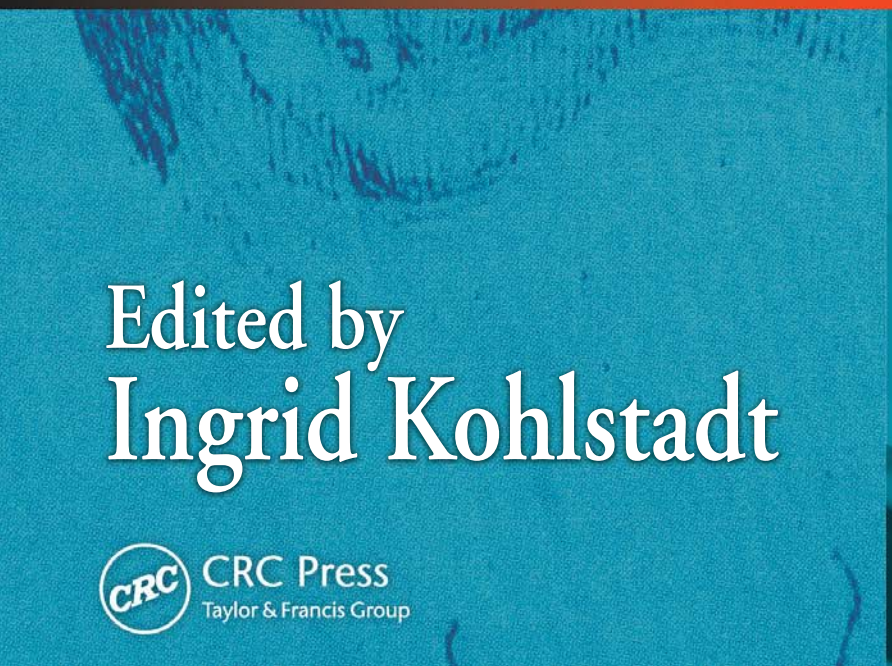
Food and Nutrients in Disease Management



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INTRODUCTION

Russell Jaffe, MD, Ph.D., CCN and Jayashree Mani, MS, CCN have written a chapter about Diabetes for Ingrid Kohlstadt's new book, *Food and Nutrients in Disease Management*. Kohlstadt's book became available in February 2009. The full text of this chapter is included in this valuable document for your reference.

18 Diabetes: Food and Nutrients in Primary Practice

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I. INTRODUCTION

This chapter provides a contemporary overview of diabetes. Dietary patterns and nutrients that can improve glucose-insulin-energy function are emphasized. Strategic food choices and adequate essential nutrients improve outcomes in people with the continuum from metabolic syndrome to diabetes. Cellular metabolic homeostasis is disrupted long before diabetes becomes clinically apparent by elevated blood glucose or insulin. A direct consequence of these metabolic disturbances is free radical oxidative damage secondary to nutrient deficits detailed in this chapter.

II. EPIDEMIOLOGY AND DISEASE DEFINITIONS

One in every three children born today is likely to develop diabetes based on current trends [1]. Diabetes afflicts over a quarter of a billion people worldwide, 10% of them within the United States. It is the leading source for all-cause mortality in many industrialized countries. The epidemiology points to different types of diabetes intersecting and causing more aggressive disease in those who are overfed yet undernourished:

1. Type 1 diabetes (5% to 10% of cases) is deficiency of insulin production usually following an autoimmune destruction of pancreatic islets (insulitis). Genetic and immunologic markers are being developed.
2. Type 2 diabetes (90% to 95% of cases) is usually due to insulin resistance and inadequate compensatory insulin secretion from the pancreas [2].
3. Gestational diabetes is a variant of type 2 diabetes, occuring in about 4% of all pregnancies. Gestational diabetes increases offspring risk of developing diabetes [3]. Tight glycemic control before and during pregnancy can decrease the risk of adverse outcomes. Low birth weight has been linked to an increased risk for type 2 diabetes in later life.
4. Latent autoimmune diabetes of the adult (LADA) occurs in nonobese, anti-insulin antibody positive patients, and can be diagnosed decades before they become frankly diabetic [4, 5]. People with metabolic syndrome, prediabetes, and syndrome X are usually LADA positive. In contrast, people who are not insulin resistant are rarely LADA positive.
5. Type 1.5 diabetes is a new syndrome that includes anti-insulin antibody-positive patients with phenotypic type 2 diabetes. These patients are usually obese and insulin resistant [5].

6. Type 3 diabetes is the emerging link between insulin resistance and neurodegeneration. The brain makes insulin. Insulin resistance in the brain results in accelerated nerve cell oxidative stress, cell damage, poor function, and early death [6]. The hippocampus, frontal cortex, hypothalamus, and other regions of the brain responsible for memory have measurably lower levels of insulin and insulin-like growth factor in patients with Alzheimer's type dementia. Several lines of research now indicate that Alzheimer's type dementia is diabetes on the other side of the blood-brain barrier.

III. PATHOPHYSIOLOGY

In utero nutrition may be as powerful as genetics in determining future diabetes risk.

The rate of increase in diabetes is too rapid to be explained by genetics. Emerging epigenetic studies suggest that risk acquired in utero is primarily mediated nutritionally [7, 8]. A mother with diabetes therefore confers not only heritable susceptibility but a nutritionally induced epigenetic susceptibility, where the fetus misgauges the energy availability in the outside world. Gestational diabetes, short of optimal treatment, creates an unfavorable in utero environment, which confers risk of diabetes later in life to the fetus, superimposed on any genetic risk.

Therefore, prevention of type 2 diabetes would ideally begin in utero and continue for life [2–4, 9, 10]. Diabetes management of women of childbearing age is both disease treatment of a future mother and disease prevention for the next generation. To primary care physicians, the emerging science of epigenetics poses what may be the greatest challenge and opportunity in diabetes management, for which nutrition has a powerful and underutilized role.

Diabetes is an Energy Crisis

Feast in the midst of famine is a common metaphor for diabetes [2]. However "feast" is not necessarily synonomous with overeating. Feast means too much sugar in the bloodstream; cell famine means too little sugar converted to energy to keep up with cell needs. In molecular terms, diabetes is sugar-hormone-electron transport dysregulation.

Blood sugar levels are regulated by hormones such as insulin and insulin-like growth factors counterbalanced by glucagon, growth hormones, adrenaline, and autocoids [2, 4]. A relative or absolute deficit of insulin tips metabolic balance from protective to defensive. Plasma glucose reflects cell energy turnover. Cells generally extract energy from foods in the following order:

1. Glucose
2. Fructose, which is isomerized to glucose
3. Amino acids, which are canabilized from protein and turned into keto acids after extracting energy from and removing the amine
4. Fat from two carbon units by beta oxidation

Generally fat is metabolized where sugar and amino acids leave off so that cell energy production can be sustained. Hyperlipidemia is a consequence of impaired cell energy production [3]. Heart muscle, in contrast to other tissues, derives most of its energy from beta oxidation of fats. Intestinal lining cells use butyrate and 1-glutamine as primary energy sources.

The hormone insulin is largely responsible for regulating sugar uptake by cells. Insulin resistance is a decrease in sensitivity or response to the metabolic actions of insulin [2, 11]. Hyperinsulinism is the adaptive response. If maintained over a prolonged period, refractive hyperinsulinism leads to pancreatic beta cell exhaustion and insulin deficits. Insulin resistance plays a central role in the pathogenesis of diabetes, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular diseases, commonly referred to as metabolic syndrome, syndrome X, and insulin resistance syndrome [11]. Appreciable pancreatic β-cell destruction has already occurred by the time glucose intolerance is present [4].

Diabetes is Characterized by Immune System Dysregulation and Oxidative Stress

The immune system has responsibility for both repair and defense. Autoimmune pancreatic insulitis leads to type 1 diabetes [2]. Autoimmunity is also important in the pathogenesis of LADA [5]. Circulating antibodies to pancreatic antigens are typified by anti-glutamic acid decarboxylase antibodies. Loss of immune tolerance in the gut potentiates diabetes [12]. Improvement in gut tolerance improves glucose tolerance [13]. At the same time, diabetes includes immune system dysregulation with loss of protective immunity, activation of cytokine cascades, increased free radical mediated injury, and impaired healing and repair [14]. Further, protein glycation depresses the activities of antioxidant scavengers and enzymes. This altered redox equilibrium accentuates inflammatory injury, in which antioxidants may therefore have a therapeutic role.

The clinical consequences of these deficits are inflammation, as measured by elevated C-reactive protein (CRP), tumor necrosis factor, fibrinogen, ferritin, and inflammatory cytokines.

Oxidative stress plays a major role in the pathogenesis of diabetic macro- and microvascular complications [15]. Ascorbate is of particular importance as it protects serum lipids from oxidation as reflected in plasma oxidized cholesterol. It is associated with both blood lipid and HbA_1C reduction, perhaps reflecting its pro-repair and antioxidant functions. Improving glycemic control enhances the action of ascorbate since high glucose concentrations can reduce ascorbic acid uptake by as much as 40% [16–21].

Diabetes Begins at the Molecular Level but Quickly Imposes Multi-Organ Compromise

Atherosclerosis accelerates in poorly controlled diabetes and manifests as endothelial or dendritic cell injury, hyperlipidemia, and hypertension, as well as increased myocardial infarction, strokes, aortic aneurysms, and peripheral vascular disease. Organ specific microvascular complications include macular degeneration, optic neuritis, nephropathy, peripheral neuropathy, and autonomic neuropathy including gastrointestinal, genitourinary, and cardiovascular symptoms, and sexual dysfunction. Macrovascular and microvascular pathologies are prominent in diabetes.

Diabetes involves simultaneous muscle compromise and fat accumulation. Obesity, particularly abdominal fat, suggests the presence of insulin resistance with release of nonesterified fatty acids, glycerol, hormones, fibrinogen, pro-inflammatory cytokines, and C-reactive protein [22]. The inflammatory state perpetuated by fat also reflects an ongoing deterioration in lean tissue. As protein is directed to cellular energy production, less is available for repair functions. In a healthy state muscle turnover is approximately 2% a day but decreases during metabolic compromise. At the same time inflammation causes more muscle damage and need to repair. The ongoing repair deficit and diversion of dietary protein to energy production eventually results in physical changes of muscle atrophy and obesity.

Diabetes and obesity are important determinants of fatty liver disease and steatohepatitis [23]. Of note, the hepatitis C virus (HCV) also induces insulin resistance due to the enhanced production of tumor necrosis factor by the HCV core antigen. Routine glucose tolerance testing has been suggested in patients with chronic hepatitis C [24].

Diabetes frequently involves renal compromise. Since the kidneys help regulate blood pH, when people with nephropathy eat a diet high in acidifying foods such as sugar, starch, and meat the kidneys may be slow to adapt to it. Avoiding excess dietary protein is one way of slowing the progression of diabetic renal disease [25]. Reduction in protein intake improves insulin sensitivity and has beneficial influences on different steps of carbohydrate metabolism. Low glycemic index (GI) and low phosphate diets are also recommended in these patients [25–27].

People with diabetes also develop a more recently appreciated neurodegeneration of the central nervous system. Vascular consequences related to carotid and cerebrovascular disease, hypertension, and changes in the blood-brain barrier are common. Metabolic consequences that arise are related to repeated hypoglycemic episodes, hyperglycemia, hyperosmolarity, acidosis, ketosis, uremia, neuroendocrine, or neurochemical changes [6, 28]. The newly emerging link between

neurodegeneration and diabetes may focus future nutritional interventions on reducing inflammation and preventing cognitive decline. Diets high in fat, especially trans and saturated fats, and high copper, abundant in processed foods and high GI foods, adversely affect cognition [29, 30], while those high in fruits, vegetables, cereals, and fish are associated with better cognitive function and lower risk of dementia [31–35].

Gastrointestinal symptoms as a consequence of autonomic neuropathy also result. Delayed gastric emptying is observed in 40% of patients with longstanding type 1 and type 2 diabetes. Accelerated gastric emptying, on the other hand, is manifested in about 20% of recently diagnosed patients [36]. This usually results from loss of glycemic control. Gastroesophageal reflux, dyspepsia, dysbiosis, maldigestion, impaired uptake of nutrients from the GI tract, and unhealthfully long transit times also exist [36–38]. The recently developed ^{13}C-octanoic acid breath test (OBT) can be useful in detecting and studying gastric emptying [39]. Major symptoms of gastroparesis include nausea, vomiting, postprandial fullness, early satiety, bloating, belching, and vague abdominal discomfort. Restoring hydration, glycemic, and electrolyte status are the main goals of therapy. Hyperglycemia slows gastric emptying whereas hypoglycemia may accelerate it and optimizing glycemic control is the key [40].

Polycystic ovary syndrome (PCOS) is a complex disorder affecting up to 10% of all American women. It is the leading cause of female infertility and comprises both hormonal and metabolic abnormalities that include impaired glucose tolerance, type 2 diabetes, vascular disease, dyslipidemia, and obstructive sleep apnea. A post-receptor-binding defect in insulin action leads to insulin resistance, which is the central pathogenic issue. This leads to an imbalance of the hypothalamic-pituitary-adrenal axis to which there is usually increased compensatory cortisol production. The high stress and high cortisol cycle is linked to increased refined carbohydrate and sweet foods cravings and this underlies glucose dysregulation [41–43].

Sleep Improves Glycemic Control

Getting sufficient sleep has been shown to improve insulin sensitivity. Glucose metabolism and insulin sensitivity are implicated in sleep disorders such as restless leg syndrome and sleep apnea [44, 45]. People with diabetes are therefore in a conundrum, with a condition that is treated by adequate sleep and side effects, which undermine quality sleep. Screening and diagnosis create the opportunity for treating sleep disorders. Sleep disturbance is often responsive to supplementation with select amino acids and the cofactors needed to synthesize neurotransmitters [46–48].

IV. EVALUATION

The ADA guideline for plasma glucose is 70 to 100 mg/dl fasting, and not more than 140 mg/dl 2 hours after a meal [3]. Table 18.1 details the interpretation of blood glucose levels and conveys the often gradual onset of diabetes.

Laboratory tests such as plasma glucose are the basis of diagnosing diabetes, maintaining glycemic control, as well as identifying risks [3, 49, 50]. Glucose to insulin ratio, fasting insulin levels, and homeostatic model assessment are common indices of insulin sensitivity in clinical practice [11, 51]. Insulin-like growth factor binding protein-1 (IGF1) is emerging as a useful marker of insulin resistance [51].

Progressive dysfunction of the hypothalamic-pituitary-adrenal axis, with elevated levels of circulating cortisol, is implicated in visceral and abdominal obesity risk [52]. Measurement of salivary cortisol and dehydroepiandrosterone can identify underlying adrenal stress and help in diabetes management [53]. Saliva is an ultrafiltrate and therefore may more closely reflect tissue levels, although certain conditions common among those with diabetes may limit its accuracy in some circumstances.

Recent research findings on sleep and insulin resistance suggest that administering a brief sleep survey to patients with diabetes would be a useful diagnostic screening tool.

TABLE 18.1
Diabetes Diagnostic Criteria

Category	Routine Tests (ranges) Fasting Plasma Glucose	Tests of Diabetics 2-hr Plasma Glucose
Usual	<100 mg/dl (<5.6 mmol/l)	<140 mg/dl (<7.8 mmol/l)
Healthy	<85 mg/dl (<5 mmol/l)	<115 mg/dl (<6.3 mmol/l)
Impaired fasting glucose (prediabetes, metabolic syndrome)	100–125 mg/dl (5.6–6.9 mmol/l)	—
Impaired glucose tolerance (prediabetes, syndrome X)	—	140–199 mg/dl (7.8–11.0 mmol/l)
Diabetes*	≥126 mg/dl (≥7.0 mmol/l)	≥200 mg/dl (≥11.1 mmol/l)

Source: From the Expert Committee on Diagnosis & Classification of Diabetes Mellitus including suggested healthy range values (3)

* A diagnosis of diabetes needs to be confirmed on at least two occaisions to avoid transient, stress-related hyperglycemia being misunderstood as diagnostic of diabetes.

Information available on neurodegeneration and diabetes might suggest more frequent use of a cognitive screening tool.

The role of oral tolerance and the immunotoxic effects of xenobiotics and anthropogenics in potentiating and maintaining the diabetic state have only recently been recognized. Immune reactivities to food and environmental antigens in diabetics are clinically important and patient specific. Food reactivities to dairy are common and may partly explain why diabetes is less common in nonmilk drinkers and insulin resistance is more common in milk drinkers [13, 54, 55]. Diagnostic tests are available to evaluate for food reactivities and to guide treatment (Chapter 15, "Food Reactivities").

Evaluation of B12, folate, and other B vitamins (including metabolites such as homocysteine) could be valuable in patient workup due to the risk of dementia and peripheral neuropathy. This may be especially important in hypochlorhydria and in patients on metformin, which interacts with these nutrients.

CRP, fibrinogen, and ferritin assessed for separate clinical indications can guage systemic inflammation. Since inflammation is mediated in part by the balance of omega-3 and omega-6 fats, red cell fatty acid analysis can help guide supplemental fatty acids.

A self-assessment monitoring tool that some patients find useful is the first morning urine pH. A urine pH of 6.5 to 7.5 suggests that the body's buffering systems are adequate and there is not a net acid excess, and it may correlate with glycemic control in some patients. A target pH can reinforce the recommended daily dietary intake of 13 servings of fruits and vegetables [56] or the equivalent.

V. TREATMENT

Diet Patterns

Diet management of diabetes is shifting from a focus on calorie quantity and caloric excess to a focus on lifelong diet quality and essential nutrient sufficiency to avoid or correct deficit.

Diets should include 13 servings daily of fresh fruits and vegetables or the equivalent in antioxidant protection. Diets with optimal antioxidants are also high in fiber and alkalinizing.

We review alkalinizing diets. The internal acid-base balance of the body is tightly controlled in health and is maintained in a slightly alkaline state (pH 7.4). Acids produced as a result of metabolism are buffered by bicarbonate, intracellular magnesium, potassium, calcium, and sodium. Diets prominent in refined sugars, fat, and protein result in increased cell acid production. This saturates the cell's buffering capacity. Over time, if these mineral buffers are not replenished, net

acid excess (NAE) can lead to depletion of mineral stores from tissues to bone and result in chronic metabolic acidosis. Repair mechanisms and resilience are reduced and the organism is more susceptible to fatigue, illness, disease, and pain when cells are acidotic. Oats, quinoa, lentils and other pulses, vegetables with the exception of peas and carrots, herbs, and nonsodium spices are alkalinizing and low glycemic [57].

The preferred distribution for a diabetic patient's diet would be comprised of 45% to 65% of energy intake from carbohydrates, 10% to 35% from protein, and 20% to 35% from fat [58]. Emphasis is placed on the type and quality of each macronutrient, which is emerging as more important than the precise distribution of each.

Carbohydrates

Although many current popular weight-loss diets advocate low carbohydrate diets [59], the Food and Nutrition Board suggests a minimum recommended dietary allowance (RDA) of 130 g carbohydrates, in part due to brain dependence on glucose to meet energy needs [60].

Carbohydrates are broadly divided into simple sugars, complex carbohydrates known as starches, and fiber. Each has a different effect on blood glucose. It is this response of food on blood glucose levels that is known as the Glycemic Index (GI) [61, 62]. (See Table 18.2.) A GI of above 75 is considered high and foods below 50 have a favorably low GI [61–64]. GI is most applicable to whole foods. It becomes less helpful and even confusing when applied to food components. For example, fructose in the diet should be minimized, but it has a low GI because it converts to glucose once inside the cell. In contrast D-ribose is a 5 carbon sugar rather than a 6 carbon sugar like fructose and glucose. It is a sugar energy source that can regenerate low ATP levels in both the skeletal and cardiac muscle [65]. GI is also unhelpful when portion size is disregarded. Large portions of a low GI food can represent a large glycemic load, which undesirably increases the need for insulin. Food preparation also alters GI. In general the more breakdown there is in the food structure, the higher the GI. For example wild, minimally cooked, long-grain rice has approximately half the GI of rice crackers. This brings us to the very important and frequently overlooked role of fiber.

Preferred fibers are unprocessed and provide 80% soluble or fermentable and 20% insoluble or viscous fiber content. Foods with low GI and a high fiber content such as dried peas, beans, and lentils lower postprandial glucose and insulin response, reduce insulin resistance, reduce weight, improve blood lipid levels, and reduce markers of inflammation such as C-reactive protein (CRP), thus decreasing the risk of developing diabetes and cardiovascular disease [63, 66].

High fiber foods have a low GI. People who eat 3+ servings per day of whole grain foods have a 20% to 30% reduced risk of developing type 2 diabetes [63, 66]. The ADA recommends a daily intake of at least 14 g fiber/1000 kcal and foods with whole grains to prevent diabetes [67]. The extent to which the structure of grains and legumes is kept intact, method of cooking, type of starch, satiety, and nutrient retention also play a role [68]. Foods high in fiber also tend to provide more magnesium and antioxidants. We suggest 40+ grams of total dietary fiber to improve digestive transit and to improve glycemic response. Oat bran flour and barley are good examples of fibers high in beta-glucan and can decrease postprandial glycemic response in diabetes [69–71]. It is essential that the fibers are minimally processed to maintain fiber integrity [72].

Many patients in our clinical practice need to transition into a high fiber diet due to barriers in food preparation, taste acquisition, and gastrointestinal tolerance. In such settings supplemental fiber can be used to achieve target levels and can confer similar benefits.

Proteins

Protein restriction is not generally recommended in diabetes unless there is nephropathy; even so it is wise to limit proteins to < 20% of the total energy intake, within the usual Western diet range of 15% to 20% of energy intake [67]. Protein has increasing metabolic cost when taken above 50 to 60 g/day, typically about 15% of caloric intake. Protein-containing foods tend to increase net acid

TABLE 18.2
Glycemic Index of Certain Traditional and Contemporary Foods

Food	GI with Glucose as 100	GI with White Bread as 100	Serving Size (g)	Amount of Carbohydrate g/serving	GL per Serving
Grains/cereals					
Cornflakes (Kellogg's)	92	130	30	26	24
Doughnut	76	108	47	23	17
Bagel, white	72	103	70	35	25
White flour	70	100			
Angel food cake	67	95	50	29	19
Coca Cola, soft drink	63	90	250 mL	26	16
White rice	56	80	150	41	23
Brown rice	55	79	150	33	18
Muesli bread, made from packet mix	54	77	30	12	7
Bulgur wheat	48	68	150	26	12
Oat bran bread	47	68	30	18	9
Barley kernel bread	43	62	30	20	9
Whole wheat	41	59	50 (dry)	34	14
All-Bran (Kellogg's)	38	54	45	30	23
High amylase rice	38	54	150	39	15
Rye kernels	34	48	50 (dry)	38	13
Dairy					
Milk, skim	32	46	250	13	4
Milk, full fat	27	38	250	12	3
Fruits					
Banana	52	74	120	24	12
Apple raw	38	52	120	15	6
Apricot (dried)	31	44	60	28	9
Grapefruit, raw	25	36	120	11	3
Pulses/Peas/Beans					
Chickpeas	28	39	150	30	8
Kidney beans	28	39	150	25	7
Red lentils	26	36	150	18	5
Soya beans	18	25	150	6	1
Sweeteners					
Sucrose (table sugar)	68	97	10	10	7
Honey	55	78	25	18	10
Fructose	19	27	10	10	2
Organic agave cactus nectar	10	14	10	8	1
Xylitol	8	11	10	10	1
Lactitol	2	3	10	10	0
Vegetables					
Russet potato	85	121	150	30	26
Instant mashed potato	85	122	150	20	17
Peas	48	68	80	7	3
Carrots	47	68	80	6	3

Source: [61, 62]

Note: Glycemic index is based on whole foods. Food components should be evaluated in the context of the foods in which they are eaten. Variation in food preparations also alter glycemic index.

load. People with diabetes also commonly have trouble digesting and absorbing protein due to hypochlorhydria and maldigestion. The body is also likely to use additional, metabolically expensive protein in place of carbohydrates for energy. Requirement for taurine, carnitine, and tryptophan go up in response to increased protein intake. Diabetes is associated with impaired protein synthesis, wound healing, and all needed repair functions. Higher protein intake can improve glycemic control. In sum, protein is necessary but metabolically costly.

Strategies to optimize protein intake in patients with diabetes include the following:

- Digestive enzymes are reported as helpful in increasing absorption of dietary protein, particularly in those who have functional hypochlorhydria.
- Protein sources should be carefully selected lean meats, which are not charbroiled.
- Meat should be preferably from grass-fed animals and most protein overall should be derived from plant sources.
- Protein should be consumed with ample alkalinizing minerals, adequate ascorbate, and with other antioxidants.
- Supplementation can be used to bring select amino acids into healthful range.

Fats

Fat intake and the body's ability to process these dietary fats into the necessary energy and structural components are critical. Diet and strategic supplementation can help compensate for deficits in fat metabolism associated with diabetes:

- Trans fats from processed food need to be avoided at any dose.
- Saturated animal fats should be used but in moderation [73].
- Omega-6 fats should be reduced and omega-3 fats increased to move the omega-6 to omega 3 ratio from a proinflammatory state of 20–30:1 to 4:1 [73, 74].
- Elevated blood glucose impairs the delta-6-desaturase enzyme that converts omega-3 and omega-6 essential fatty acids into eicosapentaenoic acid (EPA) and subsequently docosahexaenoic acid (DHA), which are omega-3 fats and gamma linolenic acid (GLA), which is an omega-6 fat. Patients with diabetes have a demonstrated benefit from supplementation with all three of these fats even though GLA is an omega-6 fat. Evening primrose and borage oils are supplemental sources of GLA. Fish oil, which is a source of EPA and DHA, helps normalize glucose metabolism and modify the fatty acid composition of membrane phospholipids. In isolated beta cells, lipid contents and glucose oxidation return to normal. All these effects contribute to the normalization of glucose-stimulated insulin secretion and muscle insulin sensitivity in diabetes and metabolic syndrome [75, 76].
- Fat-soluble phytonutrients such as lycopene, lutein, quercetin, zeaxanthines, and all eight forms of vitamin E are partly or even completely removed during extensive food processing. This is a disadvantage of partially hydrogenated, hydrogenated, and inter-esterified fats even if the label reads "contains zero grams trans fats."
- Conjugated linoleic acid (CLA) contains a trans isomer of oleic acid that is produced by microorganisms in ruminant animals. Conjugated linoleic acid enters the human diet by eating the meat and dairy products of ruminant animals. Unlike the synthetic trans fats CLA may provide biochemical advantage in reducing insulin resistance and is available as a supplement taken 1 to 6 g/day. The salient point may be that CLA is produced in higher concentrations in ruminant animals fed grass than in those fed grain, so that by altering agricultural practices we are altering the nutrient content of our own food.
- In addition, incorporation of foods rich in oleic acid (omega-9) as found in extra virgin olive oil, helps produce a more fluid lipid cell membrance with less prothrombotic risk of blood clotting [77, 78].

- Carnitine's metabolic role is to bring fatty acids to the mitochondria for ATP synthesis. Supplemental carnitine may facilitate fat metabolism in patients with diabetes. Carnitine reduces total fat mass with an increase in lean mass.
- Medium chain triglycerides are derived from plant sources of fatty acids and may be absorbed directly from the intestine. Their use is limited by gastrointestinal intolerance, but can be effectively used in small, frequent doses.

Minerals and Vitamins

Magnesium

Magnesium is the second most abundant intracellular cation and appears to modulate hormonal and biochemical aspects of cellular glucose utilization and carbohydrate metabolism. Magnesium is critical in regulating insulin sensitivity, vascular tone, and blood pressure homeostasis. Magnesium deficiency is a common feature of diabetic, cardiovascular, and other metabolic processes such as aging. Serum magnesium levels have a bearing on morbidity in patients with diabetes [79]. Magnesium, which is ionized with citrate, malate, succinate, fumarate, glycinate, or ascorbate, is more bioavailable than magnesium oxide or magnesium chelated with soy peptides [80–82]. Magnesium absorption can be further enhanced with choline citrate. Neutral micellar droplets form in the gut and facilitate magnesium uptake through neutral pores even when the usual calcium–magnesium ATPase enzymes are inhibited by toxic minerals or hormone disrupters [80–82].

Chromium

Extensive studies have been conducted on the effect of chromium on glycemic control, because chromium increases lean body mass, reduces weight, decreases visceral fat, and improves free fatty acid levels and insulin sensitivity, when used in addition to oral anti-hyperglycemic agents [83], and low chromium concentrations can precipitate diabetes. Urinary losses of chromium occur during pregnancy, strenuous exercise, infection, physical trauma, steroid medication, and high cortisol states in general. Iron given in supplemental doses reduces chromium absorption by competitive inhibition. Because chromium is a trace mineral in concentrations two orders of magnitidue less than iron, direct measurements are not clinically available. Chromium supplementation in doses of 800 to 1000 mcg/day has been shown to improve glucose and insulin metabolism in patients with insulin resistance [84].

Iodine

Fortifying table salt with iodine might not be providing many Americans with optimal body iodine stores. People with diabetes have a higher prevalence of thyroid disorders [85] and may be disproportionately affected, because they may be low in several other trace minerals and often try to adhere to the recommended treatment of low salt intake and fresh foods whenever possible. Patients with a TSH greater than 2.5 should be given a trial of iodine supplementation, avoid goiterogenic soy foods, and consume sea vegetables as described in Chapter 16, "Hypothyroidism."

Vanadium

Ever since vanadium salts were discovered to stimulate glucose uptake in rats without raising insulin levels [86], vanadium has been shown to mimic the metabolic effects of insulin, thereby influencing glucose metabolism in diabetes. In addition, vanadium improves myocardial function by regulating metabolic processes. Side effects of vanadium supplementation include diarrhea, nausea, and flatulence in a few cases. Products with high bioavailability have minimal side effects [87]. Other trace minerals with potential roles in diabetes management include zinc, molybdenum, manganese, and selenium.

Taurine

Taurine is a semi-essential beta amino acid with antihyperglycemic, antihyperlipidemic, and hyperinsulinemic effects. In diabetes, increased intracellular accumulation of sorbitol can deplete taurine. Altered taurine metabolism is linked to the development of cellular dysfunction in diabetes complications including retinopathy, neuropathy, nephropathy, cardiomyopathy, platelet aggregation, endothelial dysfunction, and atherosclerosis [88]. Combinations of taurine and vanadium have synergistic effects [89].

Biotin

Biotin is thought to improve abnormal glucose metabolism by stimulating glucose-induced insulin secretion by pancreatic beta cells and by accelerating glycolysis in the liver and pancreas. Biotin also enhances muscle insulin sensitivity by increasing guanylate cyclase activity. Combining chromium and biotin can have added effect in maintaining optimal glycemic control and in improving cardiometabolic risk factors [90].

Alpha Lipoic Acid

Alpha lipoic acid is a fat-soluble and water-soluble antioxidant that may be directly insulin sensitizing. It may also improve diabetes outcomes by acting on hepatocytes to help repair the sugar-hormone-electron transport dysregulation. Alpha lipoic acid has been shown to reduce diabetes-related peripheral neuropathy [91].

Quercetin

Quercetin is a bioflavonoid found in several fruits, most notably apples. Quercetin dihydrate administration (10 mg/kg) improves vascular function in diabetes, reduces blood glucose levels, and shows antiatherogenic effects [92].

Botanicals

Coupled with vitamins and minerals and other nutrients, certain botanicals are emerging as valuable adjuncts to diabetes risk reduction and clinical management (see Table 18.3). They add to our arsenal of novel glucose-regulating agents. Phytonutrients with better evidence of efficacy are outlined later.

Fenugreek

Perhaps the most studied herb in the management of diabetes, fenugreek has been found to lower both blood glucose and lipids [94]. Fenugreek decreases insulin resistance and triglyceride levels. Fenugreek can safely be used as an adjunct and in combination with sulfonylureas in the treatment of type 2 diabetes [95].

Bitter Melon

Bitter melon contains various hypoglycemic extracts that work on increasing glucose utilization by the liver, decreasing gluconeogenesis and enhancing the cellular uptake of glucose. It also promotes insulin release, potentiates its effect, and increases the number of insulin-producing beta cells in diabetic animals. Dietary use of bitter melon and its juice decreases blood glucose levels, increases HDL-cholesterol, and decreases triglyceride levels, thus exhibiting antiatherogenic qualities [96].

Banaba

Corosolic acid (CRA), an active component of Banaba leaves (*Lagerstroemia speciosa L.*), has been shown to decrease blood glucose levels in diabetic animals and humans. Banaba is a medicinal plant

TABLE 18.3
Foods, Botanicals, and Supplemental Nutrients in Diabetes

Food	Role in Diabetes
Vinegar (acetic acid), apple cider and balsamic offer additional nutrients	Acetate alters glycolysis/gluconeogenic cycle in liver, reduces fasting hyperglycemia.
Ginger	Source of active thiols to increase detoxificaiton substrates and enzyme activators; similar to onions, garlic, brassica sprouts & eggs; one or more as staple in the diet recommended.
Red wine (also dealcoholized)	High resveratrol content.
Apples	High quercetin flavanoids, with vascular benefits.
Fiber	
Oat bran, beta glucan richt gum acacia, insoluble fiber glucomannan, freeze drieddextrans, low molecular weight prebiotics	Low glycemic, sterol binding, transit time shortening, and probiotic promoting 40+ g/day total fiber intake recommended; 80% soluble & 20% insoluble. Supplementation can help achieve intake goals.
Nuts and seeds	Fiber and mineral rich; low glycemic.
Berries	Rich in anthocyanidins and other polyphenolic flavanoids, especially if vine-ripened.
Cinnamon	Polyphenolics in cinnamon have demonstrated improvements in fasting glucose, glucose tolerance & insulin sensitivity.
Rosemary, green tea (EGCG), cranberries and blueberries, lemon balm	These foods contain polyphenolic compounds, which are natural alpha amylase inhibitors. They can lower postprandial blood glucose level and have been recommended in the supplementary glycemic treatment management of diabetes.
Foods to avoid	
Fructose-rich foods	Bypasses glucose/insulin control yet converts back to glucose inside the cell.
Trans fats–containing foods	Impair cell membrane actions.
Empty calorie, nutrient poor foods	Increase cortisol, contribute to nutrient deficiencies.
Botanicals	
Trigonella foenum–graecum (fenugreek)	Decreases insulin resistance and triglyceride levels.
Momordica charantia (marah, bitter melon)	Increases glucose utilization by liver; decreases blood glucose levels and increases HDL cholesterol.
Lagerstremia speciosa (corosolic acid)	48 mg/day in a 1% standardized extract: effective blood glucose reduction.
Galega officinalis (French Lilac)	The active ingredient galegine reduces insulin resistance. Metformin is a galegine derivative.
Vaccinium myrtillis (Bilberry)	Leaf extract shown to lower blood sugar.
Gymnema sylvestre	The active group polyphenolics of gymnemicates has antihyperglycemic hypoglycemic properties.
Zizyphus spina-christi	Insulinotropic and hypoglycemic effects of the Egyptian *Zizyphus spina-christi* leaves are attributed to a possible sulfonylurea-like activity.
Catharanthus roseus	Hypoglycemic action of the leaves has been attributed to increased glucose metabolism & reduces oxidative stress.
Nutrients	
Betaine (trimethylglycine), and/or l-histidine	Protein digestion enhancers; betaine [50–100 mg with each meal] & l-histidine [500 mg 30 min before each meal] can improve stomach protein digestion by helping maintain or restore adequate stomach digestive acid; Heidelberg test recommended to confirm stomach acid status; unwell people likely to be functionally hypochlorhydric.

continued

TABLE 18.3 (*continued*)

Food	Role in Diabetes
Magnesium	400–1000 mg daily as glycinate, citrate, ascorbate, or other fully ionized forms. Uptake is enhanced with concurrent choline citrate to form neutral charge droplet easily taken up by small intestine.
Chromium: can be enhanced with biotin, taurine, vanadium	800–1000 mcg/day as picolinate or citrate. Improves lean body mass and insulin sensitivity.
Iodine	Thyroid disorders more likely with diabetes; need for iodine levels.
Zinc	With other antioxidants useful for diabetic retinopathy.
Ascorbate	Adequate to quench free radicals and keep C reactive protein < 0.5.
Vitamin E	400–3200 IU/day only as mixed natural tocopherols. d-alpha tocopherol acetate or succinate not recommended.
Alpha lipoic acid	600 mg alpha lipoic acid twice daily can be neuroprotective in diabetes.
Acetyl carnitine	500–1000 mg/day can help in improvement in nerve conduction and pain reduction.

Source: [86–107]

that grows in India, Southeast Asia, and the Philippines. The antidiabetic properties of CRA include inhibition of gluconeogenesis and promotion of glycolysis. Forty-eight mg of CRA daily as a 1% standardized extract has shown to be effective in blood glucose reduction [97].

Pharmacology

The average glucose-lowering effect of the major classes of oral antidiabetic agents is broadly similar, averaging a 1% to 2% reduction in HbA1c with alpha-glucosidase inhibitors being rather less effective. Of note, neither sulphonylureas nor biguanides appreciably alter the rate of progression of complications in patients with type 2 diabetes [108]. Drug interactions have been extensively reviewed elsewhere [109].

Drug-Nutrient Interactions

Oral antidiabetic agents and nutrient interactions are reviewed in Table 18.4.

Metformin use increases homocysteine and decreases folate and vitamin B12 concentrations [110]. Older diabetics are more prone to this complication, since vitamin B12 deficiency affects at least a fifth of the elderly and may present as accelerated cognitive decline and neuropathy [110, 111]. Diabetics often have slow intestinal transit causing bacterial overgrowth and vitamin B12 malabsorption. Vitamin B12-intrinsic factor complex uptake by ileal cell membrane receptors is calcium dependent, and metformin affects calcium-dependent membrane action. Management options include calcium, folate, and hydroxocobalamin supplementation since hydroxocobalamin does not require intrinsic factor for absorption or withdrawal of metformin.

Fixed-dose pioglitazone-metformin combination tablets are best taken with food to reduce gastrointestinal side effects [112]. Rosiglitazone given alone can be administered without regard to meals unlike glipizide (glucotrol) [113]. Grapefruit juice is rich in polyphenolics that induce cytochromes and thereby alter kinetics of statins, dihydropyridines, and repaglinide in particular, increasing hypoglycemia risk [114].

TABLE 18.4
Diabetes Pharmacology and Nutrients

Pharmacological Agent	Mechanism of Action	Clinical Considerations	Nutrient Considerations	Food/Diet Interactions
Sulfonylureas: first generation (chlorpropamide, tolbutamide) and second generations (glyburide, glipizide & glimepiride)	Stimulate insulin secretion by binding to receptors on the pancreatic beta cell. Metabolized in the liver via the cytochrome P450 system.	Secondary benefit: decrease LDL, increase HDL to normal levels. Risks: weight gain, hypoglycemic episodes.	Minor	To be avoided with alcohol. For Glipizide: 30 minutes before a meal recommended for optimum results.
Meglitinides: repaglinide and nateglinide (glinides)	Similar to sulfonylureas. Metabolized in the liver via the cytochrome P450 system.	More favorable safety profile than sulfonylureas, especially in patients with renal failure. Specific caution with the following medications: Rifampicin, Ciclosporin, gemfibrozil, and Repaglinide. Also, statins such as simvastatin and lovastatin.	Minor	They have a rapid elimination rate, so recommended to be taken at the beginning of a meal 2. Not to be taken with grapefruit juice as it can enhance its effect precipitating hypoglycemia.
Biguanides (Metformin)	Reduce hepatic glucose production	Metformin: Reduction in TG, LDL, total cholesterol, HbA1C and insulin, reducing oxidative stress. GI discomfort, rare lactic acidosis.	Folate and Vitamin B12. Intrinsic factor is calcium dependent so supplementation of calcium may be indicated too. Increase in homocysteine levels.	To minimize GI disturbances, recommended to be taken with food.
Thiazolidinediones (Rosglitazone, pioglitazone)	Improve insulin action. Metabolized in the liver via the cytochrome P450 system.	Decrease in homocysteine. Rosglitazone: reduction in TG, LDL, total cholesterol, HbA1C and insulin, reducing oxidative stress. 1. increased risk of myocardial infarction and heart failure. 2. fracture risk in women, and, for rosiglitazone, more rapid bone loss. 3. To be used with caution in people with hepatic dysfunction. Specific caution when combined with statins.	Due to risk of bone loss, bone nutrient supplementation is recommended (post menopausal women especially)	No effect of food on action

(*continued*)

TABLE 18.4 (*continued*)

Pharmacological Agent	Mechanism of Action	Clinical Considerations	Nutrient Considerations	Food/Diet Interactions
Incretin analogues: exenatide and rimonabant (injectable)	Stimulate insulin secretion from pancreatic beta cell; slower absorption of carbohydrate from the gut.	Accelerated weight loss. Nausea, diarrhea, vomiting.	No specific interactions yet identified.	Not to be taken after meals.

Source: [110–116]

Pancreatic/Islet Transplantation and Stem Cell Research

A successful whole pancreas or islet transplant offers the advantages of attaining normal or near normal blood glucose control and normal HbA_1C levels without causing severe hypoglycemia that is associated with intensive insulin therapy. Pancreatic transplantation, however, carries with it a significant risk of surgical and postoperative complications. Although islet transplantation is less invasive it may not always achieve the sustained level of tight glucose control [117]. Due to the limited number of donor islet cells available, stem cell research is being actively investigated [118,119]. There is potential for synergistic treatment between nutrient interventions and stem cell research.

VI. CONCLUSIONS

Prevention is important with any disease, but none more poignant than diabetes. With an epidemic that causes disease earlier in life, women of childbearing age are increasingly affected by diabetes. Newly emerging research on epigenetics suggests that the in utero nutritional environment is a significant risk factor in the development of diabetes, and the clinical implications are profound.

Diabetes can be predicted by laboratory testing years before clinical manifestations occur and nutritional therapies have been demonstrated to be effective throughout the disease course. Dietary patterns, foods, phytonutrients, minerals, and vitamins can improve glycemic control. Diets with high antioxidant capacity, rich in fiber, and alkalinizing are recommended. The quality of the macronutrients in the diet may be more important than the precise ratio of fats, carbohydrates, and protein.

Physicians should be aware of food and nutrient-drug interactions with antihyperglycemic agents (Table 18.4). Both the disease process and the medications used to treat it place patients with diabetes at added risk of nutrient deficiencies. Adjuncts to medical treatment are listed in Table 18.3 [86–107]. Both diagnostic tests and the presence of specific organ damage can guide nutrient recommendations for a specific patient. Nutritional medicine should be patient centered and comprehensive.

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