Type 2 diabetes mellitus represents a global epidemic that is predicted to intensify. The number of individuals with type 2 diabetes mellitus (DM) worldwide was 30 million in 1985, 171 million in 2000, and 220 million in 2009. As of 2014, type 2 DM is estimated to affect 387 million individuals worldwide, representing a worldwide prevalence of 8.3%. From 1990 to 2008, the prevalence of DM doubled, and had not declined by 2012. From 1998 to 2009, the prevalence of DM rose a staggering 230% in Canada alone and is predicted to continue rising. The CDC estimates 40% of Americans will develop DM in their lifetime.

Type 2 DM is common in both the developed and developing worlds. The increasing prevalence of DM is attributed to rising obesity rates, sedentary lifestyles, aging populations, and improved survival of individuals with the disease.

Type 2 DM is also associated with huge health care costs. In a special report from 2009 entitled, An Economic Tsunami: the Cost of Diabetes in Canada, the estimated cost of type 2 DM in 2010 was $12.2 billion and projected to increase by a further $4.7 billion by 2020.

The silver lining is that type 2 DM is largely preventable, with epidemiological studies predicting primary prevention of diabetes in America could reduce the risk of all-cause and cardiovascular mortality by up to 9.0%.

PATHOPHYSIOLOGY

The pathophysiology of type 2 DM is complex and fundamentally consists of hyperglycemia, insulin resistance, and impaired insulin secretion (see Fig. 33.1 for a general overview).

Carbohydrate intake and subsequent absorption of glucose into the blood triggers insulin release from the beta cells of the pancreas. Insulin stimulates the uptake of glucose into cells via the GLUT-4 glucose transporter. Insulin resistance (IR) may ensue after chronic exposure to high serum glucose levels. Steroid administration and physical inactivity may also contribute. The development of type 2 DM is thought to be characterized by peripheral cells becoming unable to efficiently uptake glucose in response to insulin in combination with beta islet cell dysfunction and decreased insulin production.

Insulin functions in stimulating cellular glucose uptake, decreasing hepatic gluconeogenesis, and increasing adipose tissue triglyceride synthesis, glucagon regulation, and vascular tone. These important functions of insulin are all impaired in type 2 DM.

Diabetes is referred to as “starving amidst the feast.” IR refers to impaired glucose transport into muscle cells that accounts for the “starving” amidst the hyperglycemia “feast.” Additionally, cellular starvation feedback mechanisms exacerbate hyperglycemia by stimulating hepatic gluconeogenesis and fat breakdown.

IR also contributes to the production of free fatty acids and inflammatory cytokines. Inflammatory markers shown to be elevated in DM include C-reactive protein, IL-6, plasminogen activator inhibitor-1 (PAI-1), and tumor necrosis factor (TNF)-alpha, in addition to white cell count.

Adiponectin is an antiinflammatory cytokine that has been shown to reduce plasma levels of free fatty acids. High adiponectin is associated with improved lipid profiles, glycemic control, and reduced inflammation. DM has shown to be correlated with a reduction in adiponectin.

Adiponectin is a hormonal protein produced by adipose tissue. Contrary to common sense, low levels (not high) of adiponectin are bad and result from a proinflammatory state. Adiponectin levels can be increased with exercise and weight loss.

While studies on type 2 DM pathophysiology have previously focused on IR, the role of the pancreas has become increasingly recognized. Beta islet cells are well known to produce insulin; however, these are not the only pancreatic islet cells. Alpha islet cells produce glucagon, considered a counterpart of insulin. The interaction between insulin and glucagon is usually very tightly regulated; however, increased glucagon further exacerbates the hyperglycemic state in type 2 DM as a result of IR and impaired insulin secretion.

Genetics also contribute to the pathogenesis of type 2 DM. Medical genomics is considered to be a field of active research with great potential. Genomic single-nucleotide polymorphisms (SNPs) have been shown to be associated with DM risk. Genetic risk may also interact with environmental factors.

Inorganic arsenic exposure in drinking water increases risk of type 2 DM. Bisphenol A, used in hard plastics and resins, has also been linked to DM. Pesticide exposure, specifically organophosphates and chlorinated pesticides, may also be associated with increased risk.

INTEGRATIVE THERAPY

Lifestyle

Diabetes is largely preventable. The principles of preventative management apply a holistic therapeutic approach to patients with established DM.
Four large epidemiological, long-term studies are widely cited in support of lifestyle intervention as the cornerstone of type 2 DM prevention. In 2001, the Finnish Diabetes Prevention Study (DPS) investigated 522 middle-aged, overweight subjects with impaired glucose tolerance over 4–10 years. The lifestyle intervention consisted of counseling aimed at reducing weight, total intake of fat, and intake of saturated fat, and increasing intake of fiber and physical activity. Annual oral glucose tolerance testing indicated DM to be largely preventable in this cohort of high-risk individuals.

In 2002, the Diabetes Prevention Program (DPP) investigated 3234 overweight high-risk individuals with impaired glucose intolerance (mean age, 51 years) over a 3-year period. Similar lifestyle interventions to the Finnish study were found to be superior to metformin in terms of diabetic prevention.

The China Da Qing Diabetes Prevention Study, involving 577 high-risk individuals identified by a region-wide clinic screening process of >110,000 individuals, reported similar results over 6 years of lifestyle intervention.

More recently, the 2011 nationwide Zensharen Study for Prevention of Lifestyle Diseases involving 641 overweight Japanese middle-aged persons with impaired glucose tolerance reported lifestyle modifications regarding weight loss, diet scrutiny, and exercise were associated with a decreased risk of type 2 DM.

### Smoking

Several studies, including meta-analyses, have shown smoking is a preventable risk factor for type 2 DM. Mechanisms underlying the association between smoking and type 2 DM include impaired insulin sensitivity, glucose tolerance, and the metabolic syndrome.

### Exercise

Exercise is tantamount in both the prevention and management of type 2 DM. Large cohort studies over 15–20 years have reported decreased cardiovascular risk and all-cause mortality in diabetics who undertake regular physical activity. Both aerobic exercise and resistance training reduce HbA1c in patients with type 2 DM.

Studies indicate regular yoga can reduce HbA1c and fasting blood glucose levels. Hatha yoga is reported to have most evidence in reviews. In fact, Hatha yoga has shown to reduce HbA1c to the same effect as regular aerobic exercise.

Health care providers can support patients by encouraging 30 to 60 minutes of moderate-intensity aerobic activity on most days of the week. The American Heart Association, the American Diabetes Association, and the American College of Sports Medicine recommend at least 150 minutes of moderate-intensity aerobic activity per week for patients with diabetes (see Chapter 91, Writing an Exercise Prescription).

### Nutrition

Nutrition, exercise, and lifestyle are the tripartite cornerstones of integrative diabetic management. Evidence supports the use of all three of these important modalities.

Nutrition therapy alone has been shown to improve glycemic control and lower HbA1c levels by 1%–2%. This powerful evidence comes from multidisciplinary efforts between general practitioners, registered dietitians, and educators to individualize diet plans with regular follow-up. Dietitians and diabetic nurse educators are valuable resources with clear benefit in DM management.

In general, diets incorporating the principles of food guides, such as the Healing Foods Pyramid (Fig. 33.2), are a good starting point for clinicians and patients.
Education regarding glycemic index (GI) takes this approach a step further. Glycemic index refers to blood glucose spikes following the intake of certain foods. High GI foods, such as table sugar, have greater effects on blood glucose levels and generate wide swings in insulin levels, eventually contributing to IR. A large multicenter meta-analysis demonstrated that diets containing low GI foods can reduce HbA1c by 0.43%. GI tables are widely available online (http://www.diabetes.ca/diabetes-and-you/healthy-living-resources/diet-nutrition/the-glycemic-index).

Another important concept is glycemic load (GL). GL is based on GI but also incorporates the quantity of carbohydrate in a typical serving size. For example, bananas have a low GI (52) but a high GL (10.5) due to high carbohydrate content by weight. Conversely, watermelon has a high GI (72) but low GL (3.6) (see Chapter 87).

**Specific Foods**

**Fiber**

Soluble dietary fibers, such as psyllium, oats, beans, and eggplant, have been shown to lower postprandial blood glucose. Pulses, such as lentils, chickpeas, and beans, also lower blood glucose. Soy, walnuts, and other nuts have demonstrated similar benefits. Almonds in particular have been shown to reduce both HbA1c and postprandial blood glucose levels in small trials. A growing body of research supports the beneficial effects of vegetarian and vegan diets for patients with type 2 DM. In addition to vegetable protein, whole grains are also rich in minerals and antioxidants. In a large prospective cohort study, fiber from whole grains improved glycemic control in patients with type 2 DM.

**Alcohol**

Light to moderate alcohol consumption may be beneficial in DM. Studies have shown decreased risk of type 2 DM and death due to CAD in established diabetics. The majority of studies included in this review favored red wine, indicating the antioxidant effects of resveratrol to be a potential mechanism. Further, moderate alcohol consumption has been linked with higher adiponectin levels. Adiponectin, described previously, supports glucose homeostasis and improves insulin sensitivity.

The resveratrol and alcohol in red wine may raise adiponectin levels and maintain insulin sensitivity.
**Dietary Fat**

Diets higher in saturated versus polyunsaturated fats have been shown to be associated with increased HbA1c and IR in patients with type 2 DM.\(^5\) The quality of fat is important. Research supports selective fat intake, favoring monounsaturated and polyunsaturated fats such as omega-3, which have been shown to prevent cardiovascular disease.

The Mediterranean diet captures the beneficial effects of macronutrient selectivity. A rigorous 4-year trial and subsequent 8-year follow-up comparing a low carbohydrate Mediterranean diet versus a low fat diet reported a reduction in HbA1c, decreased requirement for the initiation of diabetes medications, and an increase in cases of diabetes remission.\(^66,57\)

Other foods that may be of benefit include chia (Salvia hispanica), which is rich in alpha-linoleic acid, and onions (Allium cepa). Magnesium deficiency has been shown to be a risk factor for type 2 DM.\(^58\) Magnesium is found in dark green leafy vegetables, nuts, whole grains, and coffee. Moderate caffeine intake in the form of coffee or green tea may decrease risk of type DM according to a systematic literature review and meta-analysis.\(^59\)

**Mind-Body Therapy**

**Mindfulness**

A plethora of literature is amassing in support of the health benefits of mindfulness, with 52 papers published in 2003, rising to 477 by 2012. Nearly 100 randomized controlled trials (RCTs) of mindfulness were published in 2014. Mindfulness has been shown to reduce stress, blood pressure, and even mitigate cardiovascular risk. A particularly interesting study involving PET scans of Buddhist monk brains during meditation provided concrete evidence that meditation can induce neurophysiological changes\(^60\) (see Chapter 100).

**Cognitive-Behavioral Therapy**

Cognitive-behavioral therapy helps patients gain insight into the habits and patterns that affect their thoughts and actions and the ways in which these thoughts and actions affect their health and lives. A sizeable body of research has established the benefits of cognitive-behavioral therapy on glycemic control and self-care. In a systematic review of 25 trials in type 2 DM, 12 trials involving 522 patients used glycemic control as an outcome measure. In those trials, participants who received 6 to 16 group or individual counseling sessions had a 0.76% reduction in HbA1c levels compared to placebo.\(^61,62\)

**Biofeedback**

Biofeedback training can strengthen the mind-body connection by helping patients learn to control specific bodily functions, including muscle tension, skin temperature, sweating, breathing, heart rate, and even regional brain waves. In a published study, researchers randomized 39 patients with well-controlled type 2 DM to receive 10 weekly individual sessions of skin temperature and electromyograph biofeedback or 3 group education sessions. Biofeedback was associated with improved glycemic control and a decrease in HbA1c levels by 0.8%.\(^63\) This finding may seem surprising; however, biofeedback trials have reported changes in plasma cortisol, peripheral vasoconstriction, and other markers of sympathetic nervous system activity.

**Sleep Hygiene**

Several studies have linked poor sleep hygiene with DM risk. Systematic and meta-analyses of these studies have confirmed that too short, too long, or interrupted sleep compared to 8 hours of uninterrupted sleep significantly increases DM risk.\(^64\)

**Herbalism**

Herbalism is the most ancient practice of medicine, indeed as old as human beings. Even chimpanzees have been shown to use plant medicines for the treatment of certain gastrointestinal ailments.

As an example, metformin, a derivative of the French lilac, has been used to treat DM since the middle ages.

Personally, I advise consultation with professional herbalists, preferably registered under their respective regional guild, to ensure prescription quality. In general, I value tincture extracts more than capsules of ground material due to greater potency and bioavailability. For patients who prefer over-the-counter medications or are unable to afford a herbalist consultation, I would recommend the use of products that are standardized extracts.

Table 33.1 includes a review of literature regarding commonly used plants and supplements. Below are plant medicines that have been trialed for at least 3 months (the lifespan of a RBC is 120 days) and demonstrated reductions in HbA1c levels of at least 0.5% in patients with type 2 DM.

**Botanicals**

**Coccinia cordifolia**

*Coccinia cordifolia*, or ivy gourd, is a perennial herb of the cucumber family. It is native to India but spreads easily and is now distributed worldwide. It is an important Ayurvedic diabetes medicine with additional choleric, laxative, antiinflammatory, and demulcent properties.

The leaves appear to have insulinomimetic effects on lipolytic enzymes, protein lipase, glucose-6-phosphatase, and other glycolytic enzymes. A double-blind, placebo-controlled RCT of 60 diabetics aged 35–60 years was performed, with the treatment arm consisting of 1 g ivy gourd extract for 90 days. The results demonstrated significant decreases in fasting, postprandial blood glucose, and HbA1c levels compared to placebo.\(^65\)

**Dosage**

Dried leaves or extracts at doses equivalent to 15 g can be taken with meals.

**Precautions**

Ivy gourd is well-tolerated but may cause nausea, drowsiness, and headaches.
# TABLE 33.1 Glycemic Effects and Cardiovascular Benefits of Different Treatments for Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Effects</th>
<th>Cardiovascular Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic exposure avoidance</td>
<td>Arsenic exposure increased risk by 358% in population studies</td>
<td>—</td>
</tr>
<tr>
<td>Emotional stress avoidance</td>
<td>Emotional stress increased risk by 60% to 236% in population studies</td>
<td>CV and all-cause mortality</td>
</tr>
<tr>
<td>Egg avoidance</td>
<td>Egg consumption increased risk by 50% in two population studies</td>
<td>CV disease</td>
</tr>
<tr>
<td>Coffee</td>
<td>Reduced risk by 40% in meta-analysis</td>
<td>Lipids, CV mortality</td>
</tr>
<tr>
<td>Leafy green vegetables</td>
<td>Reduced risk by 14% in meta-analysis</td>
<td>BP, lipids, all-cause mortality</td>
</tr>
<tr>
<td>Moderate alcohol consumption</td>
<td>Reduced risk by 50% in meta-analysis</td>
<td>Lipids, CV and all-cause mortality</td>
</tr>
<tr>
<td>Avoidance of sugar-sweetened beverages</td>
<td>Sugar-sweetened beverages increased risk by 26% in meta-analysis</td>
<td>—</td>
</tr>
<tr>
<td>Treatment of periodontal disease</td>
<td>Periodontal disease increased risk by 150% to 225% in population studies</td>
<td>MI and stroke risk</td>
</tr>
<tr>
<td>Lifestyle intervention</td>
<td>HbA1c decreased 0.3% in meta-analysis</td>
<td>BP, lipids</td>
</tr>
<tr>
<td>Regular exercise</td>
<td>HbA1c decreased 0.6% in meta-analysis</td>
<td>BP, lipids, CV and all-cause mortality</td>
</tr>
<tr>
<td>Low-glycemic diet</td>
<td>HbA1c decreased 0.5% in meta-analysis</td>
<td>Lipids, CV disease</td>
</tr>
<tr>
<td>Beans and pulses</td>
<td>HbA1c decreased 0.5% in meta-analysis</td>
<td>BP, lipids</td>
</tr>
<tr>
<td>Chia</td>
<td>—</td>
<td>BP, C-reactive protein</td>
</tr>
<tr>
<td>Cognitive-behavioral therapy</td>
<td>HbA1c decreased 0.78% in meta-analysis</td>
<td>—</td>
</tr>
<tr>
<td>Biofeedback</td>
<td>HbA1c decreased 0.8% in one trial</td>
<td>—</td>
</tr>
<tr>
<td>Treatment of vitamin D deficiency</td>
<td>May decrease type 2 DM risk</td>
<td>Endothelial function</td>
</tr>
<tr>
<td>Chromium</td>
<td>HbA1c decreased 0.6% in meta-analysis</td>
<td>—</td>
</tr>
<tr>
<td>Alpha-lipoic acid</td>
<td>Decreased diabetic neuropathy</td>
<td>? Liver, CV disease</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>—</td>
<td>Lipids, platelets, CV disease</td>
</tr>
<tr>
<td>Magnesium</td>
<td>HbA1c decreased 0.3% in meta-analysis</td>
<td>Lipids, endothelial function</td>
</tr>
<tr>
<td>Reduces type 2 DM risk 16%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>L-Carnitine</td>
<td>? Insulin sensitivity</td>
<td>Lipids, lipoprotein(a)</td>
</tr>
<tr>
<td>Benfotiamine</td>
<td></td>
<td>Endothelial function</td>
</tr>
<tr>
<td>Vitamin K(_\text{a})</td>
<td>? Stimulates beta cells</td>
<td>CV disease</td>
</tr>
<tr>
<td>Avoidance of selenium</td>
<td>Selenium may increase risk 55%</td>
<td>—</td>
</tr>
<tr>
<td>Avoidance of high-dose vitamin B(_{6}),</td>
<td>These vitamins may increase nephropathy</td>
<td>Increased CV disease</td>
</tr>
<tr>
<td>vitamin B(_{12}), folate</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Berberine</td>
<td>HbA1c decreased 0.9% in one trial</td>
<td>—</td>
</tr>
<tr>
<td>Cinnamon</td>
<td>HbA1c decreased 0.5% in one trial</td>
<td>—</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Improved glucose parameters</td>
<td>—</td>
</tr>
<tr>
<td>Fenugreek</td>
<td>HbA1c decreased 1.4% in one trial</td>
<td>—</td>
</tr>
<tr>
<td>Ivy gourd</td>
<td>HbA1c decreased 0.6% in one trial</td>
<td>—</td>
</tr>
<tr>
<td>Momordica charantia</td>
<td>Improved glucose parameters in four trials</td>
<td>—</td>
</tr>
<tr>
<td>Prickly pear cactus stem</td>
<td>Improved glucose parameters in one trial</td>
<td>—</td>
</tr>
<tr>
<td>Pycnogenol</td>
<td>HbA1c decreased 0.8% in one trial</td>
<td>—</td>
</tr>
<tr>
<td>Metformin</td>
<td>HbA1c decreased 1.0%</td>
<td>CV and all-cause mortality</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>HbA1c decreased 1.25%</td>
<td>—</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>HbA1c decreased 1.0%</td>
<td>May increase risk</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>HbA1c decreased 1.25%</td>
<td>—</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>Curative in 78% of patients</td>
<td>? CV and all-cause mortality</td>
</tr>
<tr>
<td>Insulin</td>
<td>Dose-dependent</td>
<td>—</td>
</tr>
</tbody>
</table>

BP: blood pressure; CV, cardiovascular; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; MI, myocardial infarction.
Salacia Reticulate

Salacia reticulate, or kothala himbutu, was investigated in a double-blind, crossover RCT of an herbal tea containing kothala himbutu extract in 51 patients with controlled DM over 3 months. This study reported significantly lower HbA1c levels in the treatment arm.66

**Dosage**

Three times daily before meals. In the previous trial, the tea was manufactured by Siddhalepa Ayurveda Hospitals, Ratmalana, Sri Lanka and prepared in accordance with a patented formula (international patent application no. PCT/IB00/00405).

**Precautions**

Side effects are dose-dependent and predominantly include gastrointestinal disturbances, such as gas, bloating, abdominal pain, and diarrhea.

Touchi (Soy)

Water-extracted touchi, a traditional Chinese food (soybean extract), has been shown to exert a strong inhibitory effect on rat intestinal alpha-glucosidase. Touchi was also investigated in a 3-month, double-blind, randomized trial of 36 diabetics. Treatment consisted of 0.3 g of touchi in the form of tea preprandially for 3 months and resulted in a reduction in HbA1c levels by 0.5% vs placebo.67

**Dosage**

0.3 g in tea before meals.

**Precautions**

Well tolerated orally but may cause mild gastrointestinal upset.

Gynostemma Pentaphyllum

Gynostemma pentaphyllum is a Vietnamese herb used as a tea to treat DM. A double-blinded RCT of 24 drug-naïve patients with diabetes treated with 6 g tea daily for 12 weeks vs placebo reported a reduction in plasma glucose and a decrease in HbA1c levels of 2%.68

**Dosage**

6 g in tea daily.

**Precautions**

Generally well tolerated but may cause nausea and diarrhea.

Marine Collagen Peptides (Gelatin)

Marine collagen peptides from fish hydrolysate, a traditional Chinese medicine, were investigated in an RCT of 100 patients with diabetes compared to a control group. This trial reported that administration of 13 g of marine collagen peptides for 3 months significantly lowered LDL, free fatty acids, and markers of inflammation, such as C-reactive protein and nitric oxide, in addition to reducing HbA1c levels and increasing adiponectin levels.69

**Dosage**

13 g as a capsule daily.

**Precautions**

May cause an unpleasant taste, bloating, gas, or heaviness in the stomach.

Silymarin (Milk Thistle)

The antioxidant flavonoid silymarin, an extract of milk thistle (*Silybum marianum*), has demonstrated good results in several rigorous trials. As an adjunct to glibenclamide, silymarin was investigated at a dose of 200 g/day in 52 patients with diabetes for 120 days. This randomized, placebo-controlled, double-blinded trial reported reductions in HbA1c levels and body-mass index.70,71

**Dosage**

200 g/day extract.

**Precautions**

Well tolerated but may have a laxative effect or cause gastrointestinal symptoms.

Citrullus Colocynthis

Citrullus colocynthis, also known as the schrad fruit, is a traditional medicine of Iran. A clinical trial investigating 25 patients with diabetes treated with 100 mg fruit capsules versus control reported significant reductions in plasma glucose and HbA1c levels.72

**Dosage**

100 mg fruit capsules.

**Precautions**

High doses may cause irritation of the gastric mucosa resulting in bloody diarrhea and colitis. Nephrotoxicity has also been documented.

Cinnamon

Cinnamon is a culinary spice made from the bark of *Cinnamomum* sp. trees. The aqueous extract appears to improve insulin receptor function by multiple mechanisms in addition to increasing glycogen synthase activity. However, the results of clinical trials have been inconsistent, with the majority of trials being small and insufficiently powered. A proportion of trials have reported the benefit of cinnamon in reducing HbA1c levels.73 A trial compared *Cinnamomum aromaticum* (cassia cinnamon) 500 mg twice daily with usual care in 109 patients with type 2 DM for 90 days. This trial reported mean reductions in HbA1c levels of 0.83% in the cinnamon group and 0.37% in those receiving usual care, a difference that reached statistical significance.74 A Cochrane
meta-analysis of 10 RCTs did not demonstrate the efficacy of 2-g *Cinnamomum cassia* in reducing HbA1c levels. However, a separate meta-analysis concluded that cinnamon can reduce plasma blood glucose levels. More investigation is required regarding this.

### Dosage

The optimal dose of cinnamon for the treatment of type 2 DM is unclear; however, 1- to 2-g doses are commonly prescribed (1 teaspoon of cinnamon is equivalent to 4.75 g). The majority of over-the-counter cinnamon preparation are a combination of cassia and Ceylon cinnamon.

### Precautions

Stomatitis and perioral dermatitis have been reported with the use of cinnamon.

### Fenugreek

*Trigonella foenum graecum*, or fenugreek, is a legume used extensively in India, North Africa, and the Mediterranean. The defatted seeds of fenugreek have been used to treat diabetes for centuries in Ayurvedic and other healing systems. A component of fenugreek, 4-hydroxyisoleucine, has been shown to increase pancreatic insulin secretion and inhibit glucosidase activity, with studies reporting effects on satiety, gastric emptying, and insulin receptor function. Fenugreek may also have lipid-lowering effects and several studies have posited hypoglycemic effects. In 42 patients with diabetes poorly controlled with sulfonylureas, 2.1 g fenugreek extract tid for 12 weeks reduced HbA1c and fasting blood glucose levels compared to placebo.

### Dosage

Until further evidence provides clear guidance, practitioners may use crude powder or extracts at doses equivalent to 20 to 30 g of crude seeds. This dose can be titrated according to meal size and individual results.

### Precautions

Fenugreek may cause gastrointestinal intolerance, with diarrhea, dyspepsia, abdominal distention, and flatulence.

### Supplements

Table 33.1 describes the glycemic effects and cardiovascular benefits of different treatments for type 2 DM.

### Vitamin D

25(OH)D levels have been shown to be lower in type 2 DM and obesity. Studies have reported that vitamin D levels are associated with increased risk of type 2 DM, by virtue of insulin sensitivity and beta cell activity. However, while studies are supportive of the use of vitamin D supplementation in the management of type 2 diabetes, others remain inconclusive. A review of eight trials reported no glycemic benefit of vitamin D supplementation.

### Chromium

This trace element has several effects on carbohydrate and lipid metabolism. A complex containing trivalent chromium has been shown to influence glucose tolerance. Evidence suggests that chromium acts to reduce tissue lipid content and that chromium responders are more likely to be more obese, more insulin resistant, and have poorer glycemic control regardless of baseline chromium status. A meta-analysis of 41 trials evaluating the glycemic effects of various formulations identified 14 trials of chromium including patients with type 2 DM. However, the evidence was determined to be difficult to interpret because of low study quality and differences in formulation and dose, with the best results reported by trials evaluating chromium picolinate or brewer’s yeast at doses of at least 200 mcg daily. In these trials, a mean reduction in HbA1c of 0.6% compared with placebo was reported.

### Dosage

A dose of 200 to 1000 mcg daily is recommended.

### Precautions

Chromium has no known side effects.

### Alpha-Lipoic Acid

Also known as *thioctic acid*, alpha-lipoic acid (ALA) is a potent lipophilic antioxidant that is found in most eukaryotic cells. ALA also acts as a cofactor for several mitochondrial and cytosolic enzymes, with the right-sided enantiomer being the active form. In addition to its antioxidant activity, ALA can also regenerate other antioxidants via reduction reactions, including vitamins C and E, coenzyme Q10, and glutathione. ALA also chelates mercury, arsenic, iron, and other metals that act as free radicals. ALA is present in trace amounts in organ meats and some vegetables, but these amounts are negligible compared with usual therapeutic doses.

ALA has been used to treat several diseases in Europe and Japan since the 1950s. A large body of preclinical research supports the potential benefit of ALA in liver disorders, cardiovascular disease, cancer prevention, and neuropsychiatric disorders, and for heavy metal and general detoxification.

Good evidence indicates that ALA reduces painful diabetic neuropathy. First used parenterally, ALA in oral form has been shown to be effective in a multicenter trial involving 181 patients with type 2 DM who received varying doses for 5 weeks. All doses provided an overall reduction in symptoms of 50%, with the lowest dose (600 mg daily) causing the fewest side effects. This finding may be related to reduced lipid peroxidation in neuronal cell membranes or improved endothelial function and microvascular blood flow. ALA may also improve insulin sensitivity through enhanced GLUT4 translocation and glucose uptake in muscle and fat cells. This last effect was observed by trials of intravenous ALA and has yet to be firmly established with the oral form; however,
this study provides further support for the use of ALA in patients with type 2 DM.

The majority of published trials have used regular ALA (an R-S racemic mixture). R-Lipoic acid is marketed as a superior product because it is the endogenously produced form; however, there is a lack of evidence from clinical trials to support this claim. A sustained-release form of ALA is marketed as superior based on the short half-life of regular ALA; however, data to indicate whether peak or total levels are most important, and evidence of the safety and efficacy of this product are similarly lacking. At this time, regular ALA is the only recommended form.

**Dosage**
The most appropriate dose for neuropathy is 600 mg daily; however, a dose of 50 to 100 mg is sufficient for antioxidant purposes. Absorption is greatest on an empty stomach.**Precautions**
The most common side effect of ALA is nausea; however, insomnia, fatigue, diarrhea, and rashes have also been reported.

### Omega-3 Fatty Acids

Fish and other marine species are the main sources of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the human diet. Alpha-linoleic acid is an omega-3 precursor found in walnuts, flax, and other grains. Although omega-3 fatty acids have no effect on glycemic control, these fats have antiinflammatory, antithrombotic, and antarrhythmic effects that appear to prevent and treat cardiovascular disease. For this reason, omega-3 fatty acids offer important benefits to patients with type 2 DM.

A Cochrane systematic review of 23 trials involving 1075 patients who used omega-3 fatty acids at an average dose of 3.5 g daily reported improved lipid parameters and platelet function. Small trials have reported improvements in endothelial function, with one study reporting significant improvements in impaired flow-mediated dilatation with the consumption of 2 g of omega-3 fatty acids.

**Dosage**
The majority of cardiovascular benefits of omega-3 fats occur at doses of 1000 mg (EPA and DHA) daily; however, higher doses are often used.

**Precautions**
Fishy repeats and mild gastrointestinal upset are the only side effects of omega-3 fatty acid supplementation. Although bleeding in aspirin or warfarin users is often cited as a reason for caution, the literature contains no specific reports of this effect.

### Magnesium

Magnesium affects insulin secretion and action in addition to influencing lipid parameters and endothelial function. A systematic review identified nine trials that evaluated magnesium supplementation for 4 to 16 weeks in 370 patients with type 2 DM and noted improvements in fasting glucose and high-density lipoprotein cholesterol. In the five trials of sufficient duration to evaluate HbA1c, a nonsignificant reduction of 0.31% (95% CI, −0.81 to 0.19) was reported. A separate review of magnesium for the prevention of type 2 DM found seven cohort studies and reported an overall benefit, with an average daily dose of 100 mg decreasing the risk of type 2 DM by approximately 16%. The accuracy of routine tests in reflecting total magnesium body stores remains unclear.

**Dosage**
Usual starting doses are approximately 100 mg daily and can be increased as desired or to bowel tolerance. Magnesium is available as oral liquid or tablets, transdermal lotion, or Epsom salts, as well as in parenteral formulations.

**Precautions**
Gastrointestinal intolerance, mainly diarrhea, is the most common side effect. Chelated magnesium (magnesium glycinate) causes less diarrhea than do other forms of magnesium.

### Antioxidants

Individuals who consume diets rich in antioxidants are at greatly reduced risk of type 2 DM; however, commonly-used antioxidant supplements do not appear to have the same preventive effect. In 8171 women who were followed for 9.2 years in the Women’s Antioxidant Cardiovascular Study, only a mild benefit of vitamin C in the prevention of type 2 DM was indicated by a nonsignificant trend, whereas vitamin E increased the risk of type 2 DM and beta-carotene offered no benefit. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial reported no significant benefit in 1276 Scottish adults administered a low-dose mixed antioxidant supplement or placebo for 8 years.

The benefits of antioxidant-rich foods are likely attributable to the dozens of phytomedicines they contain, components that are currently poorly understood. Although antioxidants and multivitamins are commonly prescribed by integrative practitioners as “insurance against deficiency,” this practice may not be safe. High doses of vitamins have been shown to interfere with absorption and use of lesser-known but potentially more powerful antioxidants in food. High profile examples include tocopherols and carotenoids. Whole food supplements may be a reasonable alternative approach. In one study, an antioxidant supplement derived from pomegranate, green tea, and ascorbic acid improved lipid parameters and markers of oxidative stress in a placebo-controlled trial involving 114 patients with type 2 DM conducted in Turkey.

### Vitamin E

Vitamin E is one of the most commonly used specific antioxidants; however, there is a lack of evidence to support its use in patients with type 2 DM. Negative results reported by large cardiovascular and cancer trials have been the
subject of media reports, controversy, and debate among integrative medicine practitioners. Alpha-tocopherol supplementation did not decrease the risk of type 2 DM in the large Alpha-Tocopherol Beta-Carotene (ATBC) cancer trial, and a separate small trial reported prooxidant effects shortly after ingestion of a single 1200-unit dose. Although several tocopherols and tocotrienols have vitamin E–like activity, the majority of vitamin E supplements contain alpha-tocopherol only. Some investigators have posited that the negative results of vitamin E trials are attributable to decreased absorption of other, more potent molecules of this family whose absorption is inhibited by alpha-tocopherol supplementation. In fact, one study found no difference between the effects of alpha- and gamma-tocopherol on markers of oxidative stress and inflammation in patients with type 2 DM. Other trials have reported that gamma-tocopherol increases blood pressure and has no effect on platelet function.

Greater benefit from alpha-tocopherol has been demonstrated among individuals who are homozygous for a haptoglobin gene variant that has been shown to increase oxidative stress and is present in 3% to 4% of the population. In an Israeli double-blind study involving 1434 people with type 2 DM who were homozygous for haptoglobin-2, alpha-tocopherol reduced the risk of a combined cardiovascular end point by more than 50%. This is an example of how genetics may improve future treatment outcomes in personalized medicine.

Vitamin E supplements containing mixed tocopherols and trienols are increasingly available; however, clear dosing guidelines for their use for type 2 DM have yet to be published. Vitamin E has no known side effects.

**L-Carnitine**

L-Carnitine shuttles fatty acids into mitochondria and has been proposed as a potential therapy for type 2 DM based on its potential effects on intracellular lipid accumulation. A pilot study found no improvements in glycemic control after 4 weeks of L-carnitine use in 12 patients with type 2 DM; however, several trials have reported that L-carnitine improves lipid parameters and significantly reduces lipoprotein (a), an important independent inherited cardiac risk factor for which few effective therapies exist.

**Dosage**
The usual dose is 500 to 1000 mg three times daily.

**Benfotiamine**

Postprandial endothelial dysfunction has been proposed as a link between metabolic syndrome and atherosclerosis. This state is associated with oxidative stress, hyperglycemia, hypertriglyceridemia, and altered nitric oxide function, and has been attributed to glucose-protein complexes in food, named advanced glycation end products (AGEs). These complexes are formed at high temperatures and activate AGE-specific receptors, which stimulate monocytes and endothelial cells and ultimately promote inflammation.

Benfotiamine is a synthetic analogue of thiamine with significantly greater bioavailability. Benfotiamine activates transketolase, an enzyme that helps clear AGEs, thus improving postprandial endothelial function. In a pilot study, 350 mg of benfotiamine after meals completely eliminated vascular measures of postprandial endothelial dysfunction in 13 patients with type 2 DM. This important finding has not been replicated since it was reported in 2006; however, there is a substantial clinical need for corroborating evidence. Several trials have indicated that benfotiamine improves diabetic neuropathy, an unsurprising finding considering the neurological symptoms observed in cases of thiamine deficiency. While one trial reported no improvement in markers of diabetic nephropathy, a separate trial reported improvements in microalbuminuria.

**Vitamin K**

This fat-soluble vitamin exists as phylloquinone (K1) in plants, menaquinone (K2) in animals, and a fermented soybean product known as *natto*. Vitamin K2 is considered more biologically active and is a cofactor for the carboxylation of proteins. Vitamin K2 is involved in the production of osteocalcin, which strengthens bones by forming a protein scaffold. Vitamin K2 is also involved in the production of matrix Gla protein, which prevents vascular calcification by repairing smooth muscle and endothelium. Vitamin K2 is receiving growing attention as a target for the treatment of diverse disorders in addition to its established role in coagulation factors biosynthesis.

Early studies indicate that vitamin K2 stimulates beta cell proliferation and enhances insulin sensitivity. Vitamin K deficiency, as suggested by low levels of carboxylated osteocalcin, is also associated with an increased risk of type 2 DM. Recommending vitamin K2 for glycemic control is premature; however, its endothelial and cardiovascular benefits make it an appealing addition to an integrative type 2 treatment plan.

**Dosage**
The starting dose of vitamin K2 is typically 100 mcg daily; however, higher doses have been commonly used.

**Precautions**
Patients taking warfarin require close monitoring and dose adjustment after starting vitamin K2; however, vitamin K2 ultimately reduces the fluctuations in international normalized ratio observed in vitamin K2-deficient patients. Vitamin K has no other known side effects.
**Risks of Specific Supplements**

Although evidence indicates selenium has insulin-like actions and may delay microvascular complications, integrative practitioners should be aware of the association between selenium and the risk of type 2 DM. In the Nutritional Prevention of Cancer trial, 1202 individuals with localized melanoma were randomized to receive selenium or placebo for cancer prevention. After a mean follow-up duration of 7.7 years, selenium users developed type 2 DM more often (hazard risk, 1.55; 95% CI, 1.03 to 2.33), with the greatest risk observed in individuals with the highest baseline selenium levels (hazard risk, 2.70; 95% CI, 1.30 to 5.61). Selenium supplementation should only be considered in patients with low baseline selenium levels. The maximum daily dose is 200 mcg. The mechanisms underlying the difference in effects of inorganic and organic forms of selenium on the risk of type 2 DM risk have yet to be elucidated.

Practitioners should exercise caution when using B vitamins in patients with nephropathy. In the Canadian Diabetic Intervention with Vitamins to Improve Nephropathy (DIGINe) trial, 238 patients with type 1 DM or type 2 DM were administered a tablet containing folic acid 2.5 mg, vitamin B₁₂ 250 mcg, and vitamin B₁₂ 1 mg daily or placebo for approximately 3 years for the treatment of elevated homocysteine levels. Although the treatment group had lower plasma homocysteine levels, worse kidney function and a higher incidence of cardiovascular events were observed in this group. The investigators postulated that this finding may be attributable to increased cell proliferation induced by folic acid, increased methylation from folic acid and vitamin B₁₂, or nitric oxide-related mechanisms. Earlier reports noted poorer cardiovascular outcomes associated with B vitamins, indicating further studies are required to clarify this issue.

**Pharmaceuticals**

The standard approach to treating type 2 DM is focused on improving glycemic control, as reflected by serum levels of HbA1c. This approach is based on the assumption that all reductions in HbA1c are of equal benefit, regardless of how they are achieved. However, more recent evidence contradicts this assumption.

Recent systematic reviews clearly indicate that different drugs have different effects on real-world clinical measures of morbidity and mortality, independent of their ability to lower blood glucose. Growing recognition of this important gap in our understanding of type 2 DM treatment has created confusion for patients and caregivers. Bridging this gap will be crucial for providing more effective integrative treatment in the future.

**Metformin**

Metformin is a biguanide that is structurally similar to guanidines that were originally discovered in extracts of *Galega officinalis* (French lilac). Metformin has been in use since the 1950s, thus making it one of the oldest, and perhaps most effective, oral hypoglycemic drugs. Although its exact mechanism of action is unclear, metformin improves insulin sensitivity and reduces hepatic gluconeogenesis.

Metformin is the only diabetes medication shown to reduce cardiovascular mortality (OR, 0.74; 95% CI, 0.62 to 0.89) in systematic reviews, and as such should be considered first-line treatment for diabetes.

**Dosage**
The typical dose range is 500 to 1000 mg twice daily.

**Precautions**
Other than mild occasional nausea and diarrhea, the only drawback of metformin use is impaired vitamin B₁₂ absorption in the terminal ileum, which may lead to vitamin B₁₂ deficiency. Metformin may also cause lactic acidosis in patients with renal insufficiency or alcoholism.

**Sulfonylureas**

Sulfonylureas increase insulin secretion by pancreatic beta cells by binding to membrane channels. Sulfonylureas drugs have also been used for several decades but do not appear to improve cardiovascular outcomes. The use of sulfonylureas is limited by their potential to cause weight gain and association with more frequent hypoglycemic episodes, which can lead to arrhythmias and cardiac ischemia. A systematic review found that glyburide was almost twice as likely as other sulfonylureas to cause hypoglycemia; however, cardiovascular outcomes were identical for all drugs in this class. Patients using sulfonylureas and metformin in combination are reportedly at greater risk of cardiovascular mortality than patients using metformin alone.

**Dosage**
The usual dose of glyburide is 2.5 to 10 mg twice daily.

**Precautions**
Glyburide may cause hypoglycemia and weight gain.

**Thiazolidinedione**

Thiazolidinediones increase insulin sensitivity by activating peroxisome proliferator-activated receptor gamma, a nuclear receptor with salutary effects on fatty acid balance, adipocyte differentiation, adiponectin, and other factors involved in glucose and lipid metabolism. The use of rosiglitazone has decreased dramatically since it was found to increase the risk of heart attacks by more than 40% in patients with type 2 DM, possibly because of drug-related increases in LDL or congestive heart failure. Pioglitazone (Actos) is the only drug in this class currently licensed for the treatment of type 2 DM. The impact of pioglitazone on cardiovascular outcomes remains unclear; however, a systematic review did find that it improves glycemic control with a mean reduction in HbA1c levels of 0.58%. 
Incretins are hormones produced in the small intestine during a meal that enter the vasculature and trigger insulin release by pancreatic beta cells. The two incretins are glucagon-like peptide (GLP-1) and gastric inhibitory peptide (GIP). A newer class of drugs that inhibit dipeptidyl peptidase-4 (DPP-4), an enzyme that degrades GLP-1 and GIP, have demonstrated efficacy in increasing insulin and decreasing glucagon levels.

**Sitagliptin.** Sitagliptin (Januvia) is a dipeptidyl peptidase-4 inhibitor.

**Dosage**

The recommended dose of sitagliptin is 100 mg once daily.

**Precautions**

The only side effects noted in trials are nasopharyngitis and headache; however, the long-term safety of sitagliptin remains unclear because DPP-4 degrades dozens of other enzymes and sitagliptin has not been evaluated in long-term trials. The impact of sitagliptin on cardiovascular events and mortality remains unclear; however, meta-analyses indicate that the use of sitagliptin is associated with HbA1c reductions by 0.7%.109

**Exenatide and Liraglutide.** Exenatide (Byetta) and Liraglutide (Victoza) are GLP-1 analogues. In comparison trials with insulin and other oral hypoglycemic, exenatide and liraglutide have been shown to reduce HbA1c by approximately 1.0% without causing hypoglycemia or weight gain.110 Liraglutide has also been approved for weight loss.

**Dosage**

The dose of exenatide is 5 mcg twice daily for 1 month and increased to 10 mcg twice daily as required. A once-weekly injection is available as a 2 mg weekly subcutaneous dose. The dose of liraglutide is 0.6 mg subcutaneous injection daily for 1 week and then increased to 1.2 mg daily.

**Precautions**

Reported side effects include diarrhea, nausea, and vomiting. Cases of pancreatitis have been reported. Data regarding cardiovascular outcomes are not currently available.

Insulin, sulfonylureas, and thiazolidinedione all cause weight gain. Metformin, incretins, and sodium-glucose cotransporter 2 inhibitors are weight neutral or can help with weight loss.

**Sodium-Glucose Cotransporter 2 Inhibitors**

This new class of medicines inhibits the reabsorption of glucose in the kidney, thereby encouraging the excretion of glucose via the urine. Sodium-glucose cotransporter 2 inhibitors have been found to reduce HbA1c levels by 0.5 to 0.8% and result in mild weight loss.79

**Dosage**

- Dapagliflozin (Farxiga); 5–10 mg by mouth every morning.
- Canagliflozin (Invokana); 100–300 mg before breakfast.
- Empagliflozin (Jardiance); 10–25 mg by mouth every morning.

**Precautions**

Sodium-glucose cotransporter 2 inhibitors may increase the risk of lower urinary tract infections and should be avoided in patients with a GFR < 45.

**Insulin**

Although insulin administration can be lifesaving, insulin is a proinflammatory hormone. Every effort should be made to optimize glycemic control; however, it is probably best to use the lowest possible doses of exogenous insulin to achieve this goal. Insulin-dependent patients with type 2 DM can often greatly reduce their dose requirements by following an integrative treatment protocol, as described in this chapter.

One important mechanism underlying the risk of type 2 DM is stimulation of insulin-like growth factor-1 (IGF-1) and other growth hormones. IGF-1 levels predict cancer risk, with the first indication that insulin users may be at increased risk of cancer published in 1967.112 For reasons that are unclear, patients with type 2 DM are at a 20% increased risk of breast cancer113 and a 30% increased risk of colon cancer.114 Research indicates glargine, a long-acting insulin analogue, may be more carcinogenic due to greater stimulation of IGF-1 compared to other types of insulin. The hope is that the International Study of Insulin and Cancer, funded by Sanofi-Aventis (the makers of glargine), will clarify this issue. Many insulin protocols, regimens, and analogues are available; however, their use is beyond the scope of this chapter. Practitioners should be aware that, although these regimens may allow patients to take their insulin in a more convenient or practical manner, there is a lack of evidence demonstrating any approach is superior to another. Short-acting insulin analogues are commonly used; however, meta-analyses indicate these therapies do not provide any advantage over regular human insulin.115 Similarly, there is no evidence to suggest the long-acting insulin analogues, glargine and detemir, are superior to regular insulin.116 Continuous infusion pumps represent a...
newer technology that may be superior; however, their benefit has been demonstrated only among patients with type 1 DM.117

Other Drugs That Improve Outcomes

Angiotensin-Converting Enzyme Inhibitors. ACE inhibitors have been shown to have efficacy in preventing and treating type 2 diabetes. Accordingly, the integration between seemingly disparate physiological systems may have a powerful impact on health and disease. The precise mechanisms underlying the effect of the renin-angiotensin system on glucose metabolism remain unclear; however, multiple lines of evidence exist. Angiotensin II is known to mediate vasoconstriction and hyperperfusion of skeletal muscle and pancreatic islets. Angiotensin II also appears to affect insulin signaling and glucose transport by mechanisms that have yet to be elucidated. In a systematic review of 13 trials involving 93,451 patients with hypertension, the use ACE inhibitors reduced the risk of incident type 2 DM by an impressive 26%.118 A number of ACE inhibitors are available, with ramipril being the most widely studied at a recommended dose of 2.5 to 10 mg once daily.

Statins. Statins are universally recommended for patients with type 2 DM; however, their effectiveness in treating type 2 DM is increasingly complicated. As a drug class, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors are known to improve lipid parameters. However, the clear cardiovascular benefits of statins are more strongly associated with antiinflammatory effects. The absolute risk reduction observed with statins is compelling in people who have already had a cardiovascular event; however, the effectiveness of statins is limited in patients who have not. Patients with type 2 DM fall somewhere in between these two patient populations, with the higher baseline vascular risk among patients with diabetes making statin therapy more appropriate.119

Red yeast rice is a natural source of several statin compounds and may represent a reasonable alternative for patients who are unable to tolerate or do not wish to use a statin drug.

Unfortunately, recent evidence indicates some statins increase the risk of type 2 DM. In a meta-analysis of 13 trials involving 91,140 adults, the overall increase in type 2 DM risk was 9% (95% CI, 1.02 to 1.17).120 Subgroup analysis revealed that different statins have very different effects. Simvastatin, atorvastatin, and rosuvastatin increased the risk of type 2 DM, whereas pravastatin reduced the risk.121 This finding indicates pravastatin may be a more appropriate choice in patients with type 2 DM until this issue has been resolved. The recommended dose of pravastatin for the treatment of type 2 diabetes is 20 to 80 mg once daily.

Bariatric Surgery

Various surgical procedures can induce weight loss by resecting, tightening, shrinking, or bypassing the stomach and upper digestive tract. These forms of so-called bariatric surgery lead to profound weight loss and may be the most important advance in the treatment of type 2 DM in decades. Although surgery is not the most philosophically appealing solution to the worldwide epidemic of type 2 DM and other metabolic diseases related to obesity, it is increasingly recognized by governments and insurers worldwide.

In a review of 103 clinical trial treatment arms involving 3188 patients with type 2 DM, 78% had complete resolution of clinical and laboratory manifestations of diabetes postoperatively, with significant improvements observed in 87% of patients with a reported average weight loss of 38.5 kg.122 Long-term reductions in all-cause morbidity and mortality are increasingly reported.

Short-term complications include gastric dumping syndrome, hernias, wound infections, and pneumonia. The most important long-term consideration following bariatric surgery is nutrient malabsorption.

Deficiencies of vitamins A, C, D, K, and B12, and folate, iron, selenium, calcium, zinc, and copper should be expected following bariatric surgery.123 All patients who have undergone bariatric surgery should take a daily multivitamin and multimineral supplement. Anemia, hyperparathyroidism, and peripheral neuropathy are common postoperatively. Patients who report vague symptoms following bariatric surgery should be evaluated for nutrient deficiency and reminded of the importance of supplementation.

PREVENTION PRESCRIPTION

- Reduce stress.
- Obtain 6 to 8 hours of restful sleep per night.
- Eat a low-glycemic Mediterranean diet that includes whole grains, vegetable protein, vegetables, and some fruit, coffee, and moderate alcohol.
- Practice daily exercise, aerobic or resistance.
- Manage weight and treat obesity.
- Avoid air pollution by maintaining a safe distance from high-traffic roads at work and home.
- Practice a form of mindfulness or meditation.
- Treat prediabetes with aggressive lifestyle intervention and consider metformin 500 to 1000 mg twice daily.
PART II  INTEGRATIVE APPROACH TO DISEASE

THERAPEUTIC REVIEW

LIFESTYLE
- Consider referral to a comprehensive lifestyle program if available.

EXERCISE
- Encourage daily aerobic or resistance exercise.

DIET
- Low-glycemic diet and moderate carbohydrate reduction.
- Avoidance of sugar-sweetened beverages and juices.
- Consumption of more lentils, beans, pulses and soy, chia and other whole grains, onions and green leafy vegetables, almonds, walnuts, and other nuts.
- Moderate coffee and wine consumption.

MIND-BODY THERAPY
- Ask about and treat disordered sleep, stress, anxiety, and depression.
- Discuss stress reduction options and facilitate the chosen modality.

SUPPLEMENTS
- Alpha-lipoic acid: 50 to 100 mg daily.
- Chromium: 200 to 1000 mcg daily.
- Benfotiamine: 350 mg with meals.
- Omega-3 fatty acids: 1 to 4 g daily.
- L-Carnitine: 500 to 1000 mg three times daily.
- Magnesium: 200 to 500 mg daily.
- Vitamin K: 100 mcg daily (caution with warfarin).

BOTANICALS
- Cinnamon: 1 to 5 g ground bark with meals or equivalent extract.
- Fennugreek (Trigonella foenum-graecum): 30 g seed powder or equivalent extract with meals.
- touchi, water extract (soy) 0.3 g in tea daily.
- Marine collagen peptides: 13 g daily.
- Silymarin: 200 g daily.
- Ivy gourd (Coccinia indica): 15 g powdered dried leaves or equivalent extract.
- Salacia reticulate (kothala himbutu): premanufactured tea daily.
- Gynostemma pentaphylum: 6 g in tea daily.

PHARMACEUTICALS
- Metformin: 500 to 1000 mg twice daily.
- Add other drug classes as required to achieve optimal glycosylated hemoglobin levels.

SURGERY
- Bariatric surgery for morbidly obese patients.

Key Web Resources

Fooducate helps track food with the goal of weight loss.

http://www.fooducate.com/

Glooko. This app allows patients to download blood sugar readings and keep a log based on nutrition and medications used.

https://www.glooko.com/

Myfitnesspal. Monitors activity and allows user to set weight loss goals.

https://www.myfitnesspal.com/

Glycemic Index Foundation: Provides eating plans that help control diabetes and lower serum triglyceride levels.

http://www.gisymbol.com/

Diabetes Connect: A community website for the education and discussion of diabetes care.

http://www.diabeticconnect.com/

National Center for Complementary and Integrative Health: Information about an integrative approach to diabetes.

https://nccih.nih.gov/health/diabetes

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