DEFINING METABOLIC SYNDROME

The terms “syndrome of insulin resistance (IR)” and “the metabolic syndrome” were coined in the 1980s by Gerald Reaven, MD, an endocrinologist at Stanford Medical School in California. Other names used to describe the condition include syndrome X, prediabetes, dysmetabolic syndrome, and cardiometabolic syndrome.1

Metabolic syndrome is associated with a constellation of risk factors for atherosclerosis and type 2 diabetes mellitus (DM) including:2
• Elevated fasting glucose
• Elevated triglycerides
• Reduced high-density lipoprotein (HDL) cholesterol
• Hypertension
• Central obesity

The presence of three or more of these risk factors defines the metabolic syndrome. Following a joint scientific statement by several major organizations, a set of defined cut-off values were determined for all components, with the exception of waist circumference (Table 32.1).3 According to the National Cholesterol Education Program Adult Treatment Panel III, a waist circumference of more than 40 inches (101 cm) in men and more than 35 inches (89 cm) in women is a defining criteria for metabolic syndrome.4 These values apply to Western cultures only. For information regarding other ethnic groups, readers should refer to the 2010 article by Lear et al.5 that outlines existing and proposed waist circumference and waist-to-hip ratios.

Additional abnormalities posited to define the metabolic syndrome include endothelial dysfunction, and procoagulant and proinflammatory states.6

IR is the most common clinical finding associated with metabolic syndrome and is thought by many investigators to represent the predominant mechanism underlying the pathogenesis of this condition. IR is defined as decreased cellular sensitivity to insulin and varies according to cell type, organ, and particular metabolic pathway.1 Research suggests that IR is associated with an inflammatory state and the activation of inflammatory pathways sustains IR and ultimately leads to the development of metabolic syndrome.7

PREVALENCE

The incidence of metabolic syndrome has reached epidemic proportions, with nearly 35% of all U.S. adults and 50% of those aged 60 years and older estimated to have metabolic syndrome in a 2015 report. Data from the National Health and Nutrition Examination Survey (NHANES) 2003 to 2012 reported a prevalence of metabolic syndrome of 33% (95% confidence interval [CI], 32.5% to 33.5%), with a significantly higher prevalence in women compared with men (35.6% vs 30.3% respectively; P < 0.001). When stratified according to ethnicity, the highest prevalence of metabolic syndrome is observed among Hispanics (35.4%; CI, 34.2% to 36.6%), followed by non-Hispanic whites (33.4%; 95% CI, 32.6% to 34.2%) and blacks (32.7%; 95% CI, 31.5% to 33.9%). Overall, an increasing prevalence with advancing age has been reported for all ethnic groups. The prevalence of metabolic syndrome was reported as 18.3% among individuals aged 20 to 39 years and to be significantly higher at 46.7% among individuals aged 60 years or older.8

The increased prevalence of IR, metabolic syndrome, and type 2 DM is thought to be attributable to the global rise in the prevalence of obesity. Visceral fat is now considered to be involved in a number of metabolic, endocrine, and immune functions, all of which have been shown to increase risk of cardiovascular disorders.11 Metabolic syndrome is reportedly associated with a two-fold increased risk of cardiovascular disease (CVD) and a four-fold increased risk of type 2 DM compared to individuals without the condition9 (Table 32.2).

PATHOPHYSIOLOGY

The etiology of IR and the metabolic syndrome is multifactorial and encompasses genetics, nutrient deficiencies, and metabolic defects in addition to lifestyle and environmental factors. The pathophysiology of the metabolic syndrome involves a complex cascade of events that occur intracellularly. Insulin is a major hormone whose action is required for proper tissue development, growth, and maintenance of glucose homeostasis.12 Insulin also affects lipid metabolism by increasing hepatic and adipose lipid synthesis. IR is characterized by decreased responsiveness in the tissues to appropriate circulating levels of insulin and is considered the major contributor to the pathogenesis of metabolic syndrome (Fig. 32.1). Accordingly, IR in muscle tissues causes reduced glucose disposal from the bloodstream, and hepatic IR causes increased glucose production. Impairment of insulin secretion by pancreatic beta cells is a critical feature of the metabolic syndrome that leads to hyperglycemia due to defective insulin secretion and timing of the insulin response to glucose.13
The key targets of insulin action are predominantly skeletal muscle (75%), followed by cardiac muscle, adipose tissue, and the liver. In the liver, insulin inhibits the production and release of glucose in healthy subjects by inhibiting gluconeogenesis and glycogenolysis. Defects in glucose transport or in the hexokinase II pathway may represent the principle mechanism underlying the inhibition of muscle glycogen synthesis. In vivo studies using nuclear magnetic resonance spectroscopy have demonstrated defects in muscle glycogen synthesis are caused by a defect in muscle glucose itself.\(^\text{14}\) The glucose transporter 4 (GLUT4) is the major carrier of glucose into the cell. Stimuli, such as insulin and exercise, promote GLUT4 activity by embedding it into the cell membrane. Peroxisome proliferator–activator receptors (PPARs) are nuclear hormone receptor transcription factors that cause target genes to be expressed and play essential roles as regulators of insulin action.\(^\text{13}\) (Fig. 32.2).

Previous definitions of IR generally considered the condition exclusively in terms of the negative effects on glucose metabolism. Such effects include hyperglycemia following a high carbohydrate meal and overstimulation of pancreatic beta cells to produce more insulin. Eventually, pancreatic beta cells become unable to produce sufficient insulin to maintain normal blood glucose levels. This inability of beta cells to produce sufficient insulin underlies the transition from IR to type 2 DM.\(^\text{15}\) It is important to emphasize that IR
occurs at the cellular level despite pancreatic beta cell dysfunction (Fig. 32.3).

As further studies of the pathophysiology of IR have been reported, the traditional glucocentric view of IR has evolved to include the “lipocentric” concept. Scientists have discovered that abnormalities in fatty acid metabolism cause inappropriate build-up of fat in muscle tissue, the liver, and other organs. Lipotoxicity, associated with increased plasma free fatty acid levels, is a hallmark of IR. Subsequently, these lipids are associated with not only an abnormal accumulation but also increased fat oxidation with further damage to the cell.16,17

IR may involve the insulin receptor itself. The insulin receptor belongs to the receptor tyrosine kinase family which also includes insulin-like growth factor-1 receptor (IGF-1R) and the insulin receptor-related receptor (IRR). Therefore impairment of insulin-stimulated glucose uptake may also result from the upregulation of inhibitors of these signaling pathways. Furthermore, protein-tyrosine phosphatases (PTPases) may also have a role as negative regulators of the insulin-signaling cascade. A combination of the downregulation and upregulation of certain receptors may be a key element of IR pathophysiology.13

Chronic, low-grade inflammation has also been posited to have a central pathogenic role in IR. Research has shown that proinflammatory cytokines and acute-phase reactants are associated with many features of the metabolic syndrome. These inflammatory cytokines promote IR through site-specific serine phosphorylation of insulin substrates.16

Therefore, IR, predominantly in skeletal muscle, manifests as a reduction in insulin-stimulated glycogen synthesis resulting from decreased glucose transport. Once this occurs, lipid accumulates in many cells, most importantly in the liver and pancreas, causing oxidative stress and deleterious changes to cellular metabolism. These multiple defects in insulin signaling have been posited to underlie downstream impaired glucose metabolism in
Insulin Resistance and the Metabolic Syndrome

most tissues\textsuperscript{13,18} (Table 32.3). These pathways are summarized in Fig. 32.4.

Impact of Environmental Toxins on Metabolic Syndrome and Type 2 Diabetes Mellitus

New research points to the role of environmental toxins as etiological factors in the pathogenesis of IR and type 2 DM. The organic compound bisphenol A (BPA) has been found to have an association with IR and type 2 DM. BPA is used to make polycarbonate and epoxy resins and is primarily found in food and beverage containers. BPA has been used commercially since 1957, with more than 90% of U.S. residents estimated to have detectable levels in urine. Findings from the 2003–2008 NHANES report revealed an association between BPA and prediabetes, independent of traditional risk factors.\textsuperscript{19} Based on experimental studies, BPA appears to affect glucose metabolism through a number of pathways including insulin resistance, pancreatic beta cell dysfunction, adipogenesis, inflammation, and oxidative stress.\textsuperscript{19} Other pollutants, such as air pollution\textsuperscript{20} and traffic-related pollution,\textsuperscript{21} have also been implicated in IR and increased risk of mortality attributable to type 2 DM.

Persistent organic pollutants (POPs) may also play a role in the pathogenesis of the metabolic syndrome and type 2 DM. POPs are a class of compounds characterized by low water and high lipid solubility, an ability to persist in the environment, and a cause of biomagnification in the food chain. Pesticides, solvents, and foods from animals, such as seafood, are the main sources of POPs. Because POPs are lipophilic, these substances are highly resistant to degradation and have an estimated half-life of 7 to 10 years.\textsuperscript{19} Some of the most common POPs found in humans include dioxins, polychlorinated biphenyls, dichlordiphenylchloroethylene, transnonachlor, hexachlorobenzene, and hexachlorocyclohexanes.\textsuperscript{46} In the 1999–2002 NHANES report, higher concentrations of POPs (mainly pesticides and herbicides) were associated with an increased prevalence of type 2 DM. Subjects in the highest category (more than the 90th percentile) of exposure, as compared with the lowest category (less than the 25th percentile), had a 38-fold (P < 0.001) increased prevalence of type 2 DM. Obesity was not found to be a risk factor for type 2 DM in individuals with undetectable levels of persistent organic pollutants.\textsuperscript{47} A year later, the same research group reported a positive correlation between POPs (in particular organochlorine pesticides) and the metabolic syndrome.\textsuperscript{48}

According to a \textit{Lancet}
editorial, the findings from the study by Lee et al. might imply that “virtually all of the risk of diabetes conferred by obesity is attributable to persistent organic pollutants, and that obesity is only a vehicle for such chemicals.” In a 2013 review of the epidemiological evidence of an association between POPs and diabetes, Magliano et al. concluded that there is an independent relationship between POPs exposure and diabetes in the general population as well as occupationally exposed and high-risk populations.

Inorganic arsenic is another environmental toxin that appears to be associated with the metabolic syndrome and type 2 DM. The primary sources of inorganic arsenic are contaminated drinking water due to naturally occurring arsenic in rocks and soils, and food. Organic arsenic is predominately derived from the ingestion of fish and shellfish, and is considered nontoxic as it is excreted unchanged in the urine. Results from the 2003–2004 NHANES cross-sectional study revealed a positive association between increasing levels of total urinary arsenic and type 2 DM. Subjects with type 2 DM had 26% higher total arsenic levels than subjects without DM. In the fully adjusted model comparing the 80th and 20th percentiles of total urine arsenic (16.5 vs 3.0 g/L), the odds ratio for type 2 DM was 3.58. No association was observed between organic arsenic and type 2 DM. The investigators suggested that 8% of public water systems in the United States exceed the U.S. Environmental Protection Agency’s standard of 10 mcg/L for drinking water. Wang et al. also found an increased prevalence of metabolic syndrome in subjects with elevated hair arsenic levels. After adjustment for confounding variables, subjects with hair arsenic in the 2nd tertile (0.034 mcg/g) had a statistically significant increased risk of metabolic syndrome (odds ratio, 2.54; 95% CI, 1.20 to 5.39; P < 0.015). Inorganic arsenic is thought to increase the risk of type 2 DM by stimulating increased expression and secretion of high sensitivity C-reactive protein (hs-CRP), which in turn activates nuclear factor kappa-beta via the Rho-kinase pathway.

Metabolic syndrome is primarily an environmental phenotypic disorder (92%) rather than a genotypic disorder (8%).

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) has been defined as the accumulation of fat in the liver (hepatic accumulation of greater than 5% of liver weight confirmed by magnetic resonance spectroscopy or liver biopsy) in the absence of other specific causes of liver infiltration, such as recent or significant alcohol ingestion, hepatic viral infections, or other causes of liver disease. NAFLD is now the most common chronic liver disease worldwide, affecting both adults and children with an estimated prevalence of 20% to 35% in the general population. Traditionally NAFLD has been viewed as a histological continuum from pure fatty liver (steatosis) through nonalcoholic steatohepatitis (NASH) to liver fibrosis, potentially leading to liver cirrhosis associated with increased risk of hepatocellular carcinoma. The histological progression of NAFLD begins with micro-macro vesicular steatosis, which primarily affects the perivenular regions, and may extend to panacinar distribution. The diagnosis of NASH is informed by the presence of fatty infiltration accompanied by inflammation associated with one of three additional features on liver histology: hepatocyte ballooning; Mallory hyaline; or fibrosis. IR is considered the initial injury to the liver, which leads to increased uptake and synthesis of free fatty acids and impaired inhibition of adipose tissue lipolysis with resultant steatosis. Following initial fatty infiltration, the liver becomes increasingly vulnerable to multiple hits including gut-derived bacterial endotoxins, cytokine and adipokine imbalance, mitochondrial dysfunction, oxidative stress, lipid peroxidation, Kupffer cell activation, and hepatic stellate cell activation. These multiple hits are proposed to stimulate hepatocyte injury and the progression from steatosis to NASH and ultimately fibrosis and cirrhosis (Fig. 32.5).

Single nucleotide polymorphisms (SNPs) appear to be associated with NASH but not simple steatosis. NASH confers an increased risk of cirrhosis and secondary malignancy, partly attributable to genetic predisposition. Immunological events are believed to play a role in the development and progression of NASH, and to be associated with hepatic apoptosis and fibrogenic responses. Additionally, impaired regeneration of hepatic progenitor cells appears to be a unifying pathophysiological pathway for NASH, with resultant dysregulated adipokine production and fibrosis. In recognizing simple steatosis and NASH as two discrete entities with different etiologies, clinicians can identify and more closely monitor patients at greatest risk of liver fibrosis and cirrhosis, and individualize therapeutic interventions.

The Interrelationship Between Nonalcoholic Fatty Liver Disease and IR

NAFLD is considered the hepatic manifestation of metabolic syndrome, as IR is currently considered the fundamental underlying pathogenetic mechanism underlying the development of hepatic steatosis. Additionally, all key components of metabolic syndrome (abdominal obesity, impaired fasting glucose, dyslipidemia, and elevated blood pressure) have been identified as major risk factors for the development and progression of NAFLD. Based on epidemiological studies, cardiovascular disease is the leading cause of death in NAFLD patients, followed by malignancy and liver disease, respectively. These findings imply NAFLD is a strong risk factor for cardiovascular disease and cardiovascular-related mortality.

The prevalence of NAFLD is estimated to be 50% to 100% in obese and overweight patients, and 30% to 50% in patients with metabolic syndrome. NAFLD combined with metabolic syndrome is reportedly correlated with greater severity of liver disease and increased likelihood of NASH, independent of age, sex, and body weight. Given the high prevalence of NAFLD, it has
been proposed that NAFLD be incorporated into diagnostic criteria for the metabolic syndrome.\textsuperscript{55}

In the hepatic IR state, fatty infiltration is characterized by an increase in free fatty acids (FFAs) from sources including diet, adipose tissue, and de novo lipogenesis. Persistently increased glucose and hyperinsulinemia stimulate de novo lipogenesis by upregulating a number of transcription factors, which increase the activity of lipogenic enzymes. Fructose and high-fructose corn syrup have been identified as sugars that stimulate lipogenesis more profoundly than glucose. Ordinarily, FFAs are transported to the mitochondria for beta-oxidation or undergo esterification for excretion in VLDL or storage as fat droplets. IR-induced upregulation of FFAs causes direct hepatotoxicity via a number of intracellular responses. Excess FFAs activate the endoplasmic reticulum stress response, cause leakage during mitochondrial beta-oxidation, and lipid peroxidation in mitochondria (primarily), microsomes, and peroxisomes leading to reduced intracellular antioxidant capacity and increased oxidative stress. These mechanisms promote cellular apoptosis, a self-protective cellular response and key pathogenic event in NAFLD. Prolonged and increased levels of reactive oxygen species generated from mitochondrial dysfunction ultimately lead to steatosis and hepatic fibrosis.\textsuperscript{56}

**DIAGNOSIS**

Metabolic syndrome can be diagnosed using the criteria described in Table 32.1. Outside a research laboratory, standard of practice for the diagnosis of the metabolic syndrome is to conduct a 2-hour glucose and insulin tolerance test (GITT), which can easily be ordered through any outpatient laboratory. The protocol is as follows: (1) 2 days of carbohydrate loading, (2) blood sampling for fasting glucose and insulin measurements, and (3) consumption of a 75-g glucose drink. Thereafter, blood specimens for glucose and insulin measurements are obtained (but not always necessarily) at half-hour intervals for the first hour, followed by a final specimen 2 hours later. In the majority of patients, fasting and 2-hour measurements are sufficient. Essentially, this protocol is the standard glucose tolerance test (GTT) with concomitant insulin testing. A caveat of this approach is that clinicians should ensure the laboratory used is familiar with diagnostic procedures involving insulin, which is a very unstable hormone in vitro. False-negative diagnoses are possible if only a fasting insulin specimen is obtained. Regular drawing of blood specimens for the measurement of insulin is required to maintain test functionality. Clinician are required to understand the effect of insulin on managing blood glucose levels following glucose...
consumption. Baseline fasting insulin levels should normally be less than 15 microunits/mL and less than 30 microunits/mL at 2 hours following consumption of a 75-g glucose load.

Although the 2-hour GITT is considered the most accurate and functional test, other methods for the diagnosis of the metabolic syndrome include the following:

- Triglyceride-to-HDL cholesterol ratio (TG:HDL-C)—a healthy ratio is less than 2.
- Glycosylated hemoglobin (HbA1c): values for patients with IR are between 5.7 and 6.4 as per the 2010 American Diabetes Association guidelines.
- Fasting insulin: When assessed in isolation, normal values should be less than 15 microunits/mL (140 pmol/L); however, a normal fasting insulin result does not rule out IR. Reference ranges are laboratory specific, so clinicians must check with the clinical laboratories for specific values. In addition, what is “normal” and what is “healthy” can be vastly different.

Other markers of importance include elevated hs-CRP, uric acid, small dense low-density cholesterol (sdLDL-C), and inflammatory markers such as IL-6 and IL-8, TNF-alpha, PAF-1, and adiponectin. Because NAFLD is hypothesized to represent the hepatic manifestation of IR, the measurement of gamma-glutamyl transpeptidase (GGT) levels should also be considered as this transaminase enzyme is the most sensitive in detecting liver toxicity.

For the majority of clinicians, the 2-hour GITT is the most valuable in terms of diagnosis and patient education, particularly for normal-weight individuals suspected to have metabolic syndrome and women with polycystic ovarian syndrome.

INTEGRATIVE THERAPY

Lifestyle intervention offers the greatest promise for the prevention and management of the metabolic syndrome.

Lifestyle Factors

Although the pathogenesis of IR is multifactorial, lifestyle factors are known to have a profound effect on blood glucose homeostasis. According to statistics reported in 2009, at least 92% of type 2 DM cases are related to lifestyle choices. Lack of exercise, central adiposity, and a diet high in refined carbohydrates and saturated fats and low in fiber represent key lifestyle characteristics associated with IR and type 2 DM. Knowler et al., researchers in the Diabetes Prevention Program, compared lifestyle modification with diet and medication in more than 3000 patients with prediabetes. The investigators assigned patients to three groups who received one of the following: (1) metformin 850 mg twice daily, (2) a lifestyle modification program with goals of at least 7% weight loss, or (3) placebo. After 3 years of follow-up, the metformin group contained 31% fewer diabetics, and the lifestyle modification group contained 58% fewer subjects with diabetes compared with the placebo group.

Exercise, weight loss, and a healthy diet are key lifestyle interventions for reducing IR and the risk of developing type 2 DM.

Exercise

Regular exercise is a vital component of a holistic medical treatment plan and has been shown to reduce the incidence of IR by half. Patients with IR and metabolic syndrome are recommended to partake in 30 to 60 minutes of moderate-intensity aerobic workouts (e.g., brisk walking) at least five times per week. Resistance training should also be encouraged up to twice weekly. Exercise offers a number of physiological and mental/emotional benefits. One physiological benefit is that exercise enhances GLUT4 transporter activity, which in turn facilitates glucose entry into cells while bypassing the need for insulin. This effect has been demonstrated both in healthy individuals and those with IR or T2DM. Preliminary research also suggests that exercise has utility in improving the inflammatory state associated with IR by reducing levels of proinflammatory chemokines. Yoga is another modality proven to help reduce oxidative stress in patients with type 2 DM. Yoga combined with standard care reportedly improves glycemic control and reduces body mass index. Other benefits of regular workouts include increased lean muscle mass and reduced body fat (see Chapter 91).

Weight Management

Excessive food consumption, particularly dietary fat and foods with a high glycemic index, is a key contributor to the pathogenesis of IR and metabolic syndrome. Although the majority of patients with IR are overweight, a small subgroup of patients has a normal body mass index. These patients are termed metabolically obese, normal-weight individuals and share the same risks of developing type 2 DM and cardiovascular disease due to increased visceral fat. Increased visceral fat is associated with increased release of free fatty acids and initiates a self-perpetuating cycle leading to the development of increased IR. Affected patients are said to be “bathed in cortisol” and have the appearance of Cushing syndrome. As previously mentioned, this type of fat affects other organs by causing dysfunction and increasing inflammation. Adipose cells are not, as previously believed, passive depots for energy but are rather hormonally active by secreting adipokines. Adipose cells have also been shown to secrete TNF-alpha, adiponectin, resistin, leptin, and other inflammatory mediators, all of which are involved in the promotion and exacerbation of IR. Hu et al. reported sedentary behaviors (particularly watching television) are associated with significantly elevated risks of visceral adiposity, irrespective of exercise levels. Studies have reported that even small percentages of weight loss (6 to 10%) can significantly improve IR and reduce the risk of developing type 2 DM by 58%. Weight reduction (coupled with exercise) has also been shown to improve histological disease activity in patients with NAFLD.
The speed of chewing has also been shown to have an impact on diabetes risk. Fast eating is reported associated with a more than two-fold increased risk of type 2 DM compared with slower eating.\textsuperscript{71} Eating quickly has also been positively associated with body mass index, increased body weight, and weight gain based in a nationwide survey of middle-aged women.\textsuperscript{74}

**Nutrition**

For patients with insulin resistance, the focus should be on diets rich in whole grains rather than refined grains, fish and white meat instead of red meat, and plenty of fruits and vegetables along with nuts, legumes, and soy. In 2002, researchers from the Harvard School of Public Health published a set of nutritional guidelines known as the Alternative Healthy Eating Index (AHEI) with an emphasis on the foods listed previously. Results from the Whitehall II Prospective Cohort Study showed that adherence to the AHEI in a middle-aged population was associated with a reversal of the metabolic syndrome after 5 years (odds ratio 1.88; 95% CI, 1.04 to 3.41). This effect was more pronounced in subjects with central obesity and elevated serum triglycerides.\textsuperscript{75}

The Mediterranean and low glycemic index/load diets are considered the most effective nutritional regimens for the treatment of metabolic syndrome, insulin resistance, and NAFLD.

**Mediterranean Diet**

Much has been written about the Mediterranean diet, which is rich in vegetables, legumes, soy products, fish, and essential fatty acids. This type of diet is also low in refined carbohydrates and “junk foods,” as well as in red meat, which is rich in saturated fats.\textsuperscript{35} The beneficial effects associated with adherence to the Mediterranean diet relate to the nutrient-dense properties of the foods (i.e., vitamins, minerals, phytochemicals, and fiber).\textsuperscript{35} In a randomized trial, Esposito et al.\textsuperscript{76} compared a Mediterranean diet with a standard diet in 180 patients with metabolic syndrome. After 2 years, only 40 out of 90 subjects on the Mediterranean diet still had features of metabolic syndrome compared with 78 out of 90 participants in the standard diet group. A recent paper by Salas-Salvadó et al.\textsuperscript{77} also demonstrated a significant reduction in the incidence of type 2 DM with adherence to a Mediterranean diet. In this trial, nondiabetic subjects aged 55 to 80 years old were randomly assigned to either a low fat diet (control group), a Mediterranean diet supplemented with 1 L/week of free virgin olive oil, or a Mediterranean diet supplemented with 30 g/day of nuts. All diets were ad libitum. After 4 years, the incidence of type 2 DM was 18% in the control group, 10% in the Mediterranean plus olive oil group, and 11% in the Mediterranean plus nuts group. When pooling the Mediterranean diet groups, there was a 52% reduction in the incidence of type 2 DM when compared with the control group. Of particular interest was the fact that the reduced incidence of type 2 DM occurred in the absence of any significant alterations in body weight or physical activity. Adherence to the Mediterranean diet has also been associated with reduced risk of metabolic syndrome in NAFLD patients\textsuperscript{53} (see Chapter 88).

**Low-Glycemic Index Foods**

The glycemic-index is a system for classifying carbohydrate-containing foods based on glycemic response. Carbohydrates range from simple sugars to starches and can all be converted to glucose. The rate at which conversion occurs is determined by saccharide chain length, with longer chains constituting complex carbohydrates. The glycemic index value for carbohydrates can vary by more than fivefold, with starchy foods having a higher glycemic index than nonstarchy foods such as fruits, vegetables, and legumes. Diets that favor high-glycemic index foods are associated with increased 24-hour glucose and insulin levels in addition to higher levels of C-peptide and glycosylated hemoglobin. These effects have been demonstrated in both nondiabetic and diabetic individuals.\textsuperscript{78}

Research has shown that a combination of exercise and a low-glycemic index diet in obese subjects with prediabetes not only improves postprandial hyperinsulinemia but also reduces pancreatic beta cell stress. Conversely, exercise in combination with a high-glycemic index diet impairs beta and intestinal K cell function despite a similar reduction in weight loss. These findings emphasize the importance of diets rich in low-glycemic index foods that support beta cell preservation, a key factor in the prevention of type 2 DM\textsuperscript{79} (see Chapter 87).

**Fiber**

Dietary fiber, either from whole foods or dietary supplements, is a vital component of the treatment plan for IR and metabolic syndrome. Fiber helps reduce blood pressure as well as total and LDL cholesterol levels, and it modifies inflammatory markers. When taken with meals, soluble fibers, such as psyllium, have been shown to improve postprandial glycemic index and increase insulin sensitivity. Psyllium appears to work by reducing glucose absorption from the intestine and increasing GLUT-4 protein expression in muscles. Regular consumption of dietary fiber also promotes weight reduction by enhancing satiety. Oats and barley are other examples of soluble fiber that have U.S. Food and Drug Administration (FDA)-approved health claims for reducing the risk of heart disease.\textsuperscript{4}

**Cooking Techniques**

Cooking methods can also have an impact on biochemical markers associated with IR and metabolic syndrome. High-heat-treated foods typically found in the Western diet generate harmful compounds known as Maillard
reaction products. These compounds have been found to reduce insulin sensitivity and increase plasma cholesterol and triglycerides. Mild cooking techniques such as steaming, poaching, and stewing are recommended instead of roasting, barbecuing, broiling, or frying.

**Therapeutic Foods**

*Blueberries* are rich in phenolic compounds and anthocyanins and have been demonstrated to have certain health benefits, including improved cognition and reduced cardiovascular and cancer risk. Preliminary research suggests blueberries may also exhibit antidiabetic effects. In a double-blind, placebo-controlled randomized trial, consuming the equivalent of two cups of fresh blueberries a day improved IR in nondiabetic and obese insulin-resistant individuals. Consuming this quantity of blueberries has also been shown to reduce blood pressure, oxidized LDL cholesterol, and lipid peroxidation in patients with metabolic syndrome.

*Apple cider vinegar* (20 g diluted in 40 g of water) has been shown to reduce postprandial fluxes in glucose and insulin following a carbohydrate-rich meal. Acetic acid in vinegar acts similarly to medications such as acarbose and metformin by suppressing disaccharidase activity and increasing glucose-6-phosphate concentrations in skeletal muscle. Other forms of vinegar, such as white vinegar in a vinaigrette sauce, can also be used to lower postprandial glucose (20 to 28 g white vinegar mixed with 8 g olive oil). Another first step would be to promote the patient’s own acid production by stopping unnecessary chronic usage of antacid medications if possible.

**Foods and Substances to Avoid or Consume in Moderation**

Table 32.4 provides a list of foods and substances that should be avoided, given their direct or indirect role in affecting glucose and insulin metabolism.

Research has shown that low to moderate alcohol consumption (one to two standard drinks per day) increases insulin sensitivity and reduces insulin concentrations in nondiabetic postmenopausal women. However, regular consumption in this cohort also increased levels of the androgens DHEA-S and estrone sulfate, which are possible risk factors for breast cancer. Alcohol appears to have a U-shaped relationship with metabolic syndrome, with nondrinkers and heavy drinkers having a similar risk profile. This curious finding may be attributable to increased levels of HDL cholesterol observed in heavy drinkers. As the potential risks may outweigh the benefits, teetotalers should not be encouraged to start drinking to reduce their risk of developing type 2 DM. Smoking should be avoided as it is a known health hazard and shown to be associated with an increased risk for type 2 DM.

**Mind Body**

**Stress Management**

Relaxation techniques are valuable in the treatment of IR because they promote stabilization of adrenal gland function. Stress management lowers both cortisol levels and blood pressure, increases DHEA, improves immunity, and reduces anxiety and depression. Patients are therefore less likely to abuse their bodies and tend to feel better about themselves following the use of relaxation techniques. A prescription with an individualized approach involving meditation, relaxation techniques, prayer, visualization, and other stress-reducing modalities is indicated in patients with IR or type 2 DM.

**Depression**

The results of a 2009 study by Takeuchi et al. indicate the metabolic syndrome may be a predictive factor for the development of depression but not anxiety. Multivariate analysis indicated that an increase in waist circumference was the main factor influencing the relationship between metabolic syndrome and new-onset depression. Skilton et al. also found a positive association between depression (versus anxiety) and metabolic syndrome. In light of their research, the investigators posited screening for depression in patients with the metabolic syndrome.

**Supplements**

Numerous nutritional supplements have demonstrated a beneficial effect on glucose and insulin metabolism. Patients with IR and metabolic syndrome should...
include a multivitamin as a core component of their health regime. Certain nutrients, including antioxidants, may be required in therapeutic doses to ensure a physiological effect in the management of IR and metabolic syndrome.\textsuperscript{94-96} Supplementation with the following nutraceuticals should be guided by overall health and dietary habits along with laboratory parameters and current IR status.

**Vitamin B6**

A deficiency in vitamin B6 is associated with a decrease in several important enzymes that contribute to gluconeogenesis (the generation of glucose from nonsugar substrates).\textsuperscript{97} In patients taking metformin for polycystic ovarian syndrome, vitamin B6 and folate have been shown to counteract increases in homocysteine levels.\textsuperscript{98}

**Dosage**

The recommended dose of vitamin B6 is 50 mg to 100 mg/day.\textsuperscript{99}

**Precautions**

None have been reported at the recommended dose. Higher doses (>150 mg) may cause reversible neuropathy.

**Folic Acid**

The combination of IR and elevated plasma homocysteine levels is associated with cardiovascular risk. Research has shown that patients with this combination of risk factors also have altered or reduced folate levels, which are thought to lead to the progression of hypertension.\textsuperscript{100} High dose supplementation with folic acid has been shown to protect against microvascular complications associated with metabolic syndrome\textsuperscript{101} and improve metabolic profiles in women with polycystic ovarian syndrome.\textsuperscript{102} Patients heterozygous or homozygous for the methylenetetrahydrofolate reductase single nucleotide polymorphism (MTHFR C677T) may benefit from supplementation with L-5-Methyltetrahydrofolate rather than folic acid.

**Dosage**

The recommended dose of folic acid is 500 mcg to 5 mg/day.\textsuperscript{99-102}

**Precautions**

None have been reported. The administration of high doses of folic acid to patients with a concomitant vitamin B12 deficiency may correct megaloblastic anemia but increase the risk of irreversible neurological damage.\textsuperscript{103}

**Vitamin B12**

Research has demonstrated a negative correlation between B12 status and body mass index.\textsuperscript{104} In patients with metabolic syndrome, the administration of folate and vitamin B12 reportedly decreases IR and improves endothelial function. Homocysteine levels have also been shown to improve with folate and vitamin B12, affirming the beneficial effect of these treatments on cardiovascular disease risk factors.\textsuperscript{105} Because metformin has been shown to impair vitamin B12 status, practitioners should assess and monitor B12 levels in patients receiving metformin.\textsuperscript{106}

**Dosage**

The recommended dose of vitamin B12 is 500 mcg/day.\textsuperscript{107}

**Precautions**

None have been reported at the recommended dose.

**Vitamin C**

Individuals with metabolic syndrome have been found to have significantly lower levels of vitamin C compared to healthy individuals.\textsuperscript{108,109} A deficiency of vitamin C is thought to be associated with a greater resistance to fat mass loss.\textsuperscript{110} High doses of vitamin C have also been found to reverse the adverse effects of free fatty acids on vascular function.\textsuperscript{111,112}

**Dosage**

The recommended dose of vitamin C is 1000 to 2000 mg/day.\textsuperscript{113}

**Precautions**

Take with food to reduce the risk of diarrhea.

**Vitamin D**

Supplemental (and dietary) vitamin D has been shown to reduce the development of metabolic syndrome.\textsuperscript{114} In a study of young adults, an inverse relationship between blood glucose, IR, and serum 25-hydroxy (OH) vitamin D was demonstrated.\textsuperscript{115} Other research has confirmed that serum 25(OH) D levels positively correlate with insulin sensitivity.\textsuperscript{116,117} Ford et al.\textsuperscript{118} also reported significant inverse relationships between serum vitamin D levels and abdominal obesity, elevated triglycerides, and hyperglycemia. Visceral fat reduces the absorption of vitamin D from the skin.

**Dosage**

The recommended dose of vitamin D is 300 to 2000 IU/day.\textsuperscript{119,120} Dosing may also be guided by the season of the year and serum 25(OH) D levels (the preferred range is 30 to 60 ng/mL or 75 to 150 nmol/L).\textsuperscript{121}

**Precautions**

Monitor serum calcium levels in patients taking thiazide diuretics and vitamin D supplements, as this combination may cause hypercalcemia.\textsuperscript{122}
**Vitamin E**

Vitamin E supplementation has demonstrated hepatoprotective effects in patients diagnosed with NAFLD (including those with NASH when accompanied with pharmacological medications).^{38,123}

**Dosage**
The recommended dose is 400 IU per day (or 200 IU twice daily) of alpha tocopherol or 400 mg of mixed tocotrienols.\(^{123-125}\)

**Precautions**
Exercise caution in patients taking anticoagulants, as chronic high dosing may affect blood clotting and induce symptoms of muscular weakness and fatigue (reported at doses of 720 mg alpha tocopherol per day).\(^{126}\)

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**Biotin**

High-dose biotin is considered an important vitamin for preventing and treating IR and obesity.\(^{127}\) When given in quantities 10 times greater than the physiological range, biotin directly activates an enzyme that mimics the action of nitric oxide. Biotin has also been shown to improve glycemic control by reducing excessive hepatic glucose output.\(^{128}\)

**Dosage**
The recommended dose of biotin is 3 mg three times a day.\(^{127}\)

**Precautions**
None have been reported.

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**Chromium**

The trace element chromium is an important nutrient that helps prevent IR and dyslipidemia associated with obesity.\(^{129}\) Chromium also appears to have important effects on skeletal muscle IR.\(^{128}\) Chromium has been found to improve insulin sensitivity and increase glucose disposal in women with polycystic ovarian syndrome.\(^{130}\)

**Dosage**
The recommended dose of chromium is 200 to 1000 mcg/day.\(^{130-132}\)

**Precautions**
Take chromium supplements half an hour before or 3 to 4 hours after thyroid or levothyroxine medications, as chromium may bind to these medications and reduce absorption.\(^{133}\)

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**Magnesium**

Intracellular magnesium plays a vital role in regulating insulin action, insulin-mediated glucose uptake and vascular tone.\(^{134}\) Higher intakes of magnesium are associated with increased insulin sensitivity and a reduced risk of developing metabolic syndrome.\(^{135-137}\) Conversely, low dietary intake of magnesium is associated with an increased risk of developing IR and type 2 DM.\(^{138,139}\)

**Dosage**
A dose of 100 mg/day is recommended to reduce the risk of developing type 2 DM.\(^{140}\) A dose of 382 mg/day is required to improve metabolic profiles and blood pressure.\(^{134,141}\) Dosing can also be guided by assessing red blood cell magnesium levels.

**Precautions**
High-dose magnesium may cause gastric irritation and diarrhea.\(^{142}\)

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**Zinc**

Recent research has reported an inverse relationship between serum zinc concentrations and insulin resistance.\(^{143}\) The antioxidant capacity of zinc is thought to underlie its valuable effects on IR.\(^{144}\) Two randomized controlled trials reported a reduction in fasting glucose and insulin in addition to other markers of IR in obese prepubescent children following zinc supplementation.\(^{145,146}\)

**Dosage**
The recommended dose of zinc is 20 mg/day.\(^{146}\)

**Precautions**
None reported at the recommended dose.

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**Alpha lipoic acid**

Alpha lipoic acid (ALA) is a potent antioxidant that is considered important for the treatment of metabolic syndrome. The mechanisms by which ALA exerts its effects include protection against oxidative stress-induced IR, inhibition of hepatic gluconeogenesis, and increased peripheral glucose use.\(^{147}\) ALA may also exert modest reductions in plasma nonesterified fatty acid concentrations.\(^{148}\) When administered solely or in combination with the angiotensin receptor blocker irbesartan, ALA has been shown to improve endothelial function and reduce IL-6 and PAF-1 levels in subjects with metabolic syndrome.\(^{149}\)

**Dosage**
The recommended dose of ALA is 100 mg three times daily before each meal.\(^{149}\)

**Precautions**
None reported.
Coenzyme Q10

Coenzyme Q10 (CoQ10) is required for adenosine triphosphate (ATP) synthesis and is therefore important for the conversion of carbohydrates to energy.\(^{150}\) By enhancing the functioning of the mitochondrial enzyme glycerol-3-phosphate dehydrogenase, CoQ10 helps with glycemic control.\(^{128}\) A study by Singh et al.\(^{151}\) reported reductions in systolic and diastolic blood pressure, fasting and 2-hour plasma insulin, and triglycerides with the use of CoQ10 supplementation. Markers of oxidation, such as lipid peroxides, malondialdehyde, and diene conjugates, were also lowered by CoQ10, indicating a decrease in oxidative stress. Many patients with IR and metabolic syndrome are treated with statin drugs, and these medications have been found to lower plasma and tissue levels of CoQ10.\(^{152}\)

**Dosage**
The recommended dose of CoQ10 is 120 mg/day (or 60 mg twice daily).\(^{151}\)

**Precautions**
CoQ10 may decrease the anticoagulant effect of warfarin. Monitor clotting time regularly, particularly within the first 2 weeks of taking CoQ10.\(^{153}\)

Acetyl-L-Carnitine

The amino acid, carnitine, plays an important role in energy metabolism, largely through its effects on fatty acid oxidation. Carnitine deficiency has been associated with various conditions, including obesity and type 2 DM.\(^{154}\) When fatty acids are unable to enter the cell, triglycerides accumulate in the cytosol; an important contributor to the pathogenesis of IR. The administration of acetyl-L-carnitine to patients with type 2 DM and to healthy persons have been shown to improve insulin-mediated glucose disposal.\(^{155}\)

**Dosage**
The recommended dose of carnitine is 1 to 2 g/day between meals.\(^{156}\)

**Precautions**
None have been documented at the dose recommended.\(^{156}\)

Omega-3 Fatty Acids

Long term supplementation with omega-3 fatty acids has been shown to improve postprandial lipoprotein metabolism by decreasing triglycerides and increasing HDL-cholesterol.\(^{2}\) Omega-3 fatty acids have also demonstrated improvements in endothelial function and arterial stiffness, with an accompanying reduction of the proinflammatory cytokine, IL-6.\(^{157}\)

**Dosage**
The recommended dose is 1 g/day of eicosapentaenoic acid and docosahexaenoic acid (EPA and DHA). For patients with elevated triglycerides, the dose is 2 to 4 g/day of EPA and DHA.\(^{157-159}\)

**Precautions**
None have been reported at the recommended dose.

Botanicals

Ginseng (*Panax ginseng*)

The herb *Panax ginseng* has numerous medicinal effects, including antiinflammatory and antioxidant properties, and has also been used in the treatment of type 2 DM. Ginseng is thought to control and prevent type 2 DM by increasing insulin sensitivity and enhancing insulin secretion.\(^{160}\) Another proposed mechanism of action lies in the herb’s ability to modulate glucose activity by increasing GLUT-4 transporter activity.\(^{161}\)

**Dosage**
The recommended dose is 100 to 200 mg/day (standardized to contain 4% ginsenosides).\(^{162,163}\)

**Precautions**
Ginseng may decrease the effectiveness of warfarin.\(^{164}\)

Green Tea (*Camellia sinensis*)

Green tea supplementation has been shown to improve whole blood glutathione and plasma antioxidant capacity and reduce plasma iron in adults with metabolic syndrome.\(^{165}\) Based on the research by Basu et al.,\(^{166}\) supplemental green tea in patients with metabolic syndrome is thought to reduce serum amyloid alpha, an independent cardiovascular disease risk factor. Green tea may also maintain normal body composition by stimulating thermogenesis and enhancing fat oxidation.\(^{167}\)

**Dosage**
Green tea extract (270 mg to 460 mg/day of epigallocatechin gallate).\(^{165-167}\)

**Precautions**
Green tea may decrease the effectiveness of warfarin.\(^{168}\) Do not combine with ephedrine or other stimulants.\(^{169}\)

Milk Thistle (*Silybum marianum*)

Milk thistle is considered an important herb in the treatment of hepatic disorders and also appears to play a
beneficial role in maintaining normal glucose and lipid metabolism. Liver dysfunction impairs the efficiency of postprandial hepatic glucose storage and is thought to trigger hyperinsulinemia due to reduced liver clearance of insulin. Phase III clinical trials have determined silymarin (the active component of milk thistle) to be the best medication for NAFLD due to its effects in lowering aminotransferase levels and reducing steatosis severity, liver ballooning, and fibrosis. Milk thistle has also been shown to act as an insulin sensitizer in studies of patients with NAFLD.

### Pharmaceuticals

While lifestyle modification is the preferred approach to managing IR and metabolic syndrome, at times prescription drugs are necessary. The problem with such medications is that they do not correct underlying nutrient deficiencies. Medications often merely “treat” the results of the disease; that is, they reduce high serum lipid or glucose levels or high blood pressure but do not treat the overall patient. Although no FDA-approved prescription drugs exist for IR, many of the medications used for type 2 DM have studied as treatment of metabolic syndrome. Some of these medications may not specifically address IR or may have unhealthy side effects. For example, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) lower serum CoQ10, and metformin reduces folic acid and vitamin B12 levels but may increase homocysteine levels. Statin therapy can increase triglycerides, even when the lipid profile is within normal limits. Associated with this is the rise in liver enzymes, which is indicative of liver injury.

### Beneficial role in maintaining normal glucose and lipid metabolism. Liver dysfunction impairs the efficiency of postprandial hepatic glucose storage and is thought to trigger hyperinsulinemia due to reduced liver clearance of insulin. Phase III clinical trials have determined silymarin (the active component of milk thistle) to be the best medication for NAFLD due to its effects in lowering aminotransferase levels and reducing steatosis severity, liver ballooning, and fibrosis. Milk thistle has also been shown to act as an insulin sensitizer in studies of patients with NAFLD.

### DOSE

**Dosage**

Give 420 to 600 mg/day (standardized to contain 70%–80% silymarin).

**Precautions**

Exercise caution in patients taking drugs metabolized by cytochrome, the P-450 isoenzymes CYP3A4 and CYP2C9, because the silybin content of milk thistle may inhibit these hepatic isoenzymes.

### Insulin Sensitizers

Oral Medications

- Biguanides (e.g., metformin) are the most commonly used front-line medications.
- Thiazolidinediones help improve body cell sensitivity to insulin by stimulating the nuclear receptor, peroxisome proliferator activated receptor (PPAR-gamma). These receptors are primarily found in fat cells and, to a lesser extent, in liver and skeletal muscle.

### Agents That Slow the Digestive/Absorptive Process

- Alpha-glucosidase inhibitors help slow down the absorption of carbohydrate into the bloodstream following a meal, thereby reducing postprandial glucose peaks.

### Medications That Increase Insulin Production and Decrease Glucose Production

- Dipeptidyl peptidase-4 (DPP-4) inhibitors are a newer class of drugs that work by inhibiting the breakdown of incretin hormones glucagon-like peptide-1 and glucose dependent insulinotropic peptide.
- Increased levels of these hormones result in improved glucose-dependent insulin secretion, suppressed glucagon secretion, and reduced gastric emptying.

### Sodium-Glucose Transporter-2 (SGLT-2) Inhibitors

These medications work by a novel insulin-independent mechanism by blocking the reabsorption of glucose in the proximal convoluted tubules of the kidneys, thereby resulting in increased glucosuria and weight loss (due to loss of 300 to 400 kcal/day).

### Bile Acid Sequestrants

Colesteyl is a second-generation bile acid sequestrant and the only drug in this class that is approved for the treatment of hyperlipidemia and type 2 DM. Bile acid sequestrants work by binding bile acid in the intestinal lumen, thus impeding bile acid reabsorption in the terminal ileum and increasing fecal bile-acid output. A small study reported the efficacy of colesteyl in improving impaired fasting glucose levels.

### Surgery

The most dramatic, but at times successful, option for the treatment of type 2 DM is bariatric surgery. While the majority of studies have focused on bariatric surgery for type 2 DM, there is research to support the use of this procedure in obese patients. In a nonrandomized, prospective, controlled study, bariatric surgery proved to be more efficient than usual care in the prevention of type 2 DM in obese persons. Subjects were divided into patients who underwent bariatric surgery (1658) and obese matched controls (1771). No participants had type 2 DM at baseline. After 15 years, type 2 DM developed in 392 participants in the control group compared with 110 in the bariatric surgery group, corresponding to incident rates of 28.4 cases per 1000 person-years and 6.8 cases per 1000 person-years, respectively (adjusted hazard ratio with bariatric surgery, 0.17; 95% CI, 0.13 to 0.21; P < 0.001).
**PREVENTION PRESCRIPTION**

- Maintain a healthy body weight. People with an increase in visceral (truncal) fat are at higher risk.
- Exercise of 30 minutes/day is recommended on most days of the week for patients with appropriate weight and 60 minutes/day on most days of the week for those needing to lose weight.

- Manage stress and increase the relaxation (parasympathetic) response.
- Follow a low-glycemic load, Mediterranean-type diet.
- Take a high quality multivitamin that includes minerals and B-group vitamins.

**THERAPEUTIC REVIEW**

**LABORATORY EVALUATION**

- 2-hour glucose and insulin tolerance test to measure glucose and insulin levels after a glucose load.
- Serum lipid measurements (looking for increased triglyceride level, decrease in high-density lipoprotein cholesterol level, and normal or slightly increased low-density lipoprotein cholesterol level).
- Fasting glucose higher than 100 mg/dL.
- High-sensitivity C-reactive protein, a marker of inflammation, and gamma-glutamyltranspeptidase, a marker of liver toxicity.

**LIFESTYLE**

- Encourage an exercise routine that consists of moderate intensity workouts and resistance training.
- Encourage goals to achieve appropriate weight.
- Encourage the patient to stop using nicotine-containing products.

**NUTRITION**

- Low-carbohydrate, Mediterranean-type diet with a focus on low-glycemic index foods.
- High-fiber diet including soluble fibers, such as psyllium, oats, and barley.
- Decreased consumption of red meat and fried foods.

**MIND-BODY THERAPIES**

- Encourage lifestyle choices to reduce stress and anxiety. Recommend a relaxation technique tailored to the individual.

**SUPPLEMENTS**

- High-quality multivitamin with minerals and B-group vitamins.
- Omega-3 fatty acids (eicosapentaenoic acid/docosahexaenoic acid) 1 to 4 g/day to reduce inflammation, blood pressure, and triglyceride levels.
- Chromium picolinate: 200 to 1000 mcg/day.
- Vitamin C: 1000 to 2000 mg/day.
- Vitamin D: 300 to 2000 IU/day.
- Alpha-lipoic acid: 100 to 300 mg/day.
- Coenzyme Q10: 60 to 120 mg/day.
- High risk individuals may need to consider additional supplementation as outlined in the body of the text.

**BOTANICALS**

- American ginseng: 100 to 200 mg/day.
- Milk thistle: 420 to 600 mg/day.

**PHARMACEUTICALS**

- Metformin: 500 to 2500 mg each morning or twice daily.
- Pioglitazone: 15 to 45 mg/day.

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**Key Web Resources**

The National Diabetes Information Clearinghouse (NDIC) provides information on insulin resistance and prediabetes


Myhealthywaist.org offers education and tools regarding the importance of reducing large waistlines

http://www.myhealthywaist.org

Educational resources on lipids and health

https://www.lipid.org/lipidacademy

Calorie needs calculator from the Mayo Clinic

http://www.mayoclinic.com/health/calorie-calculator/NU00598

Fitday is a website that provides online education, tools, and record-keeping to help meet weight loss and exercise goals

http://www.fitday.com

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