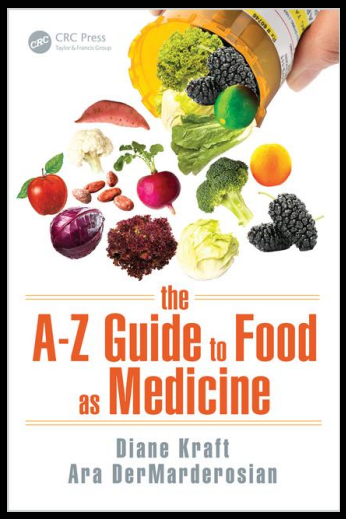

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Introduction

About this FreeBook

This FreeBook, *Food as Medicine*, is relevant to healthcare professionals and consumers including nutritionists and dietitians. This book features content from a range of CRC Press, include:

Introduction to the Health Benefits of Mediterranean-Style Dietary Patterns from *The Mediterranean Way of Eating: Evidence for Chronic Disease Prevention and Weight Management*, written by John J.B. Anderson and Marilyn C. Sparling
This book offers evidence-based information about an enjoyable, healthy way of eating that has stood the test of time, along with practical suggestions for incorporating the Mediterranean diet into your daily life.

The Letter "F" from *The A–Z Guide to Food as Medicine*, written by Diane Kraft and Ara Der Marderosian
This dictionary-style reference is intended for use by healthcare professionals and addresses food folklore by exploring the scientific findings about physiological effects of over 250 foods, food groups, nutrients, and phytochemicals.

Vitamin D in Metabolic Syndrome from *Nutritional Intervention in Metabolic Syndrome*, edited by Isaias Dichi and Andrea Name Colado Simao
Written by experts, this book brings together coverage of dietary patterns and dietary components to create a complete understanding of the mechanisms by which these diets and components may improve metabolic syndrome. It then presents information on how to treat MS through lifestyle change and nutritional intervention.

Nutrition and Mental Health from *Integrative Nutrition Therapy*, edited by Mary J. Marian and Gerard Mullin, MD
Intended for consumers and health care professionals, this book provides practical guidance on integrating nutrition therapies into disease prevention and management. It presents reliable and accurate information from experts in the nutrition field including dietitians, nutritionists, physicians, researchers, and academic professionals. Also included is information on dietary supplements, popular diets, physical activity, and food allergies.

Acne and Diet from *Advancing Medicine with Food and Nutrients, Second Edition*, edited by Ingrid Kohlstadt

This bestselling book offers an in-depth review of the evidence to support the role of nutrition in health promotion and disease prevention. The second edition expand its coverage to address issues in food safety, consumer advocacy, and preventative medicine.

Please note this Free Book does not include references, endnotes and footnotes. Fully referenced versions of each book can be accessed through crcpress.com .

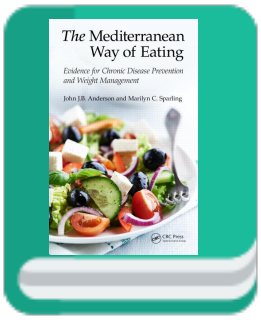
CHAPTER 1

What Is a Mediterranean Diet?

Common Components in Diverse Dietary Patterns Promote Health

Chapter 1: What Is a Mediterranean Diet?

Common Components in Diverse Dietary Patterns Promote Health



The following is excerpted from *The Mediterranean Way of Eating: Evidence for Chronic Disease Prevention and Weight Management* by John J.B. Anderson, Marilyn C. Sparling.

Learn more:

INTRODUCTION

Many books have been written about the benefits of what is generally known as the Mediterranean diet. Most books have focused on recipes and meal plans. This book offers a wider scope that emphasizes the health benefits that the Mediterranean people may derive from the nutrients of the foods consumed in this region. This book also provides a modest amount of the nutritional science lying behind the observations that the nutrient-rich dietary patterns of the Mediterranean countries contribute to good health and demonstrates how these eating patterns can be readily adapted to non-Mediterranean populations throughout the world. The historical changes in improving food availability in Mediterranean populations has led to the consumption of diverse foods that reduce the chances of having low or even deficient intakes of one or more nutrients. In our busy lives, we can utilize a wide variety of wholesome, delicious foods the Mediterranean way and enrich ourselves by living longer, feeling better, and reducing the burden of chronic diseases.

The focus here is placed on the beneficial effects on the health of those Mediterranean's who consume what is known as the traditional diet based on plant foods, fish and other seafood, olives, cheese, and red wine, plus limited servings of animal and dairy products. This type of diet exerts a strong preventive role against the development of the major chronic diseases, such as obesity, type 2 diabetes, cardiovascular diseases, diet-related cancers, and others. Because the basic Mediterranean diet can be transferred to other parts of the world, this eating pattern provides foods that as a whole can serve in the promotion of global health and the prevention of disease.

The basis of a healthy diet is a variety of foods that provide all the essential nutrients and phytochemicals (non-nutrient plant molecules) but not excessive amounts of calories. Recently, dietary pattern analysis, as opposed to assessing individual nutrients or foods, has been used as an alternative approach to understanding the relationships between the usual diet and health of a population. The Mediterranean pattern of eating has been studied using this method with respect to cardiovascular disease, type 2 diabetes mellitus, and other chronic diseases, and it has yielded important findings that establish the contributions of this dietary pattern to the promotion of health and the prevention or delay of these diseases. These diseases are covered in Chapters 4 through 6.

Chapter 1: What Is a Mediterranean Diet?

Common Components in Diverse Dietary Patterns Promote Health

John J.B. Anderson and Marilyn C. Sparling

Highlight: The basis of a healthy diet is a variety of foods that provide all the essential nutrients and phytochemicals but not excessive amounts of calories.

FACTORS CONTRIBUTING TO DIVERSE MEDITERRANEAN DIETARY PATTERNS

One Mediterranean diet does not exist for the entire region, but rather many variants of the Mediterranean eating pattern exist in the nations that border the Mediterranean Sea. .

Figure 1.1 Nations bordering the Mediterranean Sea. National Geographic and Esril have collaborated to produce a multiscale, general reference map of the world. (National Geographic, Esri, DeLorme, NAVTEQ, UNEP-WCMC, USGS, BASA, ESA, METI, NRCAN, GEBCO, NOAA, iPC.) The basemap is available for use by the general public for educational purposes. This map is the basemap to illustrate the Mediterranean area for this book.

John J.B. Anderson and Marilyn C. Sparling

Although the pattern of eating is similar in all these nations, variations in dietary patterns do exist. Nations within this region differ with respect to culture, tradition, religion, soil and agricultural capabilities, and socioeconomic status, all of which affect dietary patterns. See Figure 1.1 for a map of the Mediterranean region.

At the intersection of the Old World—Asia, Europe, and North Africa—the Mediterranean Sea served as a prominent navigational route for trade and exchange in earlier times. The spice trade is one important example that enriched the culinary traditions of most Mediterranean nations. Also, the influence at different times of Greek, Roman, Byzantine or Ottoman, and Moorish cultures on food preferences and ways of preparation has had impacts on practically all Mediterranean countries. Most people have lived near the coast or in fishing villages at the edge of the sea, and most communication had historically been by way of watercraft. Climate and geography vary in and among these countries, such as from coastal areas to inland and mountainous regions, which affects the types of foods that can be grown. Religion also has an impact on food choices.

Highlight: One Mediterranean diet does not exist for the entire region, but rather many variants of the Mediterranean eating pattern exist in the nations that border the Mediterranean Sea.

This diversity of eating patterns, however, is strongly based on plant-rich diets, including fruits, vegetables, legumes, whole grains, nuts, and seeds. When animal foods are consumed, the emphasis is on readily available fish and seafood and less so on red meats, in part because of limited land for animal husbandry. Local fishers for millennia have caught fish and other seafood, but their consumption historically has been limited to proximity to the coastal ports. Most plant foods in traditional Mediterranean diets also have been produced locally, but exceptions occur when poor soil, weather, topography, or other adverse conditions curtailed panagriculture. A few representative foods of the Mediterranean dietary pattern are given in Table 1.1.

Another similarity in dietary patterns of the Mediterranean region is the commitment to family activities, such as sitting down daily for a leisurely paced meal with conversation. Only recently have fast foods, heavily processed foods, and other changes in the food supply had major impacts on the traditional diets and lifestyles of peoples in the Mediterranean nations. Family values, roles of women in the workforce, and technological advances have helped hasten these changes, also observed in much of the rest of the world.

John J.B. Anderson and Marilyn C. Sparling

TABLE 1.1
Representative Foods of the Mediterranean Dietary Pattern by Major Food Groups

Plant Foods	Animal Foods	Wines
Fruits	Fish and seafood	Reds
Vegetables	Meats, poultry, and eggs	Whites
Olives and olive oil	Cheese and yogurt	
Legumes		
Grains		
Nuts		
Seeds		

Note: Preferences of specific foods vary from region to region, but plant foods are emphasized in all nations. Seasonal changes determine which foods are likely to be available in markets.

Nu

Early humankind likely needed large intakes of food to meet the energy needs of daily living in challenging environments. Protein consumption was probably low in most early cultures, although a few hunter–gatherer types must have consumed large quantities of wild game and, hence, more animal protein than typical plant gatherers. Physical size in early cultures was typically much different from today; people were shorter, and they weighed less, as it was difficult to consume enough calories and protein to optimize growth (height) and support bodily needs. Despite early cultures being successful in survival and reproduction, they nevertheless had suboptimal growth and development. Muscular development, however, was considered to be optimal in these early times because of the physical demands of hunting; gathering water, food, and wood for fires; and later farming, without the current availability of machines.

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Overweight or obesity was probably nonexistent in early cultures and has only emerged as some populations became relatively wealthy. Survival of the fittest back then related mainly to both physical and mental well-being— and obese individuals, if any existed, had little likelihood of surviving.

MEDITERRANEAN FOODS AND THEIR COMPONENTS CONTRIBUTE TO HEALTHY DIETS

The mixing of a variety of healthy food items in the same meals over time leads to a healthy diet. In early cultures, the healthy mix of foods was learned by trial and error. These diets contained major carbohydrates from plant sources, protein predominantly from plant sources such as legumes, fat mainly from olive oil but to a lesser extent also from fish and animal products, and micronutrients (i.e., minerals and vitamins) from all food items but especially plants. Phytochemicals were provided by a wide variety of plant sources in the diet. Alcohol use was highly variable in the dietary patterns of early cultures, but likely only small amounts, if any, were consumed. The classic report by Christakis (1965) initiated the study of the health benefits of Mediterranean dietary patterns.

The emphasis on plant foods in a Mediterranean-style dietary pattern distinguishes this diet from most Western-style diets, which are more heavily based on animal foods. The typical plant foods include fruits, vegetables, legumes, whole grains, nuts, and seeds, as well as herbs and spices. Figure 1.2 presents the Mediterranean Diet Pyramid by the Oldways Preservation and Trust organization (http://oldwayspt.org) and illustrates the foods found in Mediterranean diets in a multitier system: The lowest tier contains foods consumed in the greatest quantity each day, and the second and subsequent tiers list foods consumed in progressively less amounts each day. Animal foods are typically consumed in low-to- moderate amounts and in modest serving sizes; cheeses largely replace liquid milk. Olive oil is the preferred oil used for cooking, on breads, and in salads. Wine is typically consumed at a meal in many Mediterranean diets. This traditional general pattern of eating was accompanied by a fairly active lifestyle, but modern devices have reduced energy expenditures in daily activities, and the intakes of more sugar, fat, and fast foods have partially eroded the health benefits of Mediterranean eating patterns in these populations. Figure 1.3 depicts the U.S. Department of Agriculture's healthy eating plan, called MyPlate.

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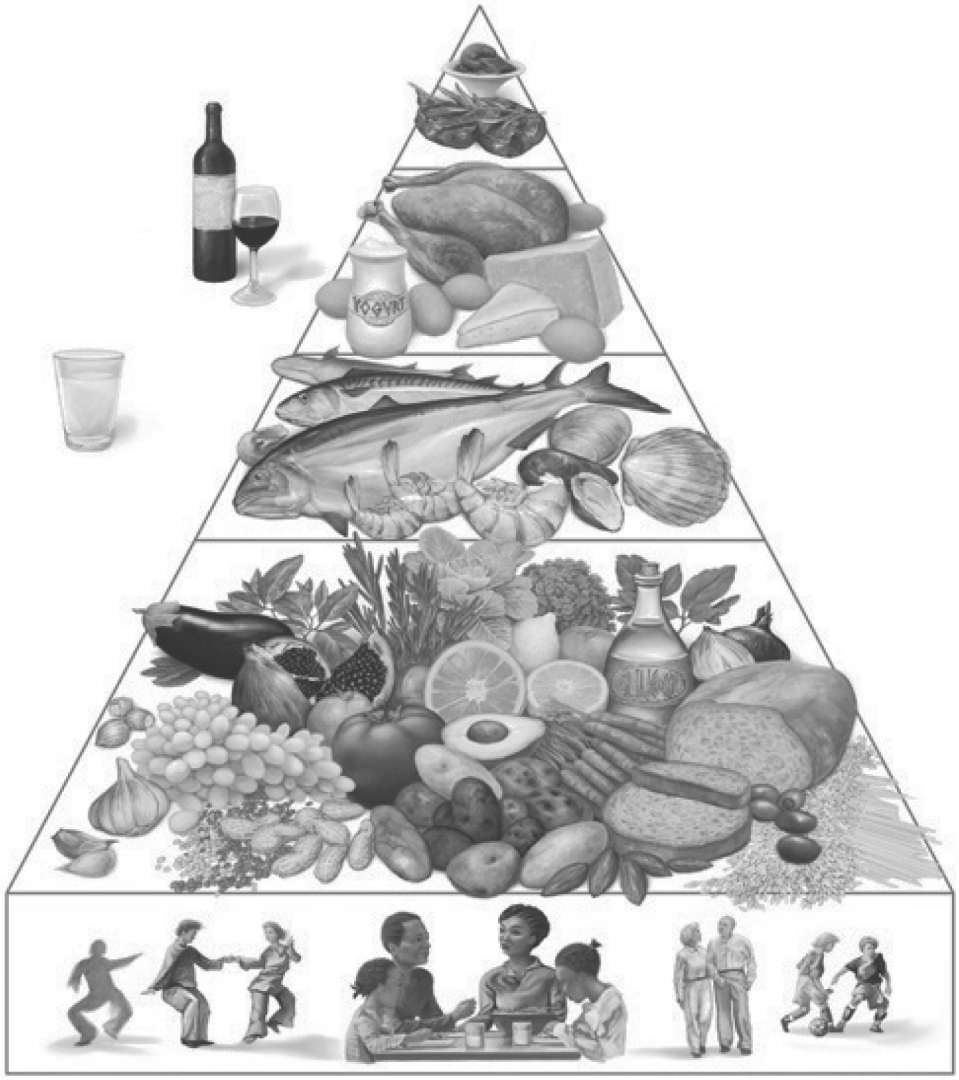

Figure 1.2 Mediterranean diet pyramid. (© 2009 Oldways Preservation and Exchange Trust, http://oldwayspt.org.)

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NUTRIENT COMPONENTS OF HEALTHY DIETS

The components of healthy diets, while somewhat variable in terms of specific foods, contain similar food items that provide the essential nutrients in sufficient amounts to support life. Macronutrients, carbohydrates, fats, proteins, and micronutrients, vitamins, and minerals, along with phytochemicals, all contribute significantly to human health and well-being (see Table 1.2). The types, amounts, and variety of foods we consume that contain, or do not contain, certain nutrients, however, can affect our health either in positive ways or in negative ways. Further information on the nutrient and phytochemical components of healthy diets, such as a Mediterranean-style diet, is discussed in Chapter 3.

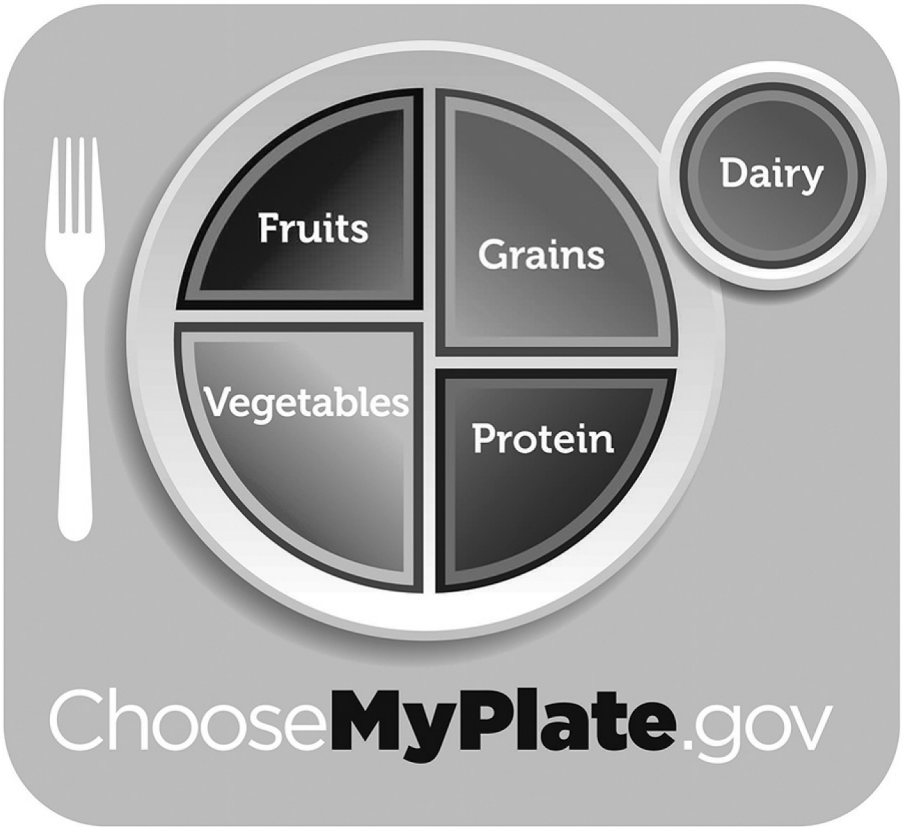

Figure 1.3 MyPlate of the U.S. Department of Agriculture (MyPlate.com). (© 2009 Oldways Preservation and Exchange Trust, http://oldwayspt.org.)

TABLE 1.2
Mediterranean Dietary Contributions of Macronutrients (Carbohydrate, Fat, and Protein) to Total Energy Intake in Kilocalories versus Typical Western Diet

	Total Energy (%)	
Macronutrient	**Mediterranean**	**Western**
Carbohydrate	47	42
Fat	38[a]	38[a]
Protein	15	20
Total	100	100

Source: Pineo, C.E., and Anderson, J.J.B. 2008. *Nutr Today* 43:114–120.

[a] Mediterranean diet contains about 22% of energy from monounsaturated fats versus 14% for the typical Western diet. Polyunsaturated fatty acid percentages are about the same for each dietary pattern.

Table 1.2, Mediterranean Dietary Contributions of Macronutrients

LIFE EXPECTANCY ACROSS THE MILLENNIA

Although difficult to ascertain age of death with no records of early culture, it is known that people long ago lived much shorter lives than today in most developed countries. Infant and child death rates were likely high. Bacterial and viral diseases must have been highly virulent in those whose immune systems were not supported by sufficiently good nutrition (i.e., diets with more high-quality protein and micronutrients). So, these cultures were successful because enough children survived to adulthood, and procreation maintained population numbers for continuation of the group.

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Longevity in the Western world is now quite high, and several nations of the Mediterranean region are among the longest in life expectancy of the world, especially Sardinia, only falling below Japanese living in Okinawa, and possibly a few other countries. Medical and technological advances, of course, have contributed to increasing longevity, but lifestyle, including diet and physical activity, also play an important part. Chronic diseases have replaced infectious diseases as the major killers today in most developed countries. These chronic diseases have reduced rates in Mediterranean populations:

- Heart disease
- Other cardiovascular diseases
- Diet-related cancers
- Obesity
- Hypertension
- Type 2 diabetes mellitus
- Metabolic syndrome

Chapters 4 through 6 discuss how healthy eating patterns, such as the traditional Mediterranean way of eating, can reduce substantially the risks of chronic debilitating diseases and lead to a longer and healthier life.

Highlight: Several nations of the Mediterranean region are among the longest in life expectancy of the world, especially Sardinia.

Lifetime expectancy currently varies among these nations, in part because of the different cultural settings and local diet customs of people living near the Mediterranean Sea. Poverty, of course, has a major impact on health and survival. Life expectancy of the coastal populations is considered to be higher than of the inland residents because of the healthier fish-based diet near the seashore compared to the more meat-based diet of those away from the coast. Chapter 7 introduces the types of foods that have the biggest impacts on diet-related chronic diseases, and then Chapters 8 through 16 follow up with coverage of important aspects of the consumption of specific foods that have favorable impacts on health.

SUMMARY

A healthy diet consists of many specific nutrients and phytochemicals that are needed for growth and to maintain body functions, including reproduction, ambulation, immune resistance

to infection, and other functions. Early humankind often was not successful in consuming sufficient amounts of nutrition-rich foods that permitted survival. Early cultures that did survive typically lived for only a few decades and "eked out" their existence, in part because of suboptimal nutrition. In most Mediterranean dietary patterns, all the essential nutrients in sufficient amounts are provided by the typical foods to support healthy lives throughout the life cycle. Consumption of these substantial and nutrient-complete diets by these nations that border the sea has been largely responsible for their historical success.

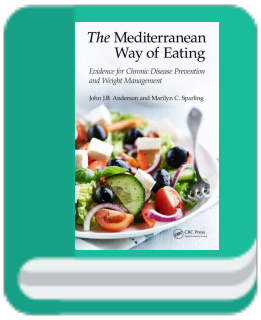
Mediterranean patterns of eating are representative of the most beneficial diets known to humankind. Because they included so many plant foods, including fruits, vegetables, legumes, whole grains, nuts, and seeds, they historically provided just enough calories each day to meet the needs of energy expenditure in daily activities. The major benefit in terms of calories was that individuals did not become obese, as occurs so frequently now in the United States and many other nations. So, calorie control was built into the typical eating pattern with little other constraint on food intake needed.

Adherence to a Mediterranean dietary pattern has been demonstrated to improve health and reduce mortality from many chronic diseases, especially cardiovascular diseases, type 2 diabetes mellitus, and diet-related cancers. Chronic disease rates are generally lower in Mediterranean populations than in other Western nations.

A Mediterranean-style diet can be easily transferred to other nations of the world. See Chapters 17 and 18 for further support of such dietary transfers to other nations and for practical approaches to incorporate a Mediterranean dietary pattern within your own lifestyle.

CHAPTER 2

The A–Z Guide to Food as Medicine, Letter "F"



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Fatty fish

definition

Characteristically strong-flavored fish owing to concentration of fish oils concentration in flesh, as opposed to white fish that has a relatively low fish oil concentration in flesh. Fatty fish are generally excellent sources of protein, vitamin D, and omega-3 fatty acids,1 and supply coenzyme q10. Bluefish, herring, salmon, trout (both wild and farmed), mackerel, sardines, and tuna are fatty fish. Canned sardines with edible bones are excellent sources of calcium: 3 oz supplies 325 mg of calcium. Marination and use October 10th of various seasonings before broiling or grilling can mask the fishy flavor.

scientific findings

Fish oil constituents DHA, EPA, and vitamin D are anti-inflammatory. A meta-analysis of 14 randomized, controlled trials (n = 682; placebo, n = 641) found omega-3 fatty acid consumption improved insulin sensitivity. 7 Fish oil reduces triglycerides by 20%–50%.

bioactive dose

The American Heart Association recommends eating two 3.5-oz servings of (ideally fatty) fish per week.

safety

Presumed safe when consumed in normal dietary quantities by nonallergic individuals. Shark, swordfish, tilefish, and king mackerel (Scomberomorus cavalla), not to be confused with North Atlantic mackerel (Scomber scombrus), are considered high-methyl-mercury fish and therefore should be avoided by pregnant and lactating women; and in addition, pregnant and lactating women may eat no more than 6 oz of

(white) albacore tuna per week. According to a review: "The vast majority of epidemiological studies have proven that the benefits of fish intake exceed the potential risks [of ... contaminated fish] with the exception of a few selected species in sensitive populations."

Fennel (Foeniculum vulgare)

Fennel. (Image from Diana Taliun/Shutterstock.)

Herb with a licorice-like flavor that contains the phenolic compound anethole. Fennel leaves are used to season pork roasts, fennel seeds are used to flavor spicy sausages, and fennel stalks are used in preparing soups or mixed dishes.

scientific findings

Fennel experimentally improved hypertension and glaucoma in animal models. Limited clinical trial data suggest fennel extracts may have the potential to treat infantile colic.

bioactive dose

Not known.

safety

Presumed safe when consumed in normal dietary quantities by nonallergic individuals.

Fenugreek (Trigonella foenum-graecum)

definition

Plant whose leaves are used as an herb and seeds as a spice. Its seeds are also used to make flour. Fenugreek is a common flavor in Middle Eastern foods. It is commonly used to fortify the maple flavor in imitation maple syrup. Flour supplemented with fenugreek fiber has been used in the production of baked goods such as bread, pizza, muffins, and cakes. The first recorded use of fenugreek is described on an ancient Egyptian papyrus dated 1500bc. Folkloric knowledge describes uses of fenugreek to induce childbirth and promote lactation.

scientific findings

Fenugreek reduced serum glucose in diabetes in a few small clinical trials and animal studies. The gum within the fenugreek seed fiber contains galactose and mannose, which are associated with reducing serum glucose and cholesterol. There is not enough evidence to support its use as a galactogogue (to promote breast milk production in lactating women) or a pregnancy inducer.19 Fenugreek fiber significantly increased satiety in a small, single-blind, randomized trial of healthy obese patients.

bioactive dose

Not known. Trials in which fenugreek was employed to reduce glucose have used varying doses and delivery forms; for example, 1 g of fenugreek extract or 100 g of fenugreek seed powder. For hyperlipidemia, 0.6–2.5 g of fenugreek two times daily with meals has been used.

safety

Presumed safe when consumed in normal dietary quantities by nonallergic individuals. Possible side effects of fenugreek when taken by mouth include gas, bloating, and diarrhea. Since fenugreek has uterine stimulant activity, intake of amounts greater than those found in food should be avoided during pregnancy. Since fenugreek has not been adequately studied during lactation for potential harmful effects to the infant or mother, it should be avoided during lactation.

Ferulic acid

definition

Phytochemical found in seeds and leaves made from the metabolism of phenylalanine and tyrosine. Found in high levels in vegetables, fruits, cereals, and coffee with the average intake estimated to be 150–250 mg/day.

scientific findings

In laboratory studies, ferulic acid exhibited antioxidant, antimicrobial, anti-inflammatory, antithrombotic, anticancer, and increased sperm viability effects.

bioactive dose

Not known.

safety

Presumed safe when consumed in normal dietary quantities by nonallergic individuals. Ferulic acid has a low toxicity potential.

Fiber

definition

Nondigestible, structural material in plant foods that is generally categorized into soluble and insoluble types, each varying in water solubility, fermentability, and viscosity, characteristics responsible for distinct physiological effects and unique food characteristics. Soluble and insoluble fibers often occur together in foods. Particularly rich sources of soluble fiber include citrus fruits, apple pulp, apple pectin, infant banana flakes, green bananas, legumes, oat bran, oatmeal, barley, beans, okra, peas, rice bran, and strawberries. Soluble fibers (also called viscous fibers), such as guar gum, pectin, psyllium, and certain hemicelluloses, retain water and form gels within the GI tract, thereby delaying gastric emptying and slowing the transit of food through the upper GI tract, slowing the absorption of nutrients from the small intestine, and entrapping bile salts and cholesterol in the large intestine; in addition, soluble fiber holds moisture in stools, softening them. Rich sources of insoluble fibers include whole-wheat breads, wheat cereals, wheat bran, rye, rice, barley, most other grains, cabbage, beets, carrots, brussel sprouts, turnips, cauliflower, and apple skin. Insoluble fibers, such as hemicellulose and cellulose, serve as bulk that increases fecal weight and promotes stool passage through the colon. The food group that is highest in fiber as a group is legumes (8 g per 1/2 cup serving) followed by vegetables (3 g per 1/2 cup), nuts and seeds (3 g per 1 oz), fruits (2 g per 1/2 cup), and whole-grain products (1–2 g per 1 slice or 1/2 cup). The

usual dietary fiber intake in the United States is 15 g/day and should be increased by expanding variety in daily food patterns to include more and different types of plant foods.

scientific findings

Foods high in dietary fiber are generally low in calories. Dietary fiber intake from whole foods may lower blood pressure, improve serum lipids, and reduce indicators of inflammation. Insoluble fibers help to prevent and alleviate constipation; reduce the risk of diverticulosis, hemorrhoids, and appendicitis; and promote satiety, which may aid in weight management. Soluble fibers help to alleviate diarrhea; reduce fasting plasma cholesterol which is associated with reduced risk of heart disease; and reduce postprandial glycemia, which is associated with reduced risk of diabetes. Soluble fibers may help to modestly reduce LDL cholesterol levels beyond that achieved by a diet low in cholesterol, saturated fat, and transfats alone.

bioactive dose

The Dietary Reference Intakes recommend 14 g dietary fiber per 1000 kcal; the AI for adults aged 19–50 is 25 g/day for women and 38 g/day for men. Due to the bulky nature of fibers, excess consumption is likely to be self-limiting.

safety

There is no UL for fiber. Increasing dietary fiber too quickly can lead to gas, bloating, and cramps. Fiber binds to minerals and increases their excretion; therefore, excessive fiber intake may have adverse effects on mineral absorption. The World Health Organization recommends an upper limit of 40 g/day.

Fig (Ficus carica)

Fig. (Image from oriori/Shutterstock.)

Purple snack fruit that is approximately the size of a ping-pong ball. It is mild in flavor and full of small edible seeds. Figs are a good source of fiber. Phytochemical components include phenolics, coumarins, flavonoids (e.g., anthocyanins, quercetin, luteolin), and terpenoids. Consumed fresh, dried, as jam, and made into fruit filling for baked products. Used orally as a laxative, for diabetes, hyperlipidemia, eczema, psoriasis, and vitiligo, although there is no reliable evidence to evaluate the effectiveness of fig for any of these conditions

scientific findings

The equivalent of one small, fresh fig produced a measurable increase in plasma antioxidant capacity in a small study (n = 10 healthy subjects).

bioactive dose

Not known.

safety

Presumed safe when consumed in normal dietary quantities by nonallergic individuals. Fig can cause allergy, and in rare cases, anaphylaxis.

Flavonoids

definition

Class of hundreds of structurally unique phytochemicals that are relatively common in the average American diet, and which "... are usually subdivided according to their substituents into: anthocyanidins, catechins, chalcones, flavones, flavonols, flavanones, and isoflavones." "Flavonoids provide the bright orange, yellow, and red pigments of various foods, along with characteristic flavors, such as the hearty taste of whole-wheat foods or the bitter taste of red grapes." Flavonoids are found in citrus fruits and citrus-based juices, other fruits, vegetables, grains, nuts, seeds, spices, flowers, tea, red wine, and products made from soy and cocoa beans. Plants and spices containing flavonoids have been used for thousands of years in traditional Eastern medicine. Flavonoids are transported in serum by albumin, thus, theoretically, protein malnutrition may reduce serum circulating levels of flavonoids.

scientific findings

"Flavonols, flavanones, and flavones are subclasses of flavonoids that exert cardioprotective and anticarcinogenic properties *in vitro* and *in vivo*." Some experimental evidence indicates that flavonoids could prevent prostate cancer. Dietary flavonoid intake and black tea, a major source of *flavonoids,* were associated with a decreased risk of advanced

stage prostate cancer in the Netherlands Cohort study (n = 58,279 men).

bioactive dose

Not known.

safety

Presumed safe when consumed in normal dietary quantities by nonallergic individuals.

Flaxseed (Linum usitatissimum)

Flaxseed. (Image from hsagencia/Shutterstock.)

definition

Usitatissimum, or "most useful," is ascribed to flaxseed because it is a source of food products such as grains, seeds, and oil, and a source of fiber, which can be made into linen. Flaxseeds are a good source of iron and potassium with 1/4 cup supplying 341 mg of potassium (7% DV) and 2.4 mg of iron (13% DV),45 omega-3 fatty acid, and β-sitosterol. Flaxseeds, flaxseed cereals and breads, and flaxseed oil may require

refrigeration to prevent rancidity; the oil should not be heated to high temperatures.

scientific findings

Flaxseed is an effective bulk-forming laxative. According to a review, studies of flaxseed preparations used to reduce cholesterol levels have been inconclusive; however, a review of six clinical trials found that those using various flaxseed preparations significantly reduced total cholesterol and LDL cholesterol in people with both normal and high cholesterol levels, and flaxseed has additional LDL-lowering capabilities when used concomitantly with statin medications. However, flaxseed does not improve triglyceride levels, and a certain type of flaxseed (defatted flaxseed with reduced linolenic acid content) may have raised triglycerides in a clinical trial. Flaxseed lignan, a component of flaxseed but not flaxseed oil, had no effect on bone mineral density body composition, lipoproteins, glucose, or inflammation in a small, randomized, placebo-controlled study (n = 100 adults aged ≥50). β-sitosterol is "likely effective" for symptoms of enlarged prostate, and improved urinary symptoms, increased maximum urinary flow, and decreased postvoid residual urine volume; however, it did not affect prostate size in clinical trials according to a review. Taking flaxseed improved renal function in patients with systemic lupus erythematosus nephritis in two clinical trials. Study results are mixed on whether flaxseed decreases hot flashes.

bioactive dose

A dose of 3–50 g (1 teaspoon–5 Tablespoons) of flaxseed daily reduced total cholesterol by 5%–9% and LDL cholesterol by 8%–18% in the majority of clinical trials performed.

safety

Presumed safe when consumed in normal dietary quantities by nonallergic individuals; however, severe allergic reactions have been reported to flaxseed and flaxseed oil, and those with known allergy to any member of the Linum genus should avoid flaxseed products. Flaxseed may stimulate menstruation and animal studies have shown possible harmful effects during pregnancy; therefore, the use of flaxseed or flaxseed oil during pregnancy and breastfeeding is not recommended.

Folate

definition

Water soluble vitamin involved in the manufacture of DNA necessary for cell division and tissue growth. Folate deficiency impairs cell division and protein synthesis and can cause megaloblastic anemia. Folate requires vitamin B12 to be converted to a form necessary to manufacture DNA. Synthetic folic acid is more bioavailable than naturally occurring folate. The quantity of this vitamin in the diet, though measured in micrograms, may be expressed in Dietary Folate Equivalents to encompass the absorption difference between the synthetic form, found in commercial grain products, and the natural form found in fruits, vegetables, and "foliage" such as spinach, in addition to legumes, beets, and orange juice.

scientific findings

To reduce the risk of in utero neural tube defects, women of reproductive age should consume 400 µg of folate/folic acid daily beginning before pregnancy, and 600 µg of folate/folic acid throughout gestation. High dietary intake of vegetables during pregnancy reduces the risk of folate deficiency. Folate deficiency impairs cell division and protein synthesis, and can cause megaloblastic anemia. Several, but not all, epidemiologic studies provide evidence of an inverse relationship between folate intake

and the risk of pancreatic cancer, according to Sanchez et al. Observational studies suggest that low folate status, particularly in women, is associated with depression. A diet rich in folate may reduce the risk of stroke in male smokers, according to a large observational trial (n = 26,556 male Finnish smokers, aged 50–69 years). "Dietary intake of folate greater than 249 µg daily in men and 400 µg in women is associated with a reduced risk of colon cancer, especially in women with a family history of the disease," according to Jellin et al.

bioactive dose

The RDA for folic acid/folate is 400 µg for adults; 600 µg for pregnant women; and 500 µg for lactating women.

safety

The UL for folic acid is 1000 µg. Patients should be warned to avoid treating undiagnosed anemia with folic acid because folic acid can mask pernicious anemia by decreasing megaloblastic anemia.

Fructan

definition

Naturally occurring polymer of fructose molecules such as inulin. Fructooligosaccharides are a type of fructan. Found in asparagus, Jerusalem artichokes, chicory, bananas, garlic, and onion.

scientific findings

Fructans are natural sweeteners that have a low caloric value, do not lead to a rise in serum glucose, do not stimulate insulin secretion, promote the growth of intestinal bifidobacteria, and may improve the absorption of certain minerals. Taking fructans orally does not seem to reduce the incidence of traveler's diarrhea; some evidence suggests that fructans may

relieve constipation by increasing fecal mass.

bioactive dose

Not known. For prebiotic effect (to increase fecal bifidobacteria), the typical dose is 4–10 g/day.

safety

Presumed safe when consumed in normal dietary quantities by nonallergic individuals.

Fruit foods group

definition

Underconsumed food group that is a good source of folate, vitamins C and A, and underconsumed potassium. Fruit phytochemicals may vary by color, where generally blue/purple plant foods contain anthocyanidins, flavonols, flavan-3-ols, proanthocyanidins, ellagic acid, and resveratrol; green plant foods typically contain flavones, flavanones, flavonols, β-carotene, lutein, xeaxathin, indoles, isothiocyanates, and organosulfur compounds; white plant foods typically contain flavonols, flavanones, indoles, isothiocyanates, and organosulfur compounds; yellow plant foods typically contain flavonols, flavanones, α-carotene, β-carotene, β-cryptoxanthin, and xeaxanthin; and red plant foods typically contain anthocyanins, flavonols, flavones, flavan-3-ols, flavanones, proanthocyanidins, lycopene, ellagic acid, and resveratrol.

scientific findings

"People whose diets are rich in plant foods such as fruits and vegetables have a lower risk of getting cancers of the mouth, pharynx, larynx,

esophagus, stomach, and lung, and some evidence suggests that maintaining a diet rich in plant foods also lowers the risk of cancers of the colon, pancreas, and prostate. This diet also reduces the risk of diabetes, heart disease, and hypertension, helps to reduce calorie intake, and may help to control weight." Consuming a diet containing high amounts of fruits is associated with fewer age-related diseases such as Alzheimer disease.

bioactive dose

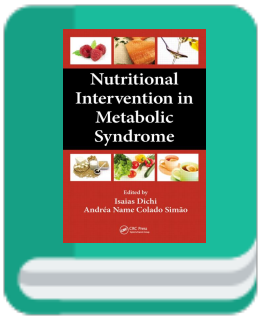
One cup for children aged 2–3 years, to 1 1/2 to 2 cups daily for people aged 19–50 for general health.65 One to 2.5 cups of fruits daily, depending on age and calorie needs, where 0.9 daily cup equivalents of fruit per 1000 cal is recommended to help prevent the cancers cited in Scientific Findings.

safety

Presumed safe when consumed in normal dietary quantities by nonallergic individuals. Allergies to different fruits have been reported.

CHAPTER 3

Vitamin D in Metabolic Syndrome



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INTRODUCTION

The metabolic syndrome (MS) is a complex disorder characterized by simultaneous occurrence of metabolic abnormalities, including high blood pressure (HBP), central adiposity, dyslipidemia (high serum LDL-cholesterol and triglycerides and low serum HDL-cholesterol) and insulin resistance (WHO 1999, Muredach et al. 2003). These conditions are highly prevalent in Western societies and are associated with a fivefold risk of developing type 2 diabetes mellitus (DM2) and a two- to threefold risk of developing cardiovascular diseases (CVD). Today, these diseases are considered some of the main health problems of the twenty-first century (Zimmet and Alberti 2006). MS is also associated with other comorbidities, such as thrombophilia, proinflammatory state (Sutherland et al. 2004), nonalcoholic fatty liver disease (Kotronen et al. 2007), and reproductive disorders (Ehrmann et al. 2006, Corona et al. 2007).

MS causes and mechanisms may be diverse and reflect the interaction of genetic environmental aspects (Laaksonen et al. 2002, Cornier et al 2008). In this context, there has been growing interest on the possible involvement of vitamin D in MS genesis, especially considering the relationship of this vitamin with energy expenditure (Teegarden et al. 2008) and insulin resistance (Pittas et al. 2007), in addition to its anti-inflammatory and immune-modulating effects (Holick 2005).

VITAMIN D

Vitamin D, a steroid hormone, is considered a vitamin since it is also obtained from food. In foods, it is found in the form of ergocalciferol (vitamin D2), produced by plants and fungi, and cholecalciferol (vitamin D3) (Miller and Portalle 1999). Although scarce, dietary sources of vitamin D, such as egg yolk, liver, butter, and milk, are essential for meeting the recommended daily requirement (Ladhani et al. 2004). In

addition to the foods fortified with vitamin D, dietary sources include

liver oil from fish such as tuna, halibut and especially cod, and fish such as salmon, mackerel, sardine, eel, and herring (Calvo and Whiting 2006, U.S. Department of Agriculture 2012). Table 4.1 shows the main natural dietary sources of vitamin D. In humans, cholecalciferol can also be synthesized in the skin from 7-dehydrocholesterol when the skin is exposed to solar ultraviolet-B radiation, forming pre-vitamin D (Holick 2005). Roughly, 80%–90% of the body vitamin D stems from skin synthesis and the remainder from the diet (Table 4.1) (Holick 1999).

TABLE 4.1
Amount of Dietary Vitamin D (Cholecalciferol) in 100 g of Food

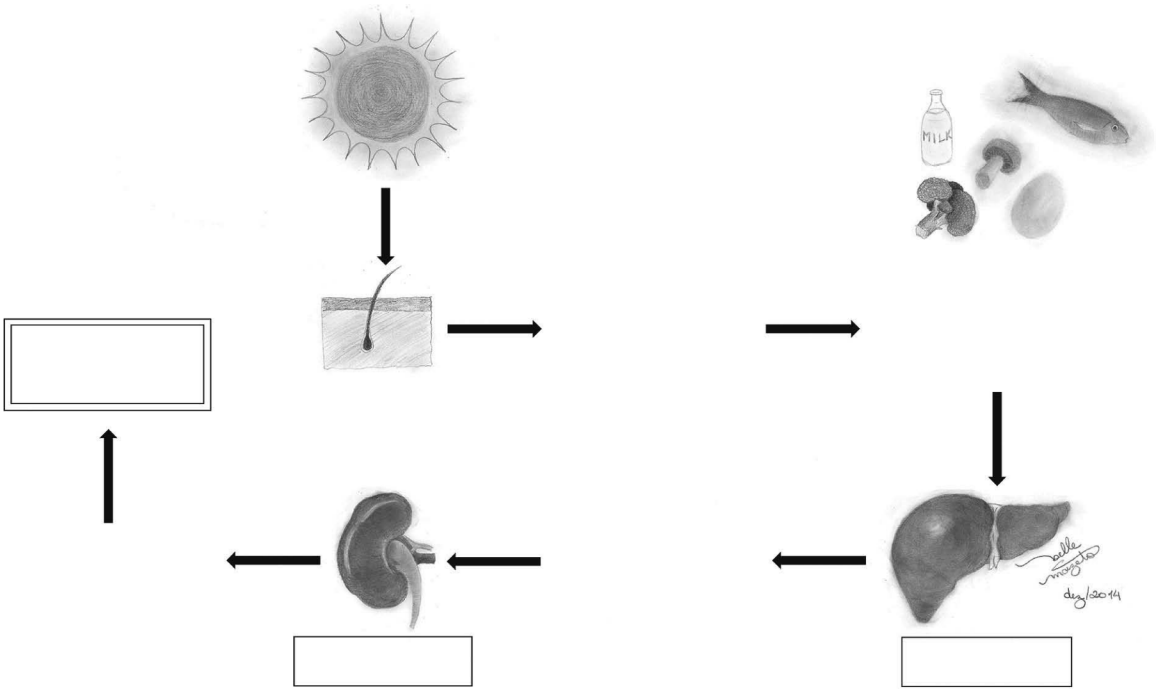
Food	Cooking Unit/Grams	Amount of Vitamin D (IU)
Fish liver oil	1 table spoon (10 g)	1000
Sardine oil	1 table spoon (10 g)	33.2
Raw Atlantic herring	100 g	1628
Salmon	100 g	763
Skimmed milk (1% fat)	1 cup (240 mL)	124.8
Whole milk (3.25% fat)	1 cup (240 mL)	96
Oat breakfast cereal	1 portion (30 g)	42.9
Raw chicken egg	1 medium unit	17.5
Mushroom	100 g	21
Salted butter	1 tablespoon (32 g)	17.9
Parmesan cheese	100 g	28

Source: U.S. Department of Agriculture, Agricultural Research Service, USDA national nutrient database for standard reference, Release 25, Nutrient data laboratory home page, http://www.ars.usda.gov/ba/bhnrc/ndl, 2012. (Accessed Apr 22, 2015.)

Table 4.1 Amount of Dietary Vitamin D (Cholecalciferol) in 100 g of Food

In order to perform its functions, vitamin D needs to be transformed into its active metabolite, a process that requires two successive hydroxylations (FAO/WHO 2002). The first phase of this process occurs in the liver, promoted by the enzyme 25-hydroxylase on carbon 25, forming

25-hydroxyvitamin D3 [25 (OH)D3], or calcifediol, the most abundant metabolite of vitamin D present in the blood, and whose measure is an indicator of its level in the body (Premaor and Furlanetto 2006). The second hydroxylation occurs mainly in the proximal tubules of the kidneys promoted by the enzyme 1 α-hydroxylase on carbon 1, forming 1,25-dihydroxyvitamin D [1,25(OH)2D3], the active metabolite known as calcitriol (Holick 1999, 2005, Miller and Portalle 1999). Figure 4.1 shows the processes involved in vitamin D activation. Once in the circulation, 1,25(OH)2D3 will act on all body tissues with calcitriol receptors (Holick 2004).



VITAMIN D SUFFICIENCY

An individual's vitamin D status is given by the plasma level of calcifediol. Determination of 1,25(OH)2D3 is not indicated because of its extremely short half-life and difficulty associated with estimating its serum level (Mosekilde 2005). Some authors suggest that adequate vitamin D status is that capable of maintaining the parathyroid hormone (PTH) in the normal

range, given that vitamin D deficiency increases PTH, stimulating bone resorption, and increasing renal calcium absorption. Studies have reported a balance between calcium absorption and appropriate PTH levels when serum 25(OH)D3 is close to 20 ng/mL (Chapuy et al. 1997, Tangpricha et al. 2002, Vieth et al. 2003). According to recent Endocrine Society guidelines, vitamin D deficiency is defined by serum 25(OH)D3 below 20 ng/mL and insufficiency by serum 25(OH)D3 between 21 and 29 ng/mL (Table 4.2) (Holick et al. 2011).

EPIDEMIOLOGY

Currently, vitamin D deficiency or insufficiency is considered a world health problem because of the implication of this condition on the development of various diseases (Kimball et al. 2008). Data published in many recent studies done worldwide indicate that vitamin D and calcium deficiencies are highly prevalent in the general population (30%–80%) and affect both genders and different age groups (Su and Zemel 2008). The National Health and Nutrition Examination Survey—2003–2006 (NHANES) assessed the prevalence of vitamin D deficiency and its correlates in the American population and found a prevalence of vitamin D deficiency of 41.6%, that is, levels of 25(OH)D3 below 20 ng/mL. Additionally, deficiency was more common in obese and hypercholesterolemic individuals (Zhao et al. 2010). Indeed, some population subgroups are at greater risk for vitamin D deficiency, especially the elderly. It is estimated that anything from 20% to 100% of the elderly American, Canadian, and European population may be vitamin D deficient (Holick et al. 2011).

TABLE 4.2
Individual Vitamin D Status according to Serum 25(OH)D_3

25(OH)D_3 (ng/mL)	Vitamin D Status
<20	Deficiency
21–29	Insufficiency
30–100	Sufficiency
>100	Excess
>150	Poisoning

Sources: Data from Grant, W.B. and Holick, M.F., *Altern. Med. Rev.*, 10(2), 94, 2005; Holick, M.F. et al., *J. Clin. Endocrinol. Metab.*, 96(7), 1911, 2011.

Despite the more favorable latitudes found in Brazil, high prevalence of vitamin D deficiency and insufficiency have been reported, especially in the elderly and during winter (Maeda et al. 2010), but they have also been seen in younger and healthy populations (Preamaor and Furnaletto 2006). Depending on the studied group, vitamin D deficiency rates may come close to 80% (Preamaor and Furnaletto 2006, Saraiva et al. 2007, Unger et al. 2010, Peters et al. 2012). The causes of vitamin D deficiency or insufficiency may be numerous, among them little sun exposure and obesity (Schuch et al. 2009). The percentages of individuals with inadequate vitamin D intake range from 85.4% to 99.0% (Peters et al. 2009, Pinheiro et al. 2009, IBGE 2010). Moreover, since vitamin D is fat soluble, its absorption is promoted by consumption of high-fat foods absorbed in the jejunum-ileum portion of the gastrointestinal tract. Thus, deficiency may also stem from consuming low-fat meals, in addition to the much studied malabsorptive component (Ruiz-Tovar et al. 2012).

VITAMIN D TARGETS

Calcitriol has many targets, such as brain, pancreatic, gastric, intestinal, skin and gonadal tissues, and immune cells (Holick 2004), among others. However, the main function of vitamin D is to maintain the intra- and

extracellular calcium levels within a physiologically acceptable range. This is possible because of the bond between 1,25(OH)2D3 and its intranuclear receptor (VDR). VDR is widely distributed not restricted to classical vitamin D target tissues, which explains the various actions of this vitamin (Holick 2004). In the nucleus, vitamin D bonds to specific DNA sequences, called vitamin D response elements (VDRE) (Barsony and Prufer 2002), resulting in the transcription of a messenger ribonucleic acid (mRNA) that regulates the translation of many proteins, including the vitamin D–dependent calcium-binding protein (CaBP) responsible for the transcellular transport of calcium in the intestine. VDR clearly controls essential genes associated with bone metabolism, oxidative stress, chronic diseases, and inflammation (Haussler et al. 2008, 2013). Yet, recently Wang and DeLuca (2011) showed the inexistence of VDR in skeletal and heart muscles, suggesting that vitamin D acts on these targets in an indirect or nongenomic manner.

ROLE OF VITAMIN D ON THE METABOLIC SYNDROME

Studies on the action of vitamin D on metabolic processes and its clinical repercussions date from the seventeenth century (Bouillon et al. 2008). The vast amount of data on vitamin D deficiency/ insufficiency published globally has aroused great interest in research centers, which frequently identify repercussions of such deficiency not only on bone metabolism, but also on vital cellular processes, such as cellular differentiation and proliferation, and on insulin secretion, immune system, and various non*communicable chronic diseases (Zemel 2003, Peterlick and Cross 2005, Bouillon et al. 2008, Heaney et al. 2008, James 2008, Kimball et al. 2008, Prentice et al. 2008, Kahn et al. 2011, Skaaby et al. 2012). As a matter of fact, recent studies suggest that low vitamin D levels may be associated with greater risk of cardiovascular and metabolic diseases, including DM2 (Knekt et al. 2008, Kahn et al. 2011) and CVD (Dobnig et al. 2008, Giovannucci et al. 2008, Wang et al. 2008, Skaaby et al. 2012). Vitamin D is strongly associated with individual risk factors for MS, with

inverse association with the presence of this syndrome (Chiu et al. 2004, Ford 2005, Pinelli et al. 2010, Yin et al. 2012). Some authors reported an approximate threefold increase in the prevalence of MS in individuals with hypovitaminosis D (Ford 2005). On the other hand, adequate vitamin D levels reduce vulnerability to MS by 54% (Chiu et al. 2004). Nevertheless, some studies have associated other vitamin D–related elements, not its deficiency, with MS. In this sense, PTH levels in obese men and women (Reis et al. 2007, Hjelmesaeth et al. 2009) and calcium levels (Liu et al. 2005) have been associated with the syndrome. Hence, the relationship of MS and its associated factors with vitamin D deficiency is not very clear.

Considering the individual risk factors for MS, the Women's Health Initiative Calcium/ Vitamin D Supplementation Study (WHI CaD Study) assessed menopausal women and found that serum 25(OH)D3 was inversely associated with serum triglyceride levels, triglyceride/ HDL-cholesterol ratio, excess weight, and MS. These associations were not dependent on demographic characteristics or on the traditional risk factors for cardiovascular and metabolic diseases (Jackson et al. 2006).

A recent review found that vitamin D deficiency can promote changes in insulin secretion, glucose intolerance, and DM2 (Pittas et al. 2010). Accordingly, 1,25(OH)2D3 acts on the pancreas, increasing insulin production (Holick et al. 2004). This action could occur directly, by VDR activation, or indirectly, by calcemic hormones and inflammatory cytokines (Thorand et al. 2011). Some cross-sectional studies indicate that hypovitaminosis D is associated with higher serum levels of inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) in healthy and obese individuals (Dobnig et al. 2008, Peterson and Heffernan 2008, Ngo et al. 2010, Jablonski et al. 2011). Moreover, its indirect effect may be mediated by the intra- and extracellular calcium flow in pancreatic β-cells induced by higher PTH and 1,25(OH)2D3 levels (Zemel 2003). In this context, calcium is essential for insulin action on fat and muscle tissues. Literature data show that changes in the calcium levels of these tissues

may increase peripheral insulin resistance, that is, vitamin D and/or calcium levels are inversely associated with insulin resistance (Chiu et al. 2004, Liu et al. 2005, Pittas et al. 2007).

Studies have shown that obese individuals have low serum 25(OH)D3 and high serum PTH (Arunabh et al. 2003, Snidjer et al. 2005). In addition to less sun exposure because of seclusion, these findings might be mainly related to the high percentage of body fat in obese individuals, which reduces vitamin D bioavailability and causes a cascade of reactions that begins in the hypothalamus and results in high sensation of hunger and low-energy expenditure (Schuch et al. 2009). This situation also generates a disproportional increase in intracellular calcium levels, preventing catecholamine-induced lipolysis, and increasing fatty acid synthase expression, thereby contributing to fat tissue synthesis (Su and Zemel 2008). Indeed, there seems to be a link between adequate vitamin D status and high-energy expenditure (Teegarden et al. 2008).

Studies have shown a positive association between vitamin D deficiency and high cardiovascular risk, and possibly HBP (Li et al. 2002, Giovannucci et al. 2008, Kendrick et al. 2009).

Some previously known mechanisms may explain such association. First, 1,25(OH)2D3 helps to regulate the renin–angiotensin axis since hypovitaminosis D directly suppresses the expression of the renin gene (Xiang et al. 2005) and may thereby increase blood pressure (Li et al. 2002). Second, smooth muscle and endothelial cells have vitamin D receptors and can convert 25(OH)D3 into 1,25(OH)2D3 (Zehnder et al. 2002, Somjen et al. 2005). Finally, secondary hyperparathyroidism caused by vitamin D deficiency promotes myocyte hypertrophy and vascular remodeling. Studies suggest that PTH has a proinflammatory effect, stimulating smooth muscle cells to release cytokines. Vitamin D deficiency and/or high PTH levels also promote calcification of heart structures, compromising cardiovascular function (Anderson et al. 2010, 2011).

Considering the various MS aspects, Bolland et al. (2011) found a correlation between serum 25(OH)D3 and blood glucose, fasting insulin, serum lipids, and adiposity, and concluded that high serum levels of this vitamin are inversely associated with diabetes, dyslipidemia, obesity, and MS. Moreover, they concluded that for each unit vitamin D level increase, there is a 3.57-fold decrease in metabolic risk (Bolland et al. 2011). This finding is in agreement with those of other authors who reported that adults with hypovitaminosis D seem to be at higher risk of insulin resistance and MS because of pancreatic beta-cell dysfunction and higher rate of DM2 (Snidjer et al. 2005). A study done with 542 Arab Americans of both genders found a negative correlation between serum vitamin D and homeostasis model assessment of insulin resistance (HOMA-IR), hypertriglyceridemia, and glycated hemoglobin (A1c) in men and a positive correlation between serum vitamin D and HDL-cholesterol (Pinelli et al. 2010). Chacko et al. (2011) found an inverse association between serum vitamin D and body fat, serum triglycerides, triglyceride/HDL ratio, and MS prevalence. No significant associations were found between serum vitamin D and LDL-cholesterol, HDLcholesterol, insulin, glucose, HOMA-IR, or homeostasis model assessment of beta-cell function (HOMA-β) (Chacko et al. 2011).

METABOLIC SYNDROME RESPONSE TO VITAMIN D SUPPLEMENTATION

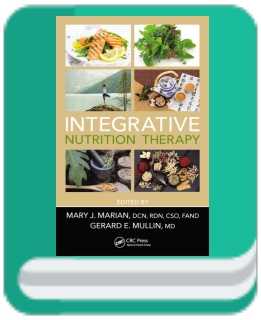
The role of vitamin D supplementation on SM and/or its main associated factors still requires further elucidation. A study done with mouse preadipocytes found an association between 25(OH)D3 level and adipogenesis inhibition (Wood 2008). Another study with postmenopausal women taking 1000 mg of calcium and 400 IU of cholecalciferol per day found that they gained less weight than the unsupplemented group (Caan et al. 2007). After 1 year of supplementation with high dosages of vitamin D, Beilfuss and colleagues (2012) found a reduction in serum IL-6 but insulin resistance and serum TNF-α remained the same.

Studies that assessed the efficiency of vitamin D supplementation suggest an improvement in insulin secretion (Orwoll et al. 1994, Chiu et al. 2004). According to Borissova and colleagues (2003), an increase in serum 25(OH)D3 from 10 to 30 ng/mL may improve insulin sensitivity by 60%. Intervention studies suggest that supplementations with dosages equal to or higher than 800 IU of 25(OH)D3 and/or calcium seem to be particularly important for preventing the development of DM2 in individuals with DM2-related risk factors (Pittas et al. 2006).

FINAL CONSIDERATIONS

The consequences of vitamin D deficiency are a global public health problem. In addition to the effects of vitamin D on bone metabolism, knowledge is needed on the nonclassical hypovitaminosis D-related aspects, such as its effects on the immune and cardiovascular systems and on insulin sensitivity, and its anti-inflammatory properties. Such knowledge will allow the development of recommendations for correcting vitamin D inadequacies related to MS genesis and/or progression.

Chapter 4: Nutrition and Mental Health



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INTRODUCTION

Psychiatric illnesses and disabilities are on the rise as much as other chronic illnesses. To this end, the burden of mental health and substance abuse disorders has increased 37.6% from 1990 to 2010 (Whiteford et al. 2013, 1575–1586). Despite the progression in disease burden, the solutions remain limited in a conventional medicine model. In contrast, in a functional medicine (Jones and Quinn 2006) model of psychiatry, nutrition is one of the major biopsychosocial factors to explore when a previously successful medication regimen suddenly stops working. It is the authors' view that barring high-risk situations requiring immediate relief, medication changes (other than dose adjustments) should not be the primary focus of treatment until other causes of medication failure are explored (nutrition, inflammation, etc.). While psychiatric medications clearly have their place in the medical armamentarium, they also have their limitations. Among these limitations is the fact that some of these medications are known to deplete certain nutrients. For example, valproic acid depletes carnitine in young children (Abd and El-Serogy 2012, 275–281), and metformin and gastric acid inhibitors are associated with vitamin B12 deficiencies (Lam et al. 2013, 2435–2442; Reinstatler et al. 2012, 327–333).

Improving nutrition can frequently correct many of the symptoms of mental and emotional disorders and, for some, completely restore health without the use of medication. Others will be able to decrease their use of medication and/or ameliorate side effects.

Furthermore, the stresses of modern life place a burden on bodily systems and increase the need for many nutrients. Nutrient-depleted soils, antibiotic/grain-fed meats, excessive sugar intake, and diets low in anti-inflammatory fats and rich in pro-inflammatory foods (Fallon and Enig 2001) are thought to be harming our health. One of the authors has been routinely successful in treating bipolar type II and obsessive compulsive disorder (OCD) without medication using a functional

medicine model (Jones and Quinn 2006). Importantly, nutrition is an important cornerstone of this model.

In this chapter, we describe how nutritional science is applicable to mental health, highlight some of the more common nutrient deficiencies associated with compromised mental health, and review some of the evidence for various nutraceuticals commonly used in psychiatric disorders. Finally, we provide a basic template of useful laboratory tests that are important in the integration of nutrition into an overall plan for improved mental and physical health.

DIET AND MENTAL HEALTH

Most psychiatric patients consume diets heavy in carbohydrates and deficient in protein (Ventura et al. 2014, 252–256), a practice that flies in the face of current core dietary guidelines generally deemed important for mental and physical health. These guidelines include minimal amounts of processed foods, good-quality fats with an emphasis on omega-3 fatty acids, complex carbohydrates, minimal or no sugar, adequate but not excessive protein from clean (no antibiotics or hormones, grass-fed) animal or plant sources, and plenty of clean water. Of course, given the biochemical and genetic diversity of the human race, one diet cannot be the appropriate one for everyone. It is important to note that Weston Price described various cultures that enjoyed good health and longevity on varied diets: some were mostly seafood with no fruit and few vegetables (Alaskan Eskimos), others were primarily rye bread and cheese (Swiss farmers), while the Masai warriors' diet consisted of animal blood and milk (Planck 2006). Processed foods do not contain the needed micronutrients and often contain trans fats and significant amounts of sugar (often high-fructose corn syrup [HFCS]) and salt. The chronic consumption of these foods causes structural change of membrane phospholipids, affecting brain neurotransmission, and has been shown to increase anxiety (Bakhtiyari et al. 2013, 107–112; Jacka et al. 2011, 483–490) and

depression (Jacka et al. 2010, 305–311). Trans fats, created by hydrogenation to make them artificially saturated fats (and solid at room temperature), raise LDL (Brouwer et al. 2013, 541–547) and cause heart disease (Brouwer et al. 2013, 541–547). Low cholesterol is associated with increased impulsivity and suicide (Troisi 2011, 83–87; Zhang 2011, 268–287).

Sugar consumption has increased dramatically as well in recent years, in part because of the advent of HFCS, the main caloric sweetener in junk food. The body is not equipped to deal with either the high doses of sugar (unbound by fiber and without micronutrients) or the compensatory release of insulin; high serum glucose levels lead to a surge in adrenalin, one of the acute stress hormones (Jones et al. 1995, 171–177). Thus, intraday depression, anxiety, panic, fatigue, difficulty concentrating, etc., can be traced back to diet-based dysglycemia and have numerous downstream consequences.

Essential fatty acids, which make up much of the cell membranes, are enormously important in mental health. However, since the 1960s, low-fat diets and the consumption of polyunsaturated vegetable fats have been championed. More recently, these assumptions are coming into question as a new debate emerges about fats and health and, by extension, mental health. A 2010 review of 21 studies looking at saturated fats did not find evidence of increased cardiac risk (Siri-Tarino et al. 2010, 535–546). It has been established that the membrane phospholipids mediate the entry of neurotransmitters (NTs) into the cell. Inadequate amounts of these essential fatty acids (omega-3s, primarily) and structural substitution by dietary trans fats are thought to alter normal neurotransmission. Studies in rats indicate that trans fats result in a preference for and augmentation of amphetamine effects. Kuhn et al. (2015) support the idea that trans fats may have a negative influence on mental health. On the other hand, the omega-3 fatty acids (found in certain fish, seaweed, algae, and eggs (hatched from chickens fed only on flaxseeds and fish meal), are clearly effective in mood disorders (Grosso et al. 2014). A wide palette of color in

the vegetable category provides much needed antioxidant and nutrient benefit, with a more minor emphasis on fruit.

Patients should be educated to balance every meal and every snack with protein, fat, and complex carbohydrates, barring medical reasons to the contrary. Generally, this approach enhances mental stability and energy within 5–6 days (Hedaya 2000). Caffeine may be healthy for some people due to its antioxidant content, but in the psychiatric population too, often it causes unstable blood sugar, depression, irritability, adrenal depletion, nutrient depletion, and irritable bowel with concomitant malabsorption, among other difficulties (Bergin and Kendler 2012, 473–482).

GENERAL RECOMMENDATIONS FOR NUTRITIONAL DEFICIENCIES

While individuals differ in their needs for certain nutrients, there are certain nutritional deficiencies that are extremely common and relevant to the psychiatric population. Most commonly, these deficiencies include omega-3 fatty acids, zinc, iron, vitamin D, and methylated B vitamins (Pfeiffer et al. 2013, 938S–947S), hence our discussion later.

Because of individual variation, it is best to conduct appropriate lab tests before recommending many, if not most of these supplements. In cases where deficiencies are identified, it is useful to supplement with the single micronutrient necessary. However, many other micronutrient deficiencies can exist and can affect mental health. Given that (1) individuals vary in their specific needs for certain nutrients and (2) micronutrients work in concert, it is also useful to consider a broad-spectrum micronutrient mixture in patients with mental illness. For an excellent review of the literature on single and broad-spectrum micronutrient supplementation affecting mental health, Popper's review in *Child and Adolescent Clinics of North America* is much recommended (Popper 2014, 591–672).

Omeg a-3 Essential Fatty Acids

Omega-3 fatty acids, one of the nutrients most commonly deficient in Western diets, have been implicated in attention-deficit hyperactivity disorder (Arnold et al. 2013, 381–402), depression, bipolar disorder (Song 2013, 75–89), alcoholism, and violence (Simopoulos 2011, 203–215). The two omega-3 essential fatty acids of note are EPA and DHA.

While studies examining the relevance of omega-3s in ADHD are somewhat mixed, the generally recommended dose for ADHD is 2–3 g/day, with a preponderance of DHA (Richardson 2006, 155–172). A meta-analysis of the use of omega-3s in bipolar disorder found "strong evidence that bipolar depressive but not manic symptoms may be improved by adjunctive use of omega-3 fatty acids" (Sarris et al. 2012, 81–86). The doses used in various studies for unipolar depression range from 1 to 4 g of EPA daily with 1 g being more efficacious than 4 g (Osher and Belmaker 2009, 128–133).

It is safe to say that the best dose for optimal mental health is yet to be determined. Different forms of fish and krill oil are available; when using high doses, liquid may be better tolerated. When using omega-3 essential fatty acids, some clinicians also recommend balancing them with GLA (from primrose or borage oil), an anti-inflammatory omega-6 and a precursor to prostaglandin E1 (Vasquez 2009, 561).

When recommending omega-3 fatty acids, be cautious of their use in patients with diabetes or coagulation disorders.

Zinc

The highest concentration of zinc is normally in the brain. It is necessary for efficient serotonergic neurotransmission and immune function, yet it is one of the most commonly deficient minerals. Low zinc is associated with learning difficulties (Yorbik et al. 2008, 662–667) and ADHD (Bloch and Mulqueen 2014). Zinc deficiency is quite common in adolescence

(Schenkel et al. 2007, 264–271), leaving young people more vulnerable to mood disorders, irritability, and OCD (Ozuguz et al. 2013). Because requirements for zinc vary, based on copper status, genetic factors, and soil content, testing must be done.

Iron

Many micronutrient deficiencies can be linked to inadequate dietary intake, and certainly vegetarians/vegans are at increased risk for low iron. But so are women of childbearing age. Iron is necessary to ensure oxygenation and for the synthesis of NTs and myelin and affects behavior in a variety of ways (Kim and Wessling- Resnick, 2014). Deficiency is found in children with ADHD (Bourre 2006, 377–385) and is often implicated in fatigue.

Vitamin D

Vitamin D is necessary for the function of every cell in the body; and so, it is critical to mental health. In psychiatry, deficiency has been associated with seasonal affective disorder and depression, although causality has not been established (Parker and Brotchie 2011, 243–249). Still, given modern lifestyles with often minimal sun exposure and a paucity of vitamin D–rich food sources, supplementation to bring levels into the normal range may be useful. However, there are dangers to over-supplementing, and vitamin D functions in a balance with other nutrients, such as vitamin A. High levels of vitamin A can decrease the benefits/levels of vitamin D (Oh et al. 2007, 1178–1186). Testing and retesting are always recommended.

B Complex Vitamins

Deficiencies of B vitamins, particularly folate, B6 and B12, are overwhelmingly linked to mood disorders and depression (Herbison et al. 2012, 634–638; Mischoulon and Raab 2007, 28–33; Penninx et al. 2000, 715–721). Vitamins B6 and B12 also play crucial roles in methylation (see discussion later) and NT metabolism (Midttun et al. 2007, 131–138; Miller 2008, 216–226).

DIGESTION AND MENTAL HEALTH

Absorption

Even the best diet cannot overcome persistent difficulties in the digestion and absorption of food. Digestion requires normal gastric function (including production of appropriate levels of hydrochloric acid [HCl]) and pancreatic digestive enzymes. HCl (whose production is commonly reduced with age and acid blocking agents often used for acid reflux) serves at least three functions. First, it helps break down protein components of the diet, so that amino acids such as tryptophan and tyrosine (essential for the production of NTs) can be available for absorption by facilitating the action of pepsin in the small intestine. Second, it helps maintain normal bacterial flora in the proximal small intestine, which facilitates normal absorption and digestion, and bacterial production of micronutrients such as B12 (Dukowicz et al. 2007, 112–122). Finally, when administered as a supplement (betaine HCl), the betaine moiety supplies an alternative pathway in the methylation cycle (Crider et al. 2012, 21–38), which is a critical factor in the regulation of NT availability. The parietal cell, which produces HCl, also assists in the absorption of B12. Thus, all factors that affect parietal cell function (e.g., age and medications used for gastroesophageal reflux) affect the earlier processes, which in turn affect NT availability. Pancreatic digestive enzymes are needed for the breakdown and absorption of fats, complex carbohydrates, and proteins, and so decreased production of pancreatic enzymes will have broad effects on the availability of multiple micronutrients.

Inflammation

Gastrointestinal (GI) inflammation is relevant to brain function, hence mental illness (Rosenblat et al. 2014, 23–34). A large portion of the immune system is associated with the gut. Inflammatory processes originating in the GI tract affect brain function both through impaired nutrient absorption and through cytokine-mediated vagal endocrine

signaling (Mayer et al. 2014, 1500–1512) to the brain. Therefore, all factors affecting the GI inflammation must be a consideration in establishing good mental health.

Gluten Sensitivity

A growing concern in the mental health field is gluten sensitivity (of which celiac disease is a subcategory) since it is well known to cause absorptive abnormalities. Gluten intolerance has been implicated in the pathophysiology of ADHD, schizophrenia, anxiety, depression, and autism even without any obvious GI manifestations (Genuis and Lobo 2014; Jackson et al. 2012, 91–102; Peters et al. 2014, 1104–1112).

NUTRACEUTICALS FOR PSYCHIATRIC SYMPTOMS AND DISORDERS

L-Methylfolate

Methylation, one of the fundamental processes of the body, is central to numerous physiological processes including NT and hormonal regulation, mitochondrial function, protein manufacture, detoxification, inflammatory regulation, DNA expression, and epigenetic programming (Crider et al. 2012, 21–38). It has been established that normal function of methylation is necessary for normal brain function (Martin 2008, 377–387), and folic acid has been proven to be effective as an augmentation strategy in the treatment of depression (Papakostas et al. 2014, 855–863; Sarris et al. 2011, 454–465). Establishing normal methylation function via the judicious use of folic acid (or, in the case of those with the MTHFR C677T single-nucleotide polymorphism [SNP], 5-methylfolate; Davis and Uthus 2004, 988–995), B12, betaine HCl (Obeid 2013, 3481–3495), and B6 should be a part of the nutritional evaluation of patients with psychiatric and neurological disorders. Moderation in the use of methylation factors is important as there are emerging data that hypermethylation may be associated with neuronal diseases such as genetically based frontotemporal dementia (Banz-Strathmann 2013, 16). Laboratory testing is important to establish the need for methylation-modulating nutrients in individual patients, as there is insufficient evidence that augmenting

methylation in the absence of abnormalities is efficacious in psychiatric patients.

SAM -E (S-Adenosyl Methionine)

SAM-E occurs naturally in the body and is used to treat depression (Bressa 1994, 7–14), fibromyalgia (Dibenedetto et al. 1993, 222–229), and ADHD (Shekim et al. 1990, 249–253). SAM-E works to balance NT levels, by both increasing the ability of COMT (catechol-o-methyltransferase) to degrade synaptic molecules (NTs and hormones) and increasing the production of NTs. Doses may be as low as 200 mg twice a day to as high as 1600 mg twice a day and require folate and B12 for proper utilization (Goldberg 1999, 4).

Inositol

Inositol has been shown in several studies to be helpful for depression, OCD, panic disorder, and anxiety (Benjamin et al. 1995, 167–175; Mukai et al. 2014, 55–63). The dose must be gradually increased to minimize the laxative effect (it is often used in infants for constipation). The target is a total of 9 g twice daily. Full response can take as long as 12 weeks. However, because of the large amounts needed, some patients are reluctant to try this.

N-Ace tylcysteine

N-acetylcysteine (NAC) is an antioxidant derived from the amino acid l-cysteine. In psychiatry, it has shown promise as a treatment for adult trichotillomania and self-grooming behaviors, OCD, addiction (cannabis cocaine, heroin, alcohol, nicotine) via an effect on N-methyl-d-aspartate receptors in the nucleus accumbens, augmentation in refractory bipolar and unipolar depression, and negative symptoms in schizophrenia (Dean et al. 2011, 78–86). It is useful as a liver support for those taking valproic acid. The starting dose is 600 mg twice a day and is raised as tolerated to 1200 mg twice a day in 2 weeks, with a maximum daily dose of 2400 mg/day (Dean et al., 2011) when used for stereotypy and irritability in autism.

Specific Amino Acids

Tyrosine and tryptophan are necessary for NT production and are therefore essential to normal mental health and medication response. Normal levels are conditional on adequate diet, digestion, and absorption. Tryptophan and tyrosine depletion studies (Altman et al. 2010, 171–176; McLean et al. 2004, 286–297) consistently demonstrate that 60% of responders to serotonin-, dopamine-, or norepinephrine-acting antidepressants relapse into depression within 5–6 days when fed a diet deficient in these amino acids. This loss of response is specific to the medication being used, for example, tryptophan affecting response to selective serotonin reuptake inhibitors (SSRIs) and tyrosine affecting response to bupropion. One can use tryptophan when attempting to augment production of serotonin; however, this can cause anxiety and agitation when inflammation is part of the picture. Using 5-hydroxytryptophan (5-HTP), a metabolic intermediate in the biosynthesis of serotonin from tryptophan, avoids this risk. Dosages of 5-HTP can range between 12.5 and 100 mg given at bedtime. Care must be taken to avoid serotonin syndrome with those taking SSRIs, whether using tryptophan or 5-HTP. Tyrosine, a precursor to dopamine as well as epinephrine and norepinephrine, can be used in doses of 250–1000 mg BID, with attention to blood pressure in the elderly.

TESTING

This list is by no means definitive, but is meant to be a basic template.

Conventional Labs

1. CBC: r/o anemia (microcytic iron deficiency, macrocytic B12 deficiency), infections, respiratory allergies (eosinophilia).
2. Fe: ++, TIBC, Ferritin: r/o anemia, iron malabsorption common in hypothyroidism.
3. Fasting insulin, fasting glucose, 2 h glucose tolerance test, hemoglobin A1C.
4. RBC magnesium, selenium, copper, zinc.

5. Celiac panel with antigliadin antibodies (IgG, secretory IgA), HLA DQ2 and DQ8 (only a positive response is helpful; too many false negatives); anti-IgA tissue transglutaminase antibodies, endomysium antibodies. None of these tests, however, is definitive, so the entire clinical picture must be considered.
6. Lipid profile (NMR preferable): cholesterol is a precursor to adrenal hormones.
7. Homocysteine: Used as a functional marker of methylation processes, it should be kept at a level of approximately
8. Levels are affected by B12, folate, and B6.
9. hsCRP, ESR: As general inflammatory status markers.

Specialty Labs

1. IgG and IgA food sensitivity testing useful when restoring gut health.
2. Comprehensive stool tests in cases where GI symptoms are present.
3. NT testing: There is little use in this testing procedure since urinary output of NTs is mostly reflective of NT function in body compartments other than the brain.
4. Genotype testing: to identify SNPs affecting the CYP 450 enzyme systems, which can influence medication dosing and side effects.
5. Genotype testing to identify MTHFR status.
6. Pyroluria: evaluate for kryptopyrolluria (genetically based increased need for B6 and zinc).

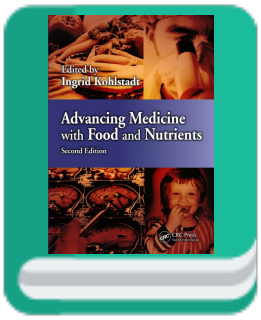
SUMMARY

The best medicine is personalized, and most mental health patients would benefit from an individually tailored nutritional program that is ideally based on a thorough history, physical exam, and laboratory testing. For those patients who do not respond fully to such an approach, we recommend a full functional medicine assessment. However, we feel strongly that a sound nutritional program is a necessary basis for successful mental health treatment.

CHAPTER 5

Chapter 5: Acne and Diet

Chapter 5: Acne and Diet



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INTRODUCTION

In the early twentieth century, dermatologists believed that diet could have a profound influence on acne. However, in 1969 and 1971, two studies authored by prominent dermatologists proclaimed the opposite, and since that time the major textbooks of dermatology have denied that diet affects acne by citing those two papers. In 2012, the website of the American Academy of Dermatology links to a patient information site that declares: "There's no need to worry about food affecting the acne". The pendulum has remained suspended in that position, defying the gravity of scrutiny for nearly 40 years. However, the drumbeat of studies challenging the acne-diet dogma has grown louder and corroborated by increasingly more sophisticated science. This chapter reviews the scientific evidence, much of it outside the dermatology literature, for the acne-diet link and concludes with a dietary treatment program for acne patients.

EPIDEMIOLOGY

Observational and epidemiologic studies support a diet-acne connection. Schaeffer, who worked among the Inuit for 30 years, observed that acne, which had been absent in that population became prevalent as the people acculturated from a fish-based diet to one rich in bread, sweets, pastries, and soft drinks. The low rate of acne among Japanese teens, half that of American teens in 1964, could be attributed to genetics except that a 2001 study shows that with the displacement of part of the traditional Japanese diet by Western fast foods, the rates equalized. Acne is nearly unknown in the Kitavan and Ache tribes still living in their hunter-gatherer tradition with a diet rich in wild game, fish, and plants. Ghanaian school children in urban areas have a strikingly higher prevalence of acne (12.9%) compared to those in rural areas (0.2%). The authors attributed this to the Westernization of urban areas. The concomitant increase in obesity seen in this study suggests that "dietary Westernization" plays a critical role. A study comparing more

than 800 Korean acne patients to approximately 500 controls correlated a high glycemic load diet, processed cheese, a highfat diet, and iodine with the exacerbation of acne. In addition, those with acne were more likely to skip breakfast. Low raw vegetable intake correlated with increased acne in females in a Norwegian study. A Chinese study found no dietary difference between subjects with acne and those without until they divided them into a Yin-predominant group and a Yang-predominant group. In the latter, those who ate desserts and fresh fruit juices were more likely to have acne, whereas those who ate dairy and soy had a lower incidence of acne. In the former group, intake of food from street stalls correlated with a lower incidence of acne. A cross-sectional study of 2300 Turkish youths found fat, sugar, and fast food consumption to be positively correlated with acne prevalence.

In Western cultures, acne appears to be increasing in incidence, occurring in older age groups and sometimes lasting longer. Goulden et al. noted that the mean age of their acne patients increased from 20.5 to 26.5 from 1989 to 1999. A British retrospective cohort study in 1998–99 found the prevalence of acne to be more than twice that previously reported for 1991–92, 3.1% compared to 1.3% respectively. A study of male students at the University of Glasgow found an increase in the incidence of acne over the period 1948 to 1968. The authors state, "We suggest that environmental exposure may underlie this, as changes in the prevalence of germ-line genetic variants are very unlikely to occur in such a short time period." If human genes have not changed, some change in the environment must account for the striking increase in acne. The uniform worldwide response does not correlate with any known industrial pollutant.

On the other hand, diet, one of the most powerful influences on physiology, has changed dramatically over the past few decades around the world. This "nutrition transition," characterized by "the introduction of fast-food chains and Westernized dietary habits...seems to be a marker of the increasing prevalence of obesity" and its related complications. Acne

as a complication or comorbidity of obesity is supported by a number of studies.

The dietary lifestyle therapy for acne seems to compete with conventional teaching; however, the concepts actually weave nicely into the matrix the pathophysiology of acne provides.

OVERVIEW OF ACNE PATHOPHYSIOLOGY

The pathophysiology of acne encompasses four problems:

1. Abnormal hyperkeratinization in the hair follicle lumen;

2. Increased sebum production by the sebaceous glands;

3. Overgrowth of Propionobacterium acnes (P. acnes) within the follicle; and

4. Inflammation.

Conventional dermatology seeks pharmaceutical agents that quell the symptoms. For example, retinoids slow hyperkeratosis and decrease sebum production while the tetracycline antibiotics suppress both *P. acnes* and inflammation (see Figure 22.1) A systems biology approach, analyzing the relationships among the elements in a system in response to genetic or environmental perturbations in order to understand the system, might instead pose the question: Why do hyper-keratinization, excessive sebum, bacterial overgrowth, and inflammation occur in the first place? Understanding the antecedents and triggers of the disease process may give us insight into the mechanisms of the dietary effects on acne.

Increased proliferation of the basal keratinocytes and decreased apoptosis and separation of the corneocytes contribute to the abnormal follicular hyper-keratinization that plugs the follicle. Rather than being shed, the cells remain in place and thicken the follicular lining. This crowding of the follicular lumen may contribute to tearing and rupture of the wall with attendant inflammation. Plugging also seals the lumen contributing to the

anaerobic environment ideal for P. acnes. As with all biological processes, the cause of the hyperkeratosis is multifactorial and still incompletely understood. Possible contributors to the process have included, but are not limited to: localized insufficient action of vitamin A, localized deficiency of linoleic acid (LA), increased insulin-like growth factor (IGF-1) action, decreased peroxisome-proliferator activated receptorgamma (PPAR gamma), disturbance of desmosomes and tonofilaments, increased dihydroepiandrostendione sulfate (DHEA-S), oxidized squalene, and increased inflammation, particularly IL-1alpha. Already the dance of interaction and complexity begins with one of the four factors, inflammation, cited as a cause of one of the others, hyperkeratosis. The increased sebaceous gland activity seen in acne leads to not only an increase in the amount of sebum but also alters the composition of the secretion. The amount of LA decreases as the quantity of lipid increases (contributing to follicular hyper-keratinization). As a nutrient source for the bacteria, sebum feeds an increasing population of *P. acnes*. Breakdown of the oils by the bacteria produces inflammatory free fatty acids. Oxidation of squalene, the lipid found nowhere in the human body except in the sebum, produces by-products that induce comedones and increase inflammatory mediators. The increased and altered sebum that produces the oiliness of the skin so characteristic of acne has been ascribed to increased testosterone and dihydrotestosterone (DHT), increased insulin, increased IGF-1, increased PPAR alpha and decreased PPAR gamma, increased corticotropin releasing hormone (CRH), increased substance P, and localized, insufficient action of vitamin A.

P. acnes, the "bug" thought to contribute to acne, is a normal inhabitant of our skin and its role in acne is not well understood. However, the numbers of this organism increase in acne and tend to decrease as treatment produces clinical improvement. Recent research shows that *P. acnes* activates Toll-like receptor 2 (TLR2) in the innate immune system, triggering an inflammatory cascade. *P. acnes* can also induce hyper-keratinization by activating the IGF-1/IGF-1 receptor system.

Overgrowth of *P. acnes* appears to be triggered by: decreased LA, increased sebum (which is its nutrient supply), and abnormally desquamated follicular keratinocytes, which increases anaerobic conditions.

Inflammation accounts for the characteristic redness, swelling, and pustule and nodule formation in acne. Originally thought to be a late player in the process, recent evidence suggests that inflammation may be a primary initiator of the acne lesion. The following factors, among others, may account for the inflammation seen in acne: TLR-2 activation by *P. acnes*, omega-6 fatty acids and eicosanoids, oxidative stress, insulin, adiposity, and testosterone.

Note that these lists tend to overlap; that is, the same proximate causes contribute to more than one of the four pathophysiologic factors of acne. Not only do the same elements repeat, the causes and factors interact. Inflammation increases the hyper-proliferation of keratinocytes; the excess cellular debris makes a more anaerobic environment optimal for *P. acnes*; *P. acnes* binds TLR-2, triggering further inflammation. The recurring themes that deserve particular attention include disturbances of: fatty acids and fatty acid signaling, insulin/IGF-1, and oxidative and psychogenetic stress. These trigger of the pathophysiology of acne are responsive to environmental input, namely diet and lifestyle.

TABLE 22.1
Food, Nutrient, and Lifestyle Approaches to Managing Acne

Diet

1. Try a dairy-free diet for three to six months. No milk, cream, yogurt, ice cream, cheese of any kind (including cream and cottage). Decrease your use of butter or switch to ghee (clarified butter).
2. Eat three nutrient-dense meals and two "mini-meal" snacks daily.
3. Eat five to eight servings of vegetables and two servings of fruit per day, all colors of the rainbow.
4. Eat 2.5 to 3 palm-sized servings of protein-rich foods (meat, poultry, eggs, fish) daily; include fish one to two times weekly.
5. Minimize refined carbohydrates, such as candy, sweets, baked goods, crackers, white bread, white rice, white potatoes, pasta. (Unless you are performing very high intensity exercise more than an hour a day on a regular basis.)
6. Eat vegetable carbohydrates, such as squash, sweet potatoes, root vegetables and, if you tolerate them, legumes and grains.
7. Eliminate hydrogenated vegetable oil; decrease liquid oil rich in omega-6 fatty acids (safflower, sunflower, peanut, soy, cottonseed).
8. Eliminate high fructose corn syrup (HFCS).
9. Do not drink liquid calories, such as soda, sports drinks, undiluted juice, chocolate.
10. Drink filtered water, sparkling water, green tea, diluted juice, herbal teas, juiced vegetables.
11. Limit alcohol intake. (If you are under legal drinking age, do not drink.)

Supplements

Consider nutritional supplements on a patient-by-patient basis:

High-quality fish oil capsules, 2 to 4 gm (600 to 4000 mg EPA/DHA) daily
Zinc gluconate (or other readily absorbed form), 15 to 30 mg daily
Vitamin E with natural mixed tocopherols, 100 to 200 IU daily
Pyridoxal-5-phosphate (B6), 25 to 50 mg daily
Vitamin C 500 mg daily
N-acetyl cysteine 500 mg daily
Selenium 100 micrograms daily
Vitamin A 5000 IU daily

Lifestyle

Complement nutritional intervention with a lifestyle that helps reduce adrenal stress and improve insulin action.

1. Aim to sleep seven to eight uninterrupted hours nightly. If you awaken wishing you could sleep more, you may have a sleep deficit and may need more than eight hours nightly for a while to make it up.
2. Practice an exercise that induces the relaxation response every day, such as meditation, yoga, tai chi, self-hypnosis, biofeedback, or progressive muscle relaxation.
3. Participate in strength, aerobic, and flexibility exercise at least three times weekly. Aim to do at least one of the three every day.

For clinical recommendations specifically written for patients refer to *The Clear Skin Diet* [137].

Figure 22.1 The four elements of acne pathophysiology: hyperkeratosis, increased sebum production, proliferation of *P. acnes*, and inflammation are targets for pharmacologic and nutrient-based treatment. (From www.merck.com, accessed March 31, 2008, used with permission.)

PATHOPHYSIOLOGY TRIGGERS AND DIET

Fatty Acids and Fatty Acid Signaling

Fatty acids serve as precursors for inflammatory mediators, the prostaglandins (PG) and leukotrienes (LT). Classically, the omega-6 fatty acid arachidonic acid (AA) is the most prevalent fatty acid in cellular membranes and is most likely to be plucked out by phospholipase A and shunted down the mediator cascade. The end products include the highly inflammatory PGE2 and LTB4, both of which have been shown to participate in acne.

Human membranes also contain the omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) that travel through the same paths and produce mediators in the odd-numbered series that have far less inflammatory action. (See Figure 22.2.) When even-numbered mediators predominate compared to odd-numbered ones, the internal milieu will be inflamed. These long-chain unsaturated fatty acids also act on genes by binding the PPARs (peroxisoneproliferator activated receptor), members of the family of nuclear receptors that act on the genes for inflammatory cytokines. PPARs inhibit the nuclear transcription factor, NFkappaB, thereby downregulating the production of inflammatory cytokines IL-1, IL-6, and TNF-alpha. Again, some fatty acids ramp the process up, while others keep things calmer. The PPAR ligands have also been shown to affect lipogenesis by sebocytes in culture. Dietary fatty acids play other relevant roles. Omega-3 fatty acids block TLR-2, the innate immunity trigger specifically activated by P. acnes. Zinc may also act at this sit. Omega-3 fatty acids appear to attenuate the proinflammatory response to psychogenic stress. When trans fats exacerbate essential fatty acid deficiency, they both increase hyperkeratosis, as demonstrated in a rat model, and contribute to inflammation.

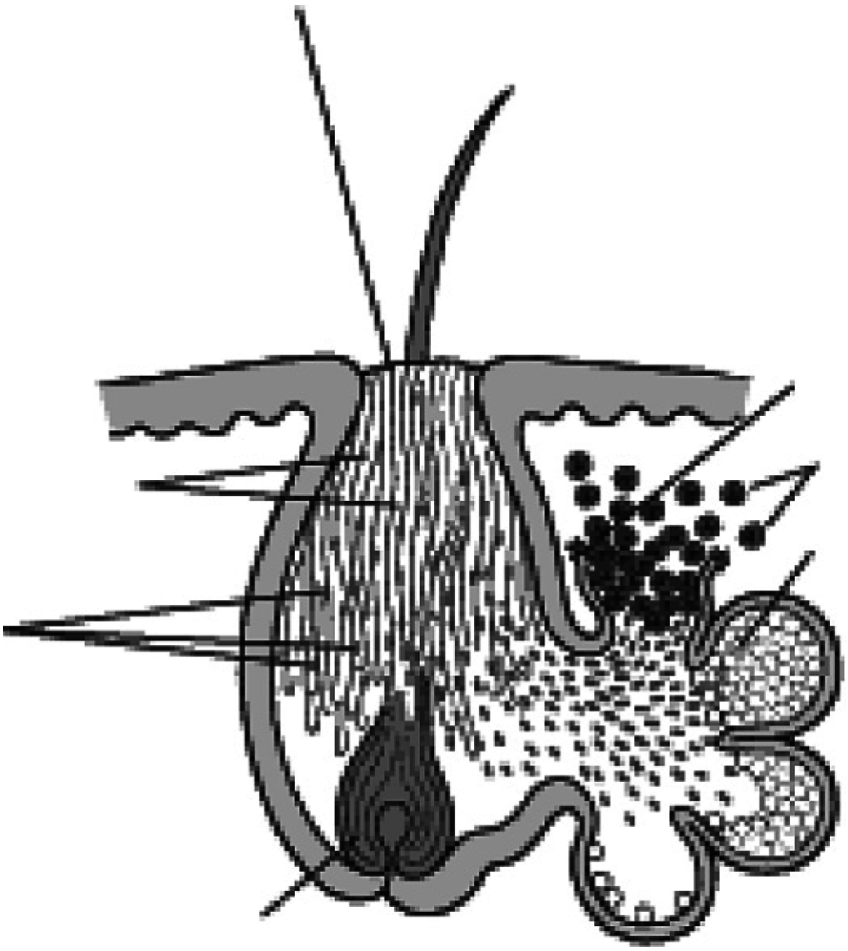

Figure 22.2 Arachidonic acid (AA) and eicosapentaenoic acid follow parallel pathways in the production of inflammatory mediators, but mediators derived from AA have greater inflammatory activity.

The role played by linoleic acid (LA) is complex and incompletely understood. LA suppresses *P. acnes* growth. *P. acnes* protects itself by biohydrogenating LA, rendering it incapable of its suppressive action. LA also controls keratinocyte proliferation and, in its absence, hyperkeratosis occurs. The proportion of LA decreases as sebum production increases. The follicular plugging of acne has been attributed to "localized LA deficiency". On the other hand, LA increases sebum production in cell culture.

In summary, fatty acids and fatty acid signaling via PPARs play important roles in all four of the components of acne pathogenesis: hyperkeratinization, sebum overproduction, *P. acnes* overgrowth, and inflammation.

Diet and Fatty Acids

Fats in the diet end up in the skin. The lipid bilayer cell membranes can be envisioned as sacks made from fatty acid fabric composed of the fats in the diet. Arachidonic acid, dominant in the US diet, is the dominant fatty acid in the bodies of most Americans. LA from vegetable oils converts readily to AA. Enriching the diet with foods containing omega-3 fatty acids will incorporate more EPA and DHA in cell membranes while decreasing AA. A diet rich in hydrogenated vegetable oils will weave a stiff fabric containing straight trans fatty acids. Since cell membranes serve as the reservoir for the building blocks of inflammatory mediators, a stockpile of AA will produce a wealth of inflammatory even-numbered eicosanoids. Omega-3 fatty acids compete for the same enzyme pathways and produce odd-numbered eicosanoids with lower activity. The PPAR and TLR-2 actions of fatty acids may also help explain why higher serum levels of omega-3 fatty acids correlate with lower serum levels of pro-inflammatory markers and higher levels of anti-inflammatory markers. Eating fish and seaweed and taking omega-3 supplements will create a less inflammatory internal milieu. Man-made hydrogenated vegetable oils brought trans fatty acids into our food supply in the early twentieth century and have achieved a dominant position over the past few decades. Intake of hydrogenated vegetable oil, the major source of dietary trans fats, has increased from 10 g/day in 1960 to 30 g/day in 1993. In women, trans fatty acid intake correlates directly with serum levels of inflammatory markers. The same eicosanoid and PPAR mechanisms previously discussed probably explain why eating less hydrogenated vegetable oil will help decrease inflammation.

Concurrent with increased intake of trans fat, the dietary ratio of omega-6 to omega-3 fatty acids changed. When human metabolism evolved, diets

were rich in hunted wild animal and bird meat, fish, and gathered root vegetables, greens, fruits, nuts, seeds, and eggs. The whole vegetable, nut, or seed accompanied by fiber and antioxidant vitamins and plant polyphenols served as the dietary source of omega-6 fats. The ratio of omega-6 to omega-3 was about 1:1. Today much of the fat in the American diet comes from sophisticated, powerful presses squeezing omega-6-rich oils from plant seeds: canola, safflower, sunflower, peanut, soy, and cottonseed. LA, one of the dominant plant seed fatty acids, is an omega-6 fatty acid that is readily converted to AA in our bodies. The heat from the pressing produces oxidized moieties, many not found in nature. Further processing includes degumming, refining, bleaching, deodorizing, additives, and winterization in order to produce the clear oil with a prolonged shelf life that we find in the grocery stores. It is devoid of the polyphenolic compounds that provide color, flavor, and antioxidant protection. The modern dietary omega-6 to omega-3 ratio is about 16:1. In genetic terms the dietary shift is extremely recent, because a 1% change in the human genome occurs approximately every 10,000 years. Given the acneigenic effects of an increased omega-6 to omega-3 ratio and increased dietary trans fats, knowledgeable observers might have predicted the "acne epidemic" that has accompanied this change in the Western diet over the past several decades.

Insulin/Insulin-Like Growth Factor-1

A little-recognized, but well-documented phenomenon of adolescence is the rise and fall of insulin resistance that mirrors acne activity. Insulin resistance peaks at about Tanner stage 3 and returns to normal at the end of the teen years. Insulin is one of our major anabolic hormones and tends to rise with elevation of growth hormone (GH); an increase in insulin levels during a period of rapid growth and development should come as no surprise. Insulin, GH, and insulin-like growth factor-1 (IGF-1) interweave in their physiologic activity. Insulin and IGF-1 can bind each other's receptors and may stimulate similar processes, albeit in different concentrations.

IGF-1 levels reflect GH levels and are used as the surrogate marker for the elusive GH. Elevation during adolescence is normal and expected. Less expected is the elevation of IGF-1 in adult women with acne that was noted by Cappel and colleagues. While men's IGF-1 levels do not correlate with acne severity, they do match DHEA-S and androstendione levels. Cappel and colleagues go on to suggest that the effects of androgens were "dependent on the influence of IGF-1". Patients with longstanding acne have increases in IGF-1 and decreased levels of the protein that binds IGF-1 and takes it out of the action, IGF binding protein-3 (IGFBP-3).

What roles do these factors play in acne? Insulin appears to decrease hepatic production of SHBG, which leads to higher circulating levels of unbound, active androgen triggering all the well-established androgen effects of proliferation and differentiation of the sebocytes as well as upregulation of lipid production. The activity of 5 alpha-reductase, the follicular enzyme that converts testosterone to its more active form, dihydrotestosterone, correlates with fasting insulin levels. Although the correlation has not been shown in acne, insulin can increase systemic inflammatory markers. Insulin and IGF-1 directly increase sebum production, insulin largely through differentiation, and IGF-1 through proliferation of the sebocytes. Free IGF-1 directly stimulates basal keratinocyte proliferation, thereby contributing to the follicular hyperkeratosis, whereas IGFBP-3 inhibits it. Also, IGFBP-3 and tretinoin, a mainstay of acne therapy, bind the same retinoid X nuclear receptor (RXR alpha).

An interesting side note illustrates the web-like interaction of the elements of acne pathophysiology. In vitro, *P. acnes* membrane fraction increases IGF-1 secretion and activates the IGF-1 receptor inducing keratinocyte proliferation. This process is blocked by pre-incubation of cell cultures with zinc gluconate. Insulin/IGF-1 affects three of the four pathophysiologic steps in acne: hyperkeratinization, inflammation, and sebum overproduction.

Diet and Insulin/Insulin-Like Growth Factor-1

Insulin levels are driven by diet. Sugars digested and absorbed into the bloodstream must be directed into cells to be used as energy or stored. The health ravages of diabetes show why our bodies strive to keep blood glucose levels within a tight range, and this is insulin's primary job. Insulin levels chase blood sugar levels, rising fast and high in response to rapidly absorbed refined carbohydrates and more slowly and lower when foods contain more fiber, fat, and protein, all of which slow the absorption of sugar into the blood.

The glycemic index (GI) measures how fast and high blood sugar is pushed by different foods. The glycemic load (GL) takes the usual size of a portion into consideration. The insulinemic response tends to track the glycemic response, so low GI foods eaten at regular intervals will help keep insulin levels moderated throughout the day. A typical American diet tends to result in spiking insulin levels and the area under the curve tends to be high. A diet with decreased fat and refined carbohydrates, an increased ratio of omega-3 to omega-6, fewer saturated fatty acids, and an increase in foods rich in "phytoestrogens" and fiber not only lowered insulin levels but also lowered serum testosterone and raised SHBG. While insulin has a prominent effect on SHBG, dietary monosaccharides, especially fructose, may also slow SHBG production allowing higher testosterone levels. In the only randomized clinical trial of diet and acne, young men with acne were randomized to either a low GI diet or a standard Western diet. Statistically significant clinical improvement in acne paralleled improved insulin sensitivity, BMI, decreased free androgen index, and increased IGFBP-1.

Dairy products are a special case; the insulinemic response is higher than predicted from the GI. In prepubertal boys, casein supplementation increased IGF-1 by 15% with no effect on insulin. Whey supplementation increased insulin by 20% with no effect on IGF-1. The effect of these milk proteins on insulin and IGF-1 may help explain the association between dairy intake and acne found in a series of studies from the Harvard School

Diet clearly affects IGF-1 and IGFBP-3. Insulin raises IGF-1 levels. IGFBP-3, on the other hand, falls after ingestion of high GI foods and rises after eating low GI foods. Lower levels of IGF-1 and higher levels of IGFBP-3 are associated with greater intake of omega-3 fatty acids, tomatoes, vegetables, and dietary fiber. In contrast, higher levels of IGF-1 are associated with dietary saturated fat, vegetable oils, milk, and dairy products.

Stress, Oxidative, and Psychogenic

The link between oxidative and psychogenic stress is not readily apparent, but the following discussion identifies inflammation with its attendant generation of reactive oxygen species as the connection between the two. Using McEwen's concept of allostatic load, stress becomes problematic when the forces impinging on an individual overwhelm the capacity to compensate for the disturbance or when the compensatory mechanisms begin to cause problems themselves. For example, UV light causes oxidative damage to squalene in cell membranes in the dermis. Vitamin E can reduce the oxidized lipid, but unless the vitamin E is replaced or reduced back to its normal state by vitamin C, the capacity to compensate for the oxidative damage becomes overwhelmed and injury/ acne ensues. The compensatory mechanism of cortisol levels rising in response to sleep deprivation keeps the metabolism running fairly smoothly in the short term, but over time, excessive cortisol causes central obesity, peripheral muscle wasting, hyperglycemia, and acne. One night of sleep deprivation causes insulin resistance. This is another example of the web-like patterns of acne pathophysiology.

Several lines of evidence suggest that psychogenic stress plays a role in acne. Examination stress appears to increase acne severity. Stress has been shown to elicit the release of the neuropeptide, substance P, which appears to increase lipogenesis in sebocytes and also increases inflammation via mast cell release of IL-6 and TNF-alpha. CRH generated in the sebaceous gland increases sebocyte lipogenesis. This is thought to be a localized stress response analogous to that of the central

hypothalamic-pituitary adrenal axis. CRH released centrally may have a similar effect. Higher levels of urinary cortisol, a marker of stress, correlate with higher 8-hydroxy-guanosine levels, a marker of DNA oxidation illustrating the connection between psychogenic stress and oxidative stress. Those who practiced a relaxation response–eliciting exercise (RR), such as meditation, progressive relaxation, or Qi gong, had different gene expression profiles compared to those without RR. The specific functional group expression suggested a greater capacity to respond to oxidative stress. The genes COX7B, UQCRB, and CASP2 responded in the opposite direction from that seen in the stress response.

More than 20 years ago, Swedish researchers noted that in men with severe acne, red blood cells carried far less of one of our most powerful antioxidants, glutathione. More recently, the stratum corneum in acne patients bore significantly less glutathione than that of subjects without acne. Measurement of markers of oxidative injury and activity of antioxidant enzymes showed significant oxidative damage in acne patients compared to controls. Reactive oxygen species (ROS) generated by neutrophils contribute to follicular wall injury and inflammation. ROS can serve as regulators of NFkappaB, a transcription factor that upregulates expression of genes for inflammatory cytokines including TNF-alpha, IL-1, IL-8, and IL-6. AP-1 is another redox-sensitive transcription factor that generates inflammatory cytokines. Among the genes reported to be upregulated in acne, the most strongly induced included IL-1, IL-8, and MMP1— all known to be generated through ROS activated pathways. IL-1 may actually "trigger the keratinocyte activation cycle" perhaps serving as one of the very first steps in the formation of an acne lesion. Matrix metalloproteinases (MMPs) degrade IGFBP-3, preventing its protective effect against hyper-keratinization and its action at the retinoid X receptor. Inflammation is triggered by and generates ROS; oxidation and inflammation intimately interconnect. And psychogenic stress, via substance P, spirals into the mix as well.

Stress impacts three of four components of acne pathophysiology:

hyper-keratinization, sebum overproduction, and inflammation.

Diet and Stress (Oxidative and Psychogenic)

Psychological stress induces the production of pro-inflammatory cytokines, IFN-gamma, TNF-alpha, and IL-6. University students with lower serum omega-3 levels or with a higher omega-6/ omega-3 ratio had significantly greater examination-induced TNF-alpha and IFN-gamma responses. Given that the gene for TNF-alpha is one of those found to be activated in acne, that the fact that examination stress increases acne is not surprising. Dietary intake of different fatty acids can alter the immunologic response to stress, broadening the scope of treatment options.

Oxidative stress is a condition of life in our earthly atmosphere. Food serves as an important source of antioxidants to contend with the ROS generated by metabolism. The richest dietary sources of antioxidants are vegetables and fruits. Not only do they contain high levels of antioxidant vitamins, but the polyphenolic compounds that give produce its colors, fragrances, and tastes appear to have even more powerful antioxidant activity than vitamins do.

While some foods offer antioxidant benefit, other foods are pro-oxidants, compounding the problem. Dietary trans fats increase markers of oxidative damage. High fructose intake enhances ROS generation and the protein and lipid damage it causes. In fact, a high fructose diet is used in experimental models to create insulin resistance in rats. Zinc alone and in combination with selenium and vitamin E decreased both the degree of insulin resistance and the oxidative damage sustained. To round out the discussion, oxidative stress appears to be instrumental in triggering insulin resistance, the biochemical finding in teens that most closely parallels acne. Following the syllogism, high fructose intake from food and especially beverages increases ROS generation and exacerbates the normal insulin resistance of adolescence, perhaps contributing to acne. Based on their findings of increased oxidation markers and decreased

antioxidant enzyme activity in acne patients, the researchers stated: "Drugs with antioxidative effects might be valuable in treatment". More prudent perhaps would be the suggestion to increase intake of foods rich in antioxidants and decrease intake of pro-oxidative foods.

Drug-Nutrient Interactions

While some effects of diet and nutrients on medications are well recognized, less known is the converse, the effect drugs can have on nutrient status. The systemic medications used in the treatment of acne include: antibiotics (particularly tetracycline, doxycycline, minocycline), oral contraceptives (for women), and isotretinoin. All are often given for months, even years, at a time. Isotretinoin is usually prescribed for 20 weeks. All have been reported to interact with nutrients.

Antibiotics in general alter the colonic flora and can interfere with production by these organisms of vitamin K, vitamins B1, B2, and B3, biotin, and folic acid, although this has not resulted in clinical reports of vitamin deficiency. A number of antibiotics cause decrease in serum vitamin C levels; the tetracylines were not evaluated in the study. Interaction between the tetracyclines and high-dose vitamin A can cause pseudotumor cerebri.

Oral contraceptives can deplete vitamin B6, at least temporarily, as well as vitamins B12, B2, C, zinc, and folic acid. Iron, copper, and vitamins A and K can be elevated. Clinical consequences are not well documented and supplementation is controversial.

Isotretinoin is a vitamin A analog used in a 20-week course of therapy to treat severe nodulocystic acne. It significantly lowers serum retinol levels in women but not in men. While isotretinoin causes symptoms of hypervitaminosis A, such as dry, peeling skin and angular cheilitis, it can also cause nightblindness, a condition of retinol deficiency. Isotretinoin slows rhodopsin regeneration in the retina; one likely mechanism is competition with 11-cis-retinal for binding proteins in the rhodopsin

system. This suggests that patients on isotretinoin may suffer deficiency of some forms of vitamin A while showing signs of excess of other isoforms, making supplementation problematic. Supplementation with vitamin A during isotretinoin therapy is specifically proscribed, but ensuring a vitamin A-rich diet especially from plant-sourced beta-carotene may be beneficial. Some researchers recommend assuring that patients are replete with vitamin A prior to instituting a course of isotretinoin treatment. The activity of biotinidase, the enzyme that recycles biotin, appears to be impaired by isotretinoin. Although biotin levels do not seem to decline, the hair loss suffered by some patients suggests that this may be clinically relevant for them. Two studies assessing the effect of isotretinoin on vitamin D metabolism produced contradictory results, but both demonstrate significant alterations in serum levels of different forms of vitamin D. Elevation of serum triglycerides and cholesterol is fairly common with isotretinoin and responds to fish oil supplementation. L-carnitine levels tend to fall during a course of isotretinoin and the decline correlates with myalgia. Supplementation with L-carnitine 100 mg/kg/day (compared to placebo) caused resolution of myalgias within five to six days and by day 45 of the study normalized both L-carnitine levels and LFTs that had risen during isotretinoin therapy. Isotretinoin raises homocysteine levels perhaps due to suppression of cystathione-beta-synthase. Elevated homocysteine levels are found in a subgroup of subjects with depression and may play a role in the connection seen between isotretinoin and depression. Supplementation with vitamin B12 and folic acid can improve homocysteine levels but may not have clinical effect.

Laboratory/Diagnostic Tests

If the patient shows signs of hyperinsulinemia, insulin resistance, or polycystic ovarian syndrome, insurance may cover fasting and Two-hour Postprandial Insulin Testing. Given the acneigenic role insulin plays, a positive test result supports an action plan of diet and lifestyle to improve

insulin metabolism. The Zinc Taste Test correlates well with serum zinc levels and can be performed easily and inexpensively in the office. Several nutrient supplement companies offer zinc solution products. The one study that evaluated this phenomenon used 2 ml of a 1% solution of zinc sulfate (approximately 4 mg test dose) held in the mouth for 10 seconds. Taste test scores of one (no particular taste sensation within 10 seconds) and two (perception of a peculiar taste within a few seconds) correlated with zinc deficiency with a serum level < 90 mcg/dl. Zinc taste test scores of three (distinctive taste is perceived immediately but is not a nasty one) and four (perception of a very nasty, distinctive taste straightaway) correlated with normal serum zinc levels, 90-110 mcg/dl. Zinc supplementation increased serum levels and zinc taste test scores significantly and in parallel. Given that the ratio of omega-3 to omega-6 fatty acids in cell membranes influences inflammation, measurement of this parameter, and trans fatty acid levels, can help guide decisions on dietary changes and fish oil supplementation.

Several fatty acid profile tests are available including a recently introduced fingerstick blood draw.

Nutrigenomics

Taking the definition from the University of California, Davis Nutrigenomics Center, "nutritional genomics, or nutrigenomics, is the study of how foods affect our genes and how individual genetic differences can affect the way we respond to nutrients and other naturally occurring compounds in the foods we eat". Individual genetic differences can unveil how foods affect our genes. Single nucleotide polymorphisms in genes can result in protein products with altered function.

In human subjects with substitution of codon 1013 G to A in the IGF-1 receptor gene, free blood levels of IGF-1 are lower than normal. While this polymorphism has not been studied in acne, those with the variant gene showed prolonged lifespan, a physiologic response that does, like

acne, correlate with IGF-1 levels. A study of subjects with Laron Syndrome, congenital IGF-1 deficiency, found only 1 of 22 had acne, a mild case. "Among the 6 treated female patients, 3 had signs of hyperandrogenism (oligo-amenorrhea) and acne during IGF-1 over-dosage. On reduction of the IGF-1 dose (to 50 mg/kg/day) or cessation of treatment, the acne disappeared in all 3 patients". Individual genetic differences in IGF-1 clearly affect the risk of acne in response to foods. Using diet to lower insulin/IGF-1 may mimic the effects seen in those with genetically low levels and improve acne (and longevity, too).

Melnik elucidates the genomic effects of increased insulin/IGF-1 by tracing its activation of the phosphoinositide-3-kinse/Akt pathway and the subsequent reduction of nuclear transcription factor Fox 01. Nuclear Fox 01 suppresses nuclear androgen receptors and PPAR gamma as well as "key genes and transcription factors of cell proliferation (cyclin D2), lipid biosynthesis (sterol response element binding protein-1) and inflammatory signaling (NF kappa-B)". Loss of nuclear Fox 01 de-represses these genes and receptors increasing androgen signaling, cell proliferation, sebum production, and inflammation—expressions of the pathophysiology of acne. Following this line of reasoning, the insulingenic effects of milk provide a genetic mechanism that accounts for the epidemiologic correlation between milk intake and acne.

PPARs are gene transcription factors activated by ligands that include EPA and DHA. Their actions are complex and sometimes contradictory. Activation of PPARs increases sebum production. On the other hand, PPAR alpha activation represses NFkappaB transcription decreasing production of inflammatory cytokines. Activation of PPAR gamma also promotes epidermal differentiation, restoring epidermal homeostasis in hyperproliferative mouse skin. Most studies of PPAR agonists have used pharmaceuticals; evidence suggests that fatty acids, among the endogenous ligands, may have similar activities.

A twin study of acne genetics found only one striking difference between twins with and without acne—decreased ApoA1 in those with acne. This

lipoprotein fraction is associated with decreased cardiovascular risk and can be raised by exercise, diet, and weight control. The dietary advice offered in the study was as follows: avoid excessive consumption of high-fat foods, reduce portion sizes, and increase daily intake of complex carbohydrates, lean meats, dairy products, fruits, and vegetables. Of note, the program also improved insulin sensitivity and decreased serum markers of lipid oxidation.

A Medline search for "nutrigenomics" produced 619 references in January 2012; the number dropped to zero when the term was crossed with "acne." This field of study is in its infancy. Our food speaks to our genes; gene expression is dictated by the environment washing over our cells and our diet is the major ruler of that environment. Other elements of lifestyle, such as stress and exercise, also modify the environment that dictates gene expression. Recognition of the critical roles these elements play in our health and disease is dawning in medicine. Soon the need to control for these variables, a rare occurrence in the gold standard, double-blind, placebo-controlled studies we revere, will alter research dramatically. Until then, lower level evidence and common sense guide our use of diet and nutrients in disease management.

Conclusion and Clinical Summary

Diet can influence the antecedents and triggers of acne—the proximate causes behind the four pathophysiologic elements of acne. Why did two widely accepted clinical trials conclude otherwise? We return to these two landmark studies that turned the tide away from the acne-diet connection. Through the lens of modern nutritional science, the two studies that form the foundation of the current diet-acne dogma demonstrate significant weaknesses, the most glaring being that neither took the underlying diet into consideration. Anderson's open study included only 27 subjects and no controls; it would not be accepted for publication under today's more stringent peer review . Fulton and

colleagues concluded that chocolate had no influence on acne by comparing a chocolate bar to a pseudochocolate bar composed of 28% hydrogenated vegetable oil, a food known to increase inflammatory markers, and 14% nonfat milk solids, the acneigenic potential of which is demonstrated by three studies from the Harvard School of Public Health. The sugar content of the bars was 44.3% and 53% respectively; both likely to induce a rapid and high insulin response. The evidence for a dietary effect on acne is a young and growing body of knowledge, but it is far more robust than the evidence against such an effect. In spite of the dearth of the controlled, blinded, human trials that clinicians rely on most heavily, the risk-benefit ratio of dietary strategies for acne remains far more favorable than any pharmaceutical agent. The implementation of a dietary treatment for acne does not preclude conventional treatment and is likely to complement it. Even when advised that these suggestions are based on biochemistry and physiology, cell culture and animal studies, but very few human clinical trials, many patients will take the opportunity to incorporate lifestyle modification. A summary clinical approach is presented in Table 22.1.

TABLE 22.1
Food, Nutrient, and Lifestyle Approaches to Managing Acne

Diet

1. Try a dairy-free diet for three to six months. No milk, cream, yogurt, ice cream, cheese of any kind (including cream and cottage). Decrease your use of butter or switch to ghee (clarified butter).
2. Eat three nutrient-dense meals and two "mini-meal" snacks daily.
3. Eat five to eight servings of vegetables and two servings of fruit per day, all colors of the rainbow.
4. Eat 2.5 to 3 palm-sized servings of protein-rich foods (meat, poultry, eggs, fish) daily; include fish one to two times weekly.
5. Minimize refined carbohydrates, such as candy, sweets, baked goods, crackers, white bread, white rice, white potatoes, pasta. (Unless you are performing very high intensity exercise more than an hour a day on a regular basis.)
6. Eat vegetable carbohydrates, such as squash, sweet potatoes, root vegetables and, if you tolerate them, legumes and grains.
7. Eliminate hydrogenated vegetable oil; decrease liquid oil rich in omega-6 fatty acids (safflower, sunflower, peanut, soy, cottonseed).
8. Eliminate high fructose corn syrup (HFCS).
9. Do not drink liquid calories, such as soda, sports drinks, undiluted juice, chocolate.
10. Drink filtered water, sparkling water, green tea, diluted juice, herbal teas, juiced vegetables.
11. Limit alcohol intake. (If you are under legal drinking age, do not drink.)

Supplements

Consider nutritional supplements on a patient-by-patient basis:

High-quality fish oil capsules, 2 to 4 gm (600 to 4000 mg EPA/DHA) daily
Zinc gluconate (or other readily absorbed form), 15 to 30 mg daily
Vitamin E with natural mixed tocopherols, 100 to 200 IU daily
Pyridoxal-5-phosphate (B6), 25 to 50 mg daily
Vitamin C 500 mg daily
N-acetyl cysteine 500 mg daily
Selenium 100 micrograms daily
Vitamin A 5000 IU daily

Lifestyle

Complement nutritional intervention with a lifestyle that helps reduce adrenal stress and improve insulin action.

1. Aim to sleep seven to eight uninterrupted hours nightly. If you awaken wishing you could sleep more, you may have a sleep deficit and may need more than eight hours nightly for a while to make it up.
2. Practice an exercise that induces the relaxation response every day, such as meditation, yoga, tai chi, self-hypnosis, biofeedback, or progressive muscle relaxation.
3. Participate in strength, aerobic, and flexibility exercise at least three times weekly. Aim to do at least one of the three every day.

For clinical recommendations specifically written for patients refer to *The Clear Skin Diet* [137].

Table 22.1 Food, Nutrient, and Lifestyle Approaches to Managing Acne;

One final note: evidence that increased IGF-1 and decreased IGFBP-3 levels are associated with increased prostate cancer dovetails with the increased risk of prostate cancer seen in those with more severe acne treated with tetracycline. While the connection to breast cancer is less clear, hyperinsulinaemia, subsequent insulin resistance, and stimulation of the insulin-like growth factor-1 axis all promote tumor progression and type 2 diabetes has been described as an independent negative prognostic factor for breast cancer. Addressing dysregulated IGF-1/ IGFBP-3/insulin to treat the underlying mechanisms of acne improves our patients' long-term health by decreasing cancer risk as well.