

Metabolic Syndrome, Obesity, and Related Cardiovascular Risk Factors

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Summary

The prevalence of obesity and diabetes in the United States is increasing dramatically. Metabolic syndrome, a precursor to cardiovascular disease (CVD) and diabetes, also is increasing dramatically. Obesity is a major risk factor for diabetes, CVD, and the driving force behind the metabolic syndrome. Weight reduction and exercise are the cornerstones of cardiometabolic risk reduction. Pharmacotherapy can be used along with lifestyle intervention to reduce cardiometabolic risk factors.

Key Points

- Obesity, particularly intra-abdominal fat, is a major contributor to CVD and diabetes.
- Interabdominal fat functions as an endocrine organ.
- Cytokines and hormones excreted by excess interabdominal fat leads to insulin resistance and atherosclerosis.
- Lifestyle changes are key in reducing cardiometabolic risk.
- Pharmacotherapy can result in modest weight loss but results in significant adverse effects.

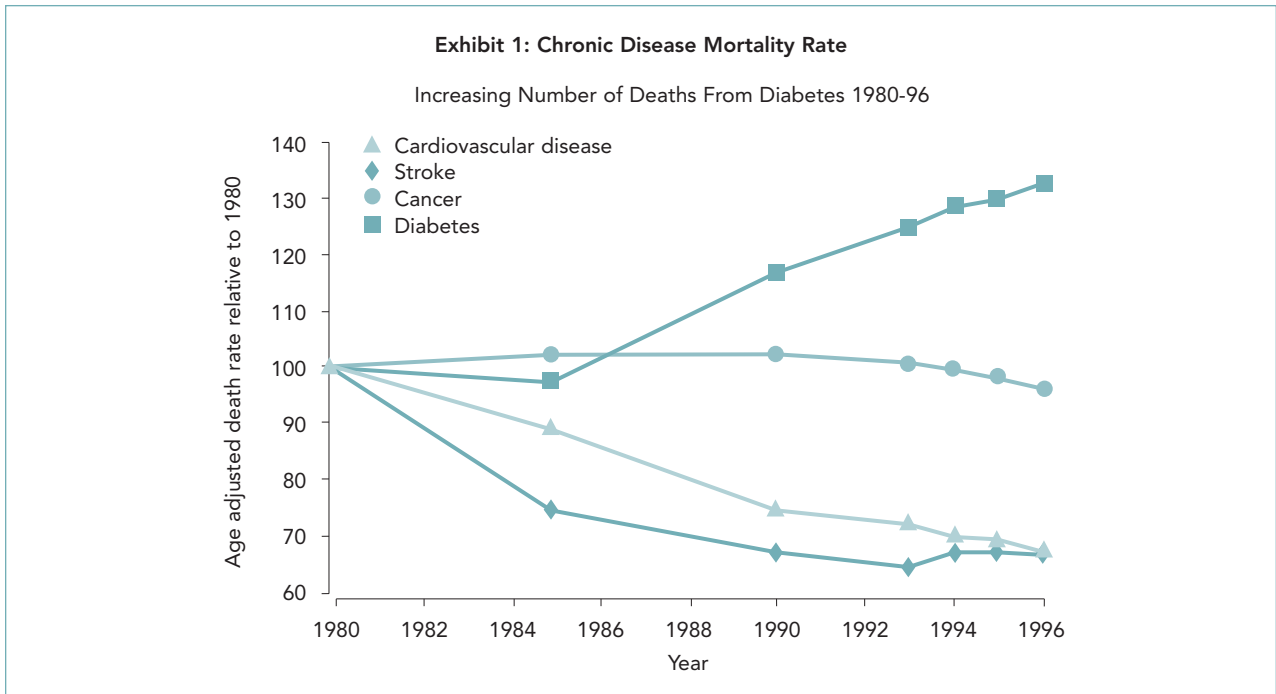
DURING THE LAST TWO GENERATIONS of the 20th century and the first few years of the 21st century, the prevalence incidence of obesity has been increasing. Rates of other classical risk factors for cardiovascular disease—hypertension, smoking, and high cholesterol—are improving, which is good news.¹ Death rates from stroke, cardiovascular disease, and cancer have been going down in the general population. The exception is in patients with diabetes, where deaths from cardiovascular disease are going up (Exhibit 1).² About 80 percent of patients with diabetes die from cardiovascular disease. Cardiovascular deaths in patients with diabetes and the prevalence of obesity parallel each other (Exhibits 2 and 3).^{3,4} The United States has a huge public health problem in front of us and, at the moment, the health care community is grappling with trying to reverse the obesity trend.

Classical risk factors for cardiovascular disease are elevated low-density lipoprotein cholesterol (LDL-C), elevated blood glucose, elevated blood pressure, and smoking (Exhibit 4). Over the past few years, several other risk factors including abdominal adiposity, inflammatory markers, elevated triglycerides, and low high-density lipoprotein cholesterol (HDL-C) have been identified.

All of these risk factors contribute to cardiometabolic risk and the development of CVD. Many of them also contribute to the development of type 2 diabetes.

Type 2 diabetes develops when two defects are present—insulin deficiency and insulin resistance. Obesity does not cause diabetes but it leads to insulin resistance. Type 2 diabetes develops when there is a relative or absolute deficiency of insulin. Many obese individuals do not have diabetes. Every woman in the third trimester of pregnancy is fundamentally as insulin resistant as a 300-pound type 2 diabetic; but not all women who are pregnant become diabetic because the beta cells can sense the insulin resistance and can increase insulin secretion to compensate.

According to National Health Survey (NHANES) data, glucose control in patients with Type 2 disease is not optimal. The number of individuals who had good glucose control (A1C below seven percent) actually declined from 1988 to 2000.⁵ This worsening of control may have come from the advent of the powerful insulin sensitizers (metformin and thiazolidinediones) in the 1990s. There was a rush to treat insulin resistance. The fundamental defect of insulin deficiency was neglected. Sulfonylurea and



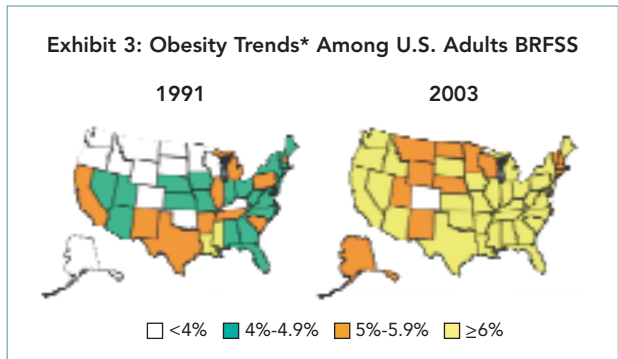
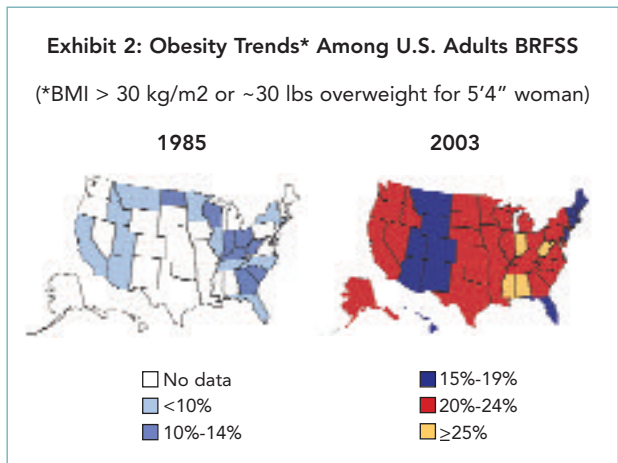
early insulin use went down during this period of time and consequently the number of people with good glucose control also went down. In recent years, the adoption of early insulin use has led to a 10 percent increase in people with good glucose control.

Also in recent years, the number of people with better blood pressure control and total cholesterol has improved.⁵ Unfortunately, the number of individuals who have their three important cardiometabolic risk factors (glucose, cholesterol, and blood pressure) under control is only seven percent.⁵

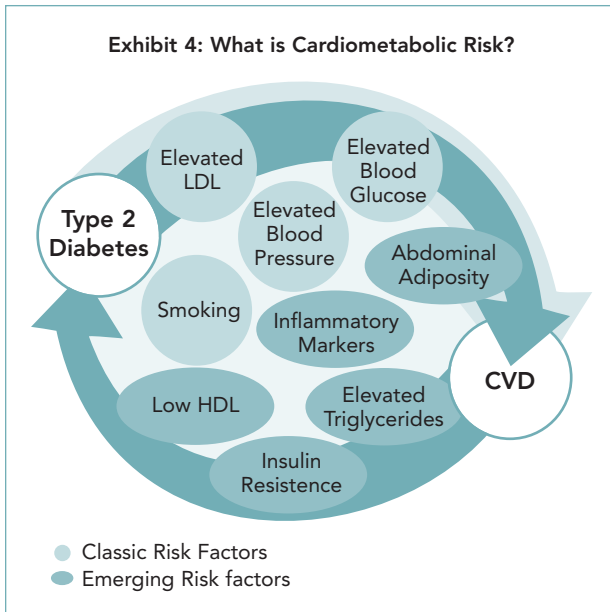
Readily accessible, highly palatable food and an increase in the number of meals eaten outside of the home are two of the factors contributing to the obesity epidemic. In the 1970s, 70 to 80 percent of meals were cooked at home and now only 20 to 30 percent of meals are cooked at home.

Because people are eating more and more often, patients with type 2 diabetes spend a lot of time in the postprandial state (Exhibit 5).⁶ To achieve blood glucose control and lower cardiometabolic risk, methods for controlling postprandial glucose in addition to fasting glucose have to be considered.

There are at least nine studies from around the world linking elevated postprandial glucose with cardiovascular mortality. Elevated postprandial glucose causes high triglycerides. It has been linked directly with microvascular disease. It also elevates oxidized LDL-C, inflammatory markers, and oxidative stress, and activates coagulation. The Decode Study demonstrated that the risk for cardiovascular mortality begins to increase in the pre-diabetic state and continues to increase as the patient progresses to diabetes.⁷



The mechanism by which postprandial hyperglycemia increases cardiometabolic risk is under study. Elevated glucose values after a meal appear to promote damage to the blood vessel walls. Endothelial function and oxygen derived free radical



levels both correlate with postprandial glucose values.⁸ Triglycerides also cause endothelial dysfunction. Unfortunately, patients with type 2 have the combined effects of elevated postprandial triglycerides and glucose causing a significant reduction in endothelial function and magnifying the risk for cardiovascular disease.

Until the early 2000's, insulin had an incorrect reputation as an atherosclerotic risk factor by itself. Retrospective or cross sectional studies found patients who had insulin resistance had elevated insulin levels and developed cardiovascular disease. It is not the insulin, but the insulin resistance causing the cardiovascular disease. In a study of basal insulin glargine, blood glucose and endothelial function dramatically improved with this therapy.⁹ Another study found that insulin analogs such as lispro insulin actually increase cardiac blood flow postprandially more than regular insulin and better than a placebo.¹⁰ The

insulin analogs not only improve glycemic control but also cause less hypoglycemia than insulin.

The criteria for diagnosis of metabolic syndrome are given in Exhibit 6.¹¹ One in four adults in the United States have diabetes or metabolic syndrome.^{12,13,14} About 21 million people have diabetes. This figure is increasing by 15 percent per year. Forty-four million people have pre-diabetes and 64 million have metabolic syndrome.¹⁴

The most prevalent component of the metabolic syndrome is abdominal obesity followed by the low HDL-C and hypertension.¹⁴ Metabolic syndrome does not equal type 2 diabetes but it is a strong risk factor for diabetes and cardiovascular disease.¹⁵ A patient with metabolic syndrome and diabetes has amplified cardiovascular risk.¹⁶

In a large study of a public health data base, individuals who had never smoked had increases in risk for cardiovascular disease starting after their weight reached a body mass index (BMI) of 26.¹⁷ Risk dramatically goes up with a BMI greater than 40 (Exhibit 7).¹⁷

In the Nurse's Health study, women with diabetes at baseline had a fivefold risk for heart attack or stroke.¹⁸ The clock begins ticking for developing cardiovascular disease when glucose begins to rise, even before the diagnosis of diabetes (Exhibit 8).¹⁸ Multiple risk factors within one person will significantly increase the risk of myocardial infarction (MI). For example, smoking leads to an odds ratio of 2.87 for having an MI. Smoking, diabetes, hypertension, and obesity combined result in an odds ratio of 21.¹⁹

Many of the problems with metabolic syndrome come from excessive fat in the abdomen (inter-abdominal adiposity). Thinking about fat deposits has evolved over the years. Previously, the adipocyte was considered an inert storage medium for excessive energy. Now it is known that fat metabolism adipocytes are an endocrine organ, which produce inflammatory cytokines and hormones. Compared

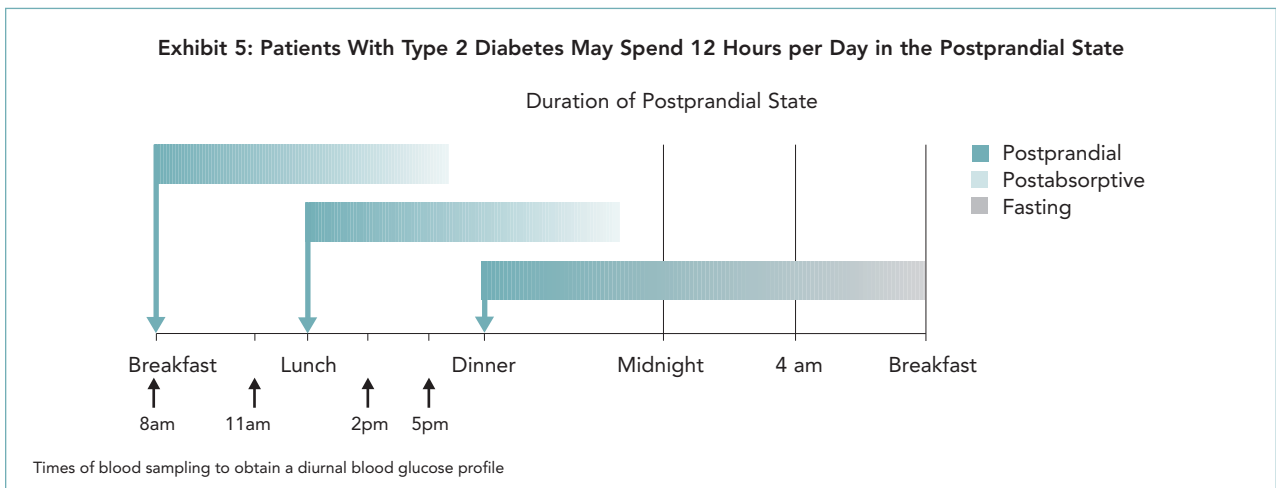


Exhibit 6: AHA/NHLBI-Modified ATP III Criteria for the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity	Waist circumference*
Men	>40 in
Women	>35 in
Triglycerides, mg/dL	≥150
HDL-C, mg/dL	
Men	<40
Women	<50
BP, mm Hg	≥130/85
Fasting glucose, mg/dL	≥100

*Lower cutpoints for Asian Americans.

Diagnose by presence of 3 or more risk factors

with other fat deposits in the body, interabdominal fat makes much more of the inflammatory cytokines that are negative and increases insulin resistance and cardiovascular disease (Exhibit 9).^{20, 21} The hormones secreted by interabdominal fat include leptin, angiotensin, resistin, and adiponectin. Leptin is a very important hormone in regulating energy balance and partitioning carbohydrates and fat. Typical obesity is a state of leptin resistance. Although important in rodent models, resistin's importance to weight maintenance in humans is controversial. It does increase insulin resistance.

Various cytokines are secreted by interabdominal fat. Tumor necrosis factor alpha (TNF-α) has been linked with insulin resistance. There are some recent studies showing use TNF-α blocking antibodies for two weeks can improve insulin sensitivity. Plasminogen activator

inhibitor (PAI-1) is a procoagulant cytokine. PAI-1 is linked very strongly with an increase of diabetes and may be a good predictor of diabetes like glucose. The role of interleukin six (IL-6) is controversial. Although it has been linked to obesity, cardiometabolic risk, and insulin resistance, exercise physiology studies find that exercise leads to large increases in IL-6. High levels of IL-6 in obesity may be the body trying to compensate for insulin resistance.

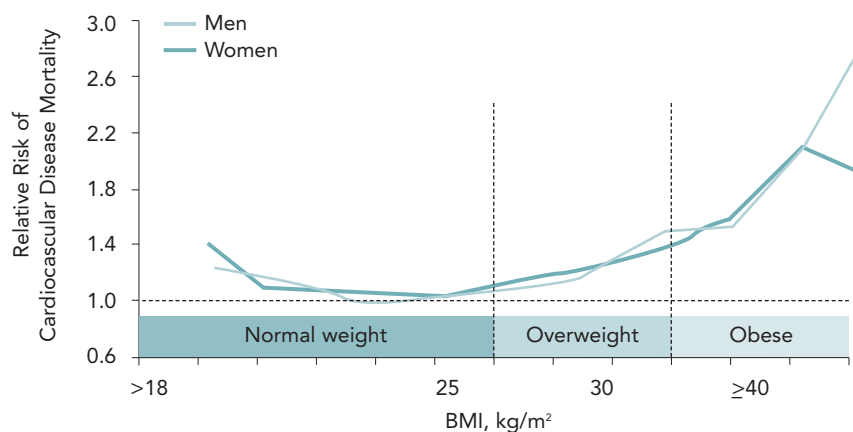
A beneficial product of subcutaneous tissue is adiponectin. It is a very powerful insulin sensitizer, which also decreases vascular inflammation. Adiponectin has mechanisms similar to the oral insulin sensitizers metformin and thiazolidinediones. Adiponectin has been shown to have positive effects on the liver, muscle, endothelium, and maybe even the brain.

Inflammation as marked by increasing levels of fibrinogen, C reactive protein (CRP), and PAI-1 is a contributing mechanism to the development of diabetes.²² Levels of these inflammatory cytokines are seen with increasing levels of abdominal obesity.

Waist circumference, a marker of interabdominal fat, correlates with increased insulin resistance, blood pressure, and thus risk of diabetes and heart disease.²³ Measuring waist circumference is an easy and inexpensive way to get a general idea of the amount of visceral fat present in a patient.

Putting this all together, excess interabdominal adipocytes release inflammatory cytokines which result in impaired thrombolysis, glucose intolerance, hypertension, dyslipidemia, endothelial dysfunction, and inflammation (Exhibit 10).²⁴ The end result of excess interabdominal fat is a vicious cycle of myocardial infarction and thrombotic stroke.

Exhibit 7: Overweight and Obesity Increase the Risk of Cardiovascular Disease Mortality

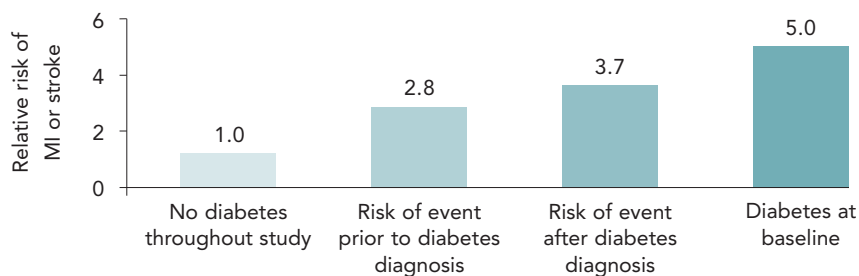


Data are from 1 million men and women (average age, 57 years) followed for 16 years who never smoked and had no history of disease at enrollment.

Calle EE, et al. *N ENGL J Med.* 1999;341:1097-1105.

Exhibit 8: The Ticking Clock: ↑CV Risk Before ↑Glucose

Nurses' Health Study; 20-year follow-up of 117,629 women



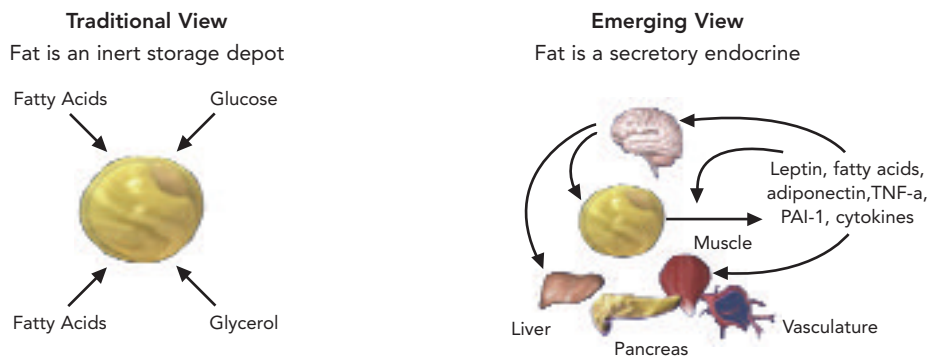
Cardiometabolic risk can be decreased with physical activity and weight loss. A 10 percent loss of body weight will decrease total cholesterol, LDL-C, and triglycerides. It will also increase HDL-C.²⁵ Weight loss also reduces inflammatory biomarkers such as TNF- α .²⁶ In the Diabetes Prevention Program study, 150 minutes of cumulative exercise per week and a seven percent weight loss reduced the progression to type 2 diabetes by 58 percent. Lifestyle changes were compared to metformin therapy, which reduced diabetes risk by 31 percent.²⁷ Lifestyle changes also reduce the risk of metabolic syndrome by 41 percent.²⁸

The practical problem is getting overweight patients to lose weight and keep it off. The current approaches to treating obesity include diet, exercise, behavioral therapies, short-term pharmacotherapy, and surgery. With most diets, patients lose weight but regain the same amount or more once they stop dieting. Dansinger and colleagues compared four major diets, Atkins, Zone, Weight Watchers, and Ornish.²⁹ Each lead to modest weight loss of 4.5 to 7 pounds over a year with a 1 to 1.5 inch decrease in waist circumference. The problem for most patients is trying to maintain one of these diets especially since some of these diets require severe changes.

Orlistat, sibutramine, and phentermine are approved drugs for treating obesity. Randomized controlled trials with these agents demonstrate modest weight loss as long as the patient continues the agent. Weight regain occurs once the medication is stopped. Orlistat, which recently became available over the counter at a lower dosage, is a pancreatic lipase inhibitor. Thus, it reduces fat absorption. The primary adverse effects of this agent are related to excess fat in the lower gastrointestinal tract. Sibutramine is a mixed serotonin, norepinephrine, and dopamine reuptake inhibitor. The most common side effects of sibutramine are elevated blood pressure and heart rate.

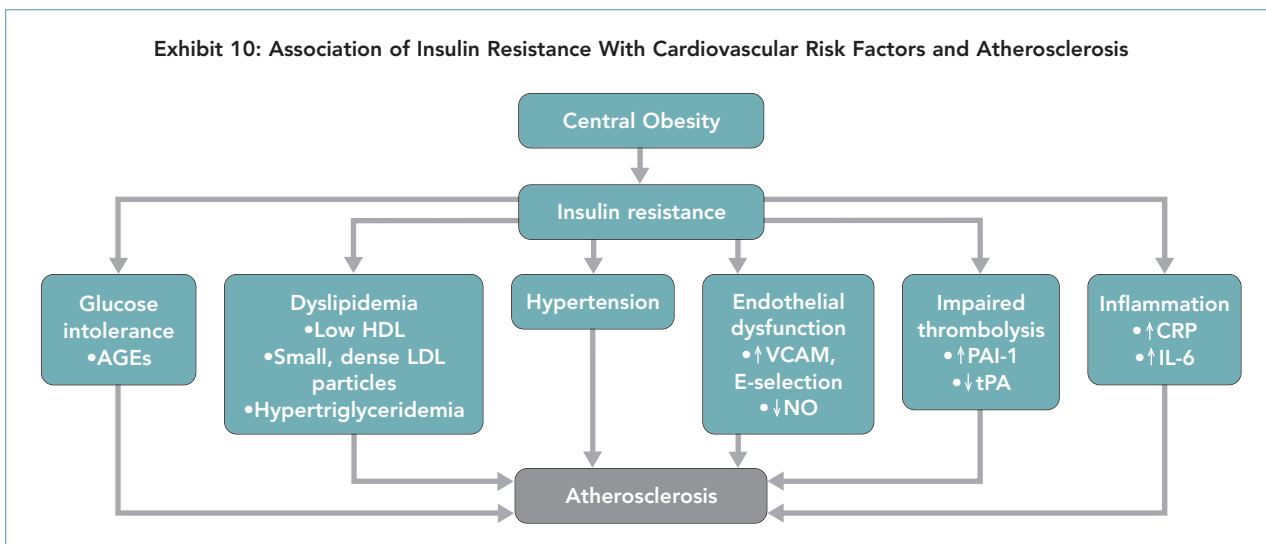
Currently available pharmacotherapy for treating obesity is not ideal. Other agents are under study for weight loss, which will possibly be more effective with fewer adverse effects. Agents targeting the endocannabinoid system example are one. The endocannabinoid system is a physiologic entity that is activated by pleasurable behavior and is classically activated by repeated intake of desirable food. Cannabinoid receptors spread throughout the brain are important in appetite and motivation to eat. These receptors also are in adipose tissue, skeletal muscle, liver, gastrointestinal tract, pancreas, adrenal medulla, and sympa-

Exhibit 9: Adipose Tissue as an Endocrine Organ



PAI-1 = plasminogen activator inhibitor-1
TN- α = tumor necrosis factor alpha

Exhibit 10: Association of Insulin Resistance With Cardiovascular Risk Factors and Atherosclerosis



thetic nervous system. When the endocannabinoid system is activated in obesity, increased insulin resistance, low HDL-C, increased triglycerides, low glucose uptake, and reduced adiponectin occur. It appears that an activated endocannabinoid system is another cardiometabolic risk factor.

Conclusion

The prevalence of obesity and diabetes is increasing dramatically. Metabolic syndrome is a precursor to cardiovascular disease and diabetes, and also is increasing dramatically. Obesity is the major risk factor for diabetes, cardiovascular disease, and the driving force behind the metabolic syndrome. Weight reduction and exercise are the cornerstones for reducing cardiometabolic risk. Pharmacotherapy at the moment has limited success. **JMCM**

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