



Effect of Insulin Resistance, Dyslipidemia, and Intra-abdominal Adiposity on the Development of Cardiovascular Disease and Diabetes Mellitus

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ABSTRACT

Abdominal obesity contributes to insulin resistance, a metabolic abnormality linked to the development of type 2 diabetes mellitus and cardiovascular disease (CVD). Insulin resistance generally precedes the development of type 2 diabetes. Currently, an estimated 10 million US adults have diabetes and another 25 million have impaired glucose tolerance (IGT), an intermediate step between insulin resistance and diabetes. The pathophysiologic mechanisms known to increase CVD risk in individuals with insulin resistance include formation of advanced glycation end products, hypertension, proinflammatory and prothrombotic states, and dyslipidemia (i.e., low levels of high-density lipoprotein cholesterol, increased levels of triglycerides, small, dense low-density lipoprotein cholesterol particles, apolipoprotein B, and inflammation). The increased flux of free fatty acids from adipose tissue to the liver promotes dyslipidemia. Insulin resistance and impaired glucose tolerance are associated with increased CVD risk. Individuals with coexisting metabolic syndrome and diabetes have the highest prevalence rates of CVD. The Nurses' Health Study showed that CVD risk was elevated even before the development of diabetes compared with women who never developed diabetes. Lifestyle modification is recommended as the first-line treatment for obesity and its metabolic sequelae. Pharmacotherapy may be useful in patients for whom nonpharmacologic approaches alone are ineffective or insufficient. Primary care physicians play a critical role in the early identification and treatment of patients at increased risk for the development of type 2 diabetes and CVD because of their obesity and associated complications. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Cardiovascular disease; Impaired glucose tolerance; Insulin resistance; Metabolic syndrome; Type 2 diabetes mellitus

The prevalence of obesity, type 2 diabetes mellitus, and the metabolic syndrome has increased dramatically in the past 2 decades.^{1,2} Obesity, specifically visceral abdominal obesity, contributes to the development of insulin resistance, which may underlie a number of the manifestations and cardiovascular complications of diabetes and the metabolic syndrome.³ Insulin resistance is associated with increased cardiovascular risk as well as the risk for developing overt

diabetes. Therefore, early intervention to treat insulin resistance is an important preventive health strategy.

PATHOPHYSIOLOGY OF INSULIN RESISTANCE

Although it is recognized that insulin resistance increases the risk for type 2 diabetes, it is not as well known that it also increases the risk for cardiovascular disease (CVD).^{4–6} A number of factors increase the risk for insulin resistance, including genetic predisposition, obesity and inactivity, aging, medications, polycystic ovary syndrome, and rare disorders such as partial lipodystrophy.⁷ Concomitant conditions that are associated with insulin resistance include type 2 diabetes, hypertension, dyslipidemia, atherosclerosis, and polycystic ovarian syndrome (**Figure 1**).

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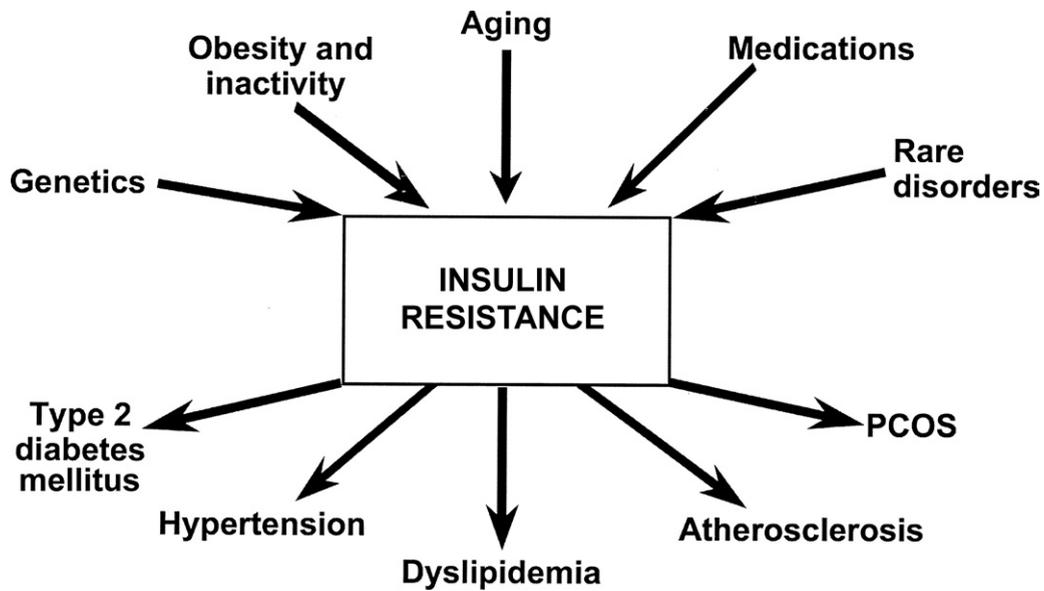


Figure 1 Causes and associated conditions of insulin resistance. PCOS = polycystic ovarian syndrome.

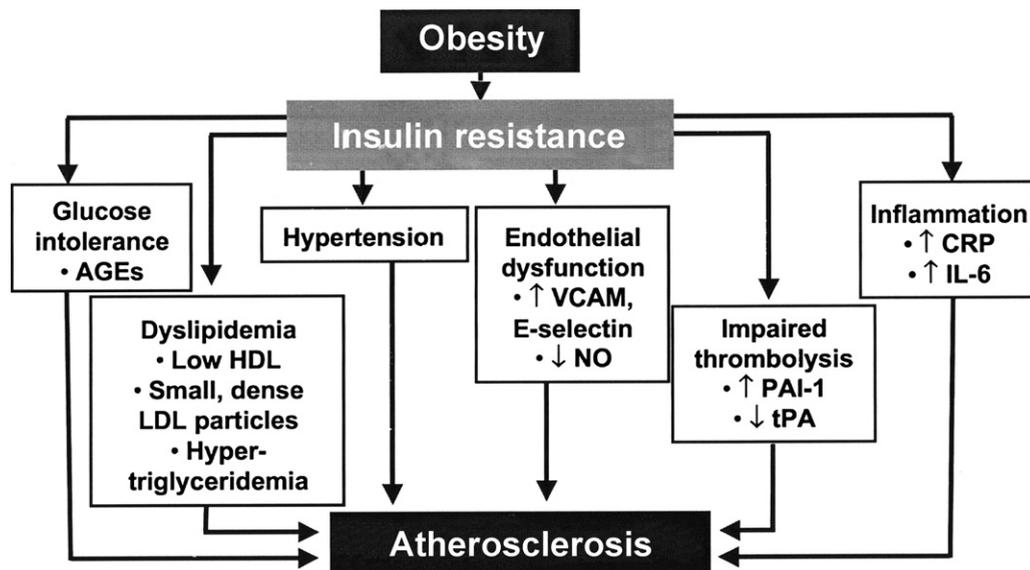


Figure 2 Association of insulin resistance with cardiovascular risk factors and atherosclerosis. AGEs = advanced glycation end products; CRP = C-reactive protein; HDL = high-density lipoprotein; IL-6 = interleukin-6; LDL = low-density lipoprotein; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor-1; tPA = tissue plasminogen activator; VCAM = vascular cell adhesion molecule; ↑ = increased; ↓ = decreased. (Adapted from *J Clin Endocrinol Metab.*⁷)

Obesity drives the development of insulin resistance, which in turn promotes the development of CVD (**Figure 2**).⁷ Insulin resistance is itself a risk factor for CVD. It affects CVD risk through several pathophysiologic mechanisms as follows:

- Glucose intolerance and hyperglycemia facilitate the accelerated formation of advanced glycation end products (AGEs), which interact with AGE-binding receptors to promote atherosclerosis directly through changes in the function of endothelial, macrophage, and smooth muscle cells.⁸
- Increased apolipoprotein (apo)-B concentrations, an increased proportion of small, dense low-density lipopro-

tein (LDL) cholesterol particles, decreased high-density lipoprotein (HDL) cholesterol, and hypertriglyceridemia characterize the dyslipidemia of visceral obesity and insulin resistance, and directly contribute to CVD.^{7,9,10}

- Insulin resistance blunts vascular production of nitric oxide, a factor crucial to the normal vasodilatory response and endothelial function.⁷
- Insulin resistance contributes to the development of hypertension, a well-established risk factor for CVD.^{7,10}
- Insulin resistance most likely impairs thrombolysis through a mechanism that involves increased levels of plasminogen activator inhibitor-1 (PAI-1).^{7,11–14}

- Insulin resistance itself is a proinflammatory state characterized by elevated levels of inflammatory markers. The link between insulin resistance and inflammation is quite provocative, especially because a growing body of data suggests that adipose tissue is an inflammatory milieu that directly produces inflammatory mediators of CVD.

PREVALENCE OF GLYCEMIC ABNORMALITIES

The prevalence of glycemic abnormalities (i.e., insulin resistance, impaired glucose tolerance [IGT], diabetes) in the US population represents a serious public health concern of enormous magnitude. CVD risk begins to increase considerably before the onset of diabetes or even impaired fasting glucose. Data from the Centers for Disease Control and Prevention (CDC) indicate that approximately 20 million US adults have diabetes—14 million have diagnosed diabetes, and 6 million have undiagnosed diabetes.¹⁵ An additional 16 million individuals have IGT, an intermediate step on the path from insulin resistance to diabetes.¹⁵

CVD risk (which is universally acknowledged to be substantially elevated in overt diabetes) begins to increase early in the progression from insulin resistance to diabetes (Figure 3). In fact, the risk for CVD increases as an individual progresses from insulin resistance to IGT to impaired fasting glucose to diabetes. Thus, identifying patients early in the process, before the onset of impaired fasting glucose, is an extremely important step in preventing and mitigating the consequences of CVD risk through lifestyle modification and medical intervention.

THE IMPACT OF PREDIABETIC STATES ON CARDIOVASCULAR DISEASE RISK

Accumulating evidence from clinical trials indicates that prediabetic states adversely affect the risk for CVD.^{16–19} In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, the investigators clearly established that IGT increased the risk for CVD mortality.¹⁶ This large database comprised 18,048 men and 7,316 women from 13 European prospective cohort studies.¹⁶

The DECODE study compared the American Diabetes Association (ADA) fasting glucose criteria²⁰ with the World Health Organization (WHO) 2-hour postchallenge glucose criteria in predicting CVD mortality.^{16,21} The ADA criteria define diabetes as a fasting plasma glucose concentration of 7.0 mmol/L (126 mg/dL) obtained with the use of the oral glucose tolerance test (OGTT).²⁰ By contrast, WHO recommends the use of the OGTT only if the blood glucose concentration is within the questionable range of 5.5 (99 mg/dL) to 11.1 mmol/L (199.8 mg/dL).^{16,21} WHO defines diabetes using the same fasting glucose concentration as the ADA in combination with a 2-hour glucose concentration of ≥ 11.1 mmol/L (≥ 199.8 mg/dL).^{16,21}

Using the WHO criteria for 2-hour glucose classification, the investigators showed that individuals with diabetes had

a significantly greater likelihood of dying over the follow-up period of up to 10 years (mean, 7.3 years) compared with persons who had normal glucose tolerance.¹⁶ Fasting blood glucose was not as accurate as 2-hour blood glucose in predicting mortality.¹⁶ Thus, these results confirm that, when used as the sole screening modality, abnormalities in 2-hour glucose concentrations predict mortality with greater accuracy compared with fasting glucose. The largest number of excess deaths was observed in the group with IGT that had “normal” fasting glucose concentrations of 6.0 mmol/L (108 mg/dL) or lower. Therefore, in clinical practice, the fasting glucose test alone will not identify all those at heightened risk. By contrast, IGT, based on the 2-hour glucose test, identifies patients at an intermediate stage between normal glucose tolerance and diabetes who are at substantially higher risk of dying from CVD over the next decade.¹⁶

Not surprisingly, the metabolic syndrome has been shown to further increase the degree of coronary heart disease (CHD) risk, regardless of diabetes status. The presence of the metabolic syndrome, with or without diabetes, correlates with an increased prevalence of CHD, although the combination of the metabolic syndrome with diabetes confers the highest degree of risk.¹⁷ Using data from the Third National Health and Nutrition Examination Survey (NHANES III), researchers categorized adults >50 years into 4 groups by the presence/absence of the metabolic syndrome (as defined by the National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III]⁵), with or without diabetes (Figure 4).¹⁷

The metabolic syndrome was shown to increase CHD risk. Individuals with the metabolic syndrome and diabetes had the highest CHD prevalence rate (19.2%). Notably, the metabolic syndrome, even without diabetes, was associated with a significantly increased prevalence rate (13.9%) of CHD. Those without the metabolic syndrome, regardless of their diabetes status, had the lowest rate of CHD prevalence.¹⁷ Thus, the presence of the metabolic syndrome, even in individuals without diabetes, was shown to markedly increase CHD risk.

The Nurses' Health Study assessed the effect of prediabetic states on CVD risk in a population of 117,629 female nurses, aged 30 to 55 years, who did not have CVD at study entry and who were followed for 20 years.¹⁸ A total of 1,508 subjects had diagnosed type 2 diabetes at baseline and 5,894 subjects developed it over the course of the study. During 2,238,288 person-years of follow-up, the investigators documented 1,556 new cases of myocardial infarction (MI) and 1,405 strokes.¹⁸ Figure 5 depicts the risk for MI or stroke by diabetes status and the risk for MI or stroke by time before diagnosis of diabetes.¹⁸ Compared with nondiabetic subjects, those who developed diabetes during follow-up had an age-adjusted increased relative risk for MI or stroke of 2.82 before diabetes diagnosis and 3.71 after diabetes diagnosis. Subjects who had diabetes at baseline had the highest risk, 5 times greater, of MI or stroke.

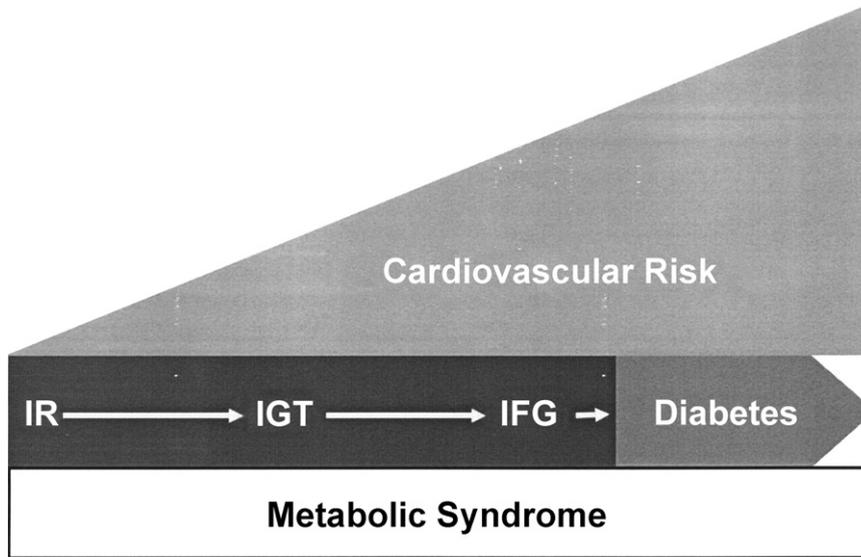


Figure 3 The metabolic syndrome, diabetes mellitus, and cardiovascular disease (CVD) risk: The risk for CVD increases as an individual progresses from insulin resistance (IR) to impaired glucose tolerance (IGT) to impaired fasting glucose (IFG) to diabetes.

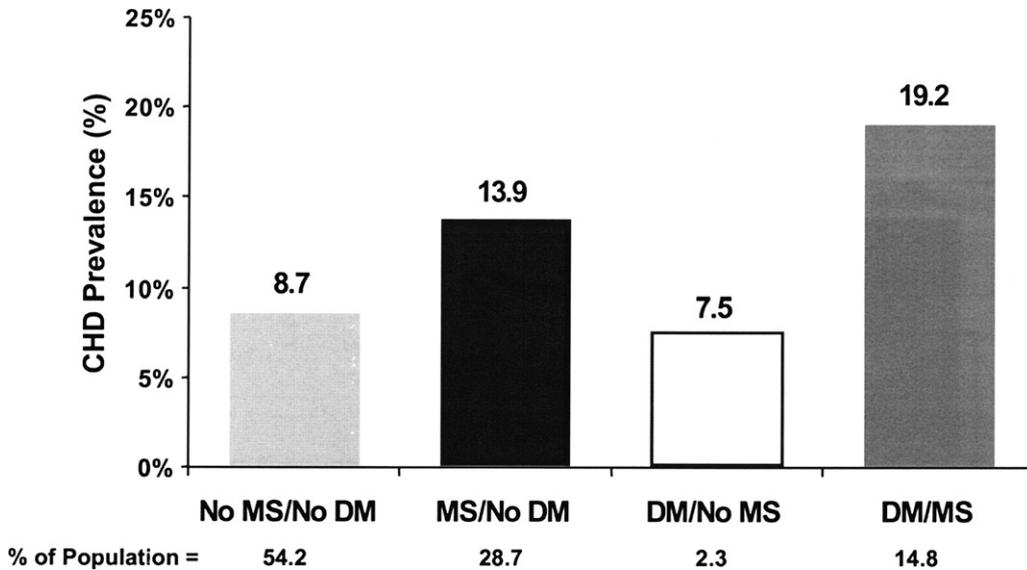


Figure 4 Age-adjusted prevalence of coronary heart disease (CHD) in the US population >50 years of age, categorized by the presence/absence of the metabolic syndrome (MS) and diabetes mellitus (DM). (Reprinted with permission from *Diabetes*.¹⁷)

Among the subjects who were free of diabetes at baseline, the relative risk for CVD was 2.4 at ≥ 15 years before diabetes onset; 10 to 15 years before onset, the relative risk increased to 3.19; and at < 10 years before onset, it increased to 3.64 (**Figure 5**).¹⁸ Clearly, the closer these individuals were to the onset of diabetes, the greater their CVD risk. The investigators concluded that their findings validated the “ticking clock” hypothesis that “it may be necessary to intervene before the onset of clinical diabetes, since the clock has already begun to tick.”^{6,18} Thus, the Nurses’ Health Study showed that prediabetes increases CVD risk, specifically MI or stroke. Because CVD risk begins to increase long before the onset of diabetes, high-risk patients should be aggressively screened and managed, with glucose

tolerance tests included as a routine part of the diagnostic work-up.

The San Antonio Heart Study, a population-based study of 2,569 individuals followed for 8 years, assessed the relation of insulin resistance to CVD risk.¹⁹ Insulin resistance was measured using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). The HOMA-IR index is defined as fasting insulin (in microunits per milliliter) times fasting glucose (in millimoles per liter) divided by 22.5.^{19,22} In this study, logistic regression analysis showed that the risk for CVD (i.e., death, MI, bypass surgery, angina) increased across quintiles of HOMA-IR after adjustment for age, sex, and ethnicity (P for trend < 0.0001).¹⁹ Individuals in the highest HOMA-IR quintiles

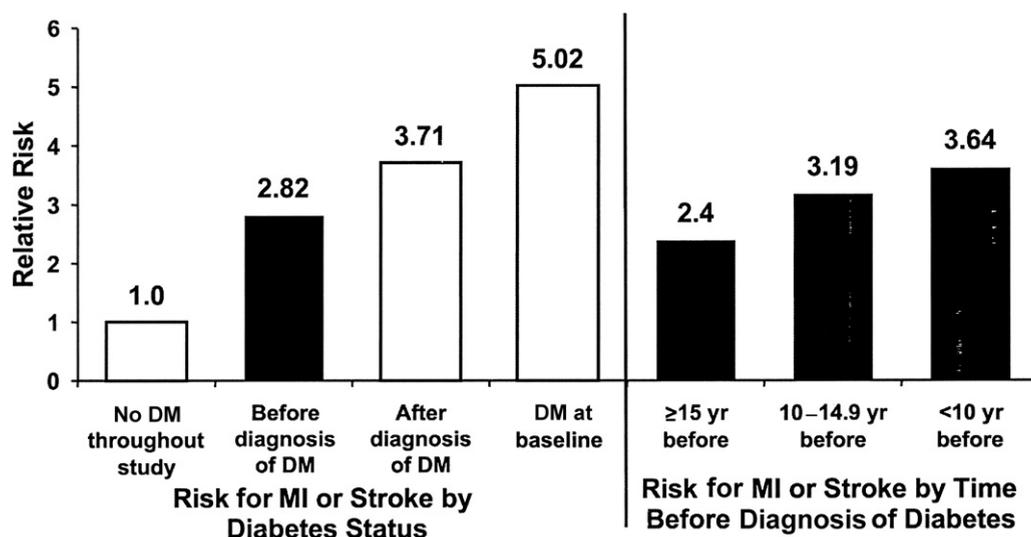


Figure 5 Multivariate relative risk for myocardial infarction (MI) or stroke according to diabetes mellitus (DM) status (*left*) and time before clinical diagnosis of DM (*right*) in the Nurses' Health Study, 1976 to 1996. (Reprinted with permission from *Diabetes Care*.¹⁸)

for insulin resistance had the greatest CVD risk, ranging from 2.47 to 4.80 for quintile 4 and 4.80 to 41.7 for quintile 5, compared with persons in the lowest quintile (risk range, 0 to 1.02).¹⁹

In summary, accumulating evidence suggests that CVD risk begins with insulin resistance, a silent condition that occurs long before overt diabetes. Therefore, proactive and aggressive clinical management of high-risk patients with insulin resistance should begin well before the onset of diabetes or even impaired fasting glucose to prevent diabetes and CVD. In this regard, the metabolic syndrome provides useful and easily applicable clinical criteria for identifying patients with insulin resistance who are at increased CVD risk.

A CLINICAL CHALLENGE: THE DYSLIPIDEMIA OF INSULIN RESISTANCE

Abnormalities in lipid and lipoprotein metabolism are among the major risk factors for CVD in insulin resistance.²³ One of the major mechanisms behind the dyslipidemia (i.e., low HDL cholesterol levels, small, dense LDL cholesterol particles, and hypertriglyceridemia) of insulin-resistant states is the increased flux of free fatty acids from adipose tissue to the liver. As illustrated in **Figure 6**, free fatty acids promote increased triglyceride synthesis in the liver, which can lead to the secretion of very-low-density lipoprotein. The accumulation of intracellular lipid metabolites in the liver appears to cause hepatic insulin resistance. Interestingly, even small degrees of weight loss increase hepatic insulin sensitivity in patients with type 2 diabetes and correspond with significant reduction in intrahepatic fat without any changes in circulating adipocytokines.²⁴ In addition, insulin resistance increases production of apo-CIII, a protein that blocks uptake of remnant lipoprotein particles.

A low HDL cholesterol level is even more common in patients with insulin resistance than is hypertriglyceridemia.

In insulin-resistant states, the following mechanisms lower HDL cholesterol: (1) cholesterol ester transfer protein mediates the transfer of cholesterol from HDL to the apo-B-containing lipoproteins; and (2) enzymes, such as hepatic lipase and endothelial lipase, are upregulated in the insulin-resistant state and, therefore, promote hypercatabolism of HDL.

TREATMENT OF DYSLIPIDEMIA IN INSULIN RESISTANCE

The ADA recommends aggressive targets for lipid management in patients with type 2 diabetes (**Table 1**).²⁵ Given the adverse prognostic implications of prediabetic states, it might be prudent to extend these lipid targets to patients with the metabolic syndrome and insulin resistance. For many patients, these goals can be met with lifestyle modification and, if necessary, adjunctive pharmacotherapy.

Lifestyle modification is the first-line approach to the management of patients with the metabolic syndrome and insulin resistance. Several studies have shown that diet and exercise can prevent or delay the onset of diabetes in patients with IGT.^{26–28} In the Diabetes Prevention Program (DPP), lifestyle modification was almost twice as effective as metformin in preventing diabetes (relative reduction, 58% vs. 31%).²⁷ The ADA recommends moderate weight loss (5% to 10% of body weight) and moderate physical exercise (30 minutes daily).²⁵

Many patients require adjunctive pharmacologic treatment of dyslipidemia to reduce CVD risk in insulin-resistant states. However, it can be difficult to achieve effective reduction of triglycerides and elevation of HDL cholesterol levels with existing therapies. In fact, many patients require >1 drug to address the various individual components of the metabolic syndrome. This often results in therapy with a statin (to reduce LDL cholesterol) plus either niacin

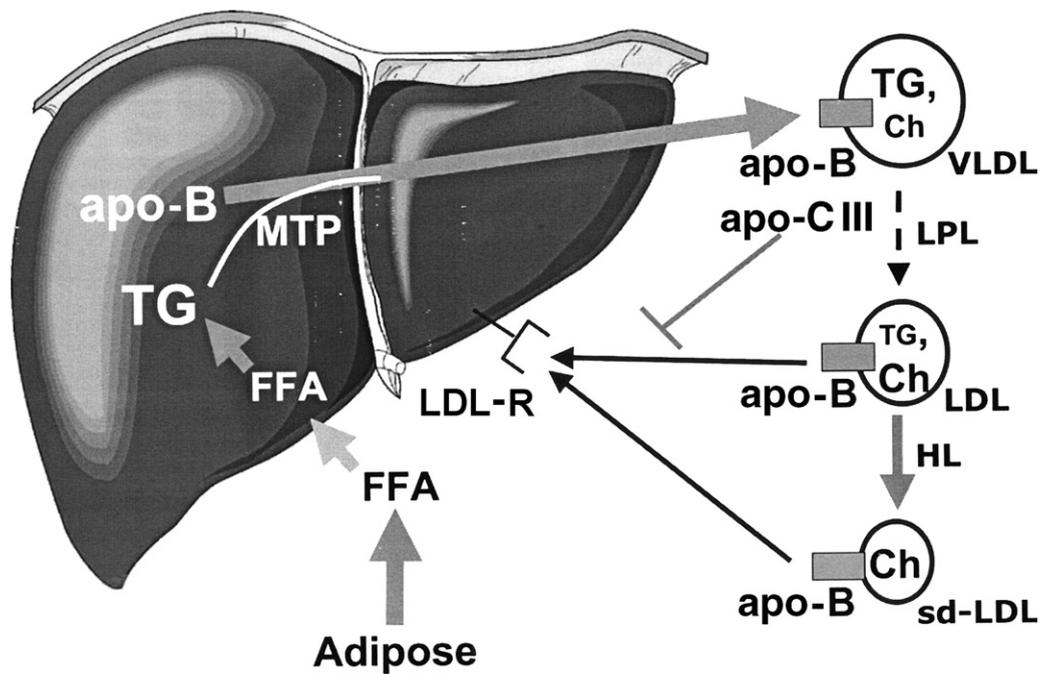


Figure 6 Mechanisms of dyslipidemia in insulin resistance are driven by increased influx of free fatty acids (FFAs) from adipose tissue to the liver. FFAs promote increased triglyceride synthesis in the liver, which can lead to the secretion of very-low-density lipoprotein (VLDL). apo = apolipoprotein; Ch = cholesterol; LDL = low-density lipoprotein; LDL-R = LDL receptor; LPL = lipoprotein lipase; MTP = microsomal triglyceride transfer protein; HL = hepatic lipase; sd-LDL = small, dense LDL; TG = triglyceride.

Table 1 American Diabetes Association (ADA) targets for lipids in type 2 diabetes mellitus

| Lipid | Target (mg/dL)* |
|--------------------|----------------------------|
| HDL-C | >40 in men >50 in women |
| LDL-C [†] | <100 |
| TG [‡] | <150 |

CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

*To achieve SI conversions in millimoles per liter, multiply HDL-C and LDL-C values by 0.02586, and TG values by 0.01129.

[†]In patients >40 years of age with diabetes and TC \geq 135 mg/dL, without CVD, therapy with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) should be considered to achieve an LDL-C reduction of 30% to 40% regardless of baseline LDL-C levels. In very high-risk patients, e.g., those with diabetes and CVD, an LDL-C goal of <70 mg/dL is an option.

[‡]NCEP ATP III guidelines suggest that in patients with TG \geq 200 mg/dL, the non-HDL-C (TC minus HDL-C) level should be used. The goal is 130 mg/dL.

Reprinted from *Diabetes Care*.²⁵

or a fibrate (to reduce triglycerides and increase HDL cholesterol).

Ultimately, effective weight reduction, especially reduction in visceral adiposity, should improve insulin sensitivity and other manifestations of the insulin-resistant state and reduce the risk for type 2 diabetes and CVD. The optimal pharmacologic strategy for reducing CVD risk in insulin resistance and in the metabolic syndrome would be to target the dyslipidemia, hypercoagulable state, hypertension, insu-

lin resistance, and obesity. However, the ADA cautions against the routine use of drug therapy to prevent diabetes until information from clinical trials establishes a clear rationale for its use.²⁵

SUMMARY

Obesity frequently contributes to insulin resistance, which increases the risk for type 2 diabetes and CVD. Insulin-

resistant states are associated with a particular dyslipidemic profile characterized by hypertriglyceridemia, low levels of HDL cholesterol, and small, dense LDL cholesterol particles. The increased flux of free fatty acids from adipose tissue to the liver exacerbates hepatic insulin resistance and promotes all of these aspects of dyslipidemia. CVD risk increases markedly as glycemic abnormalities (i.e., insulin resistance and IGT) progress to overt diabetes.

Lifestyle modifications (diet and exercise) that target weight reduction, especially reduction in abdominal adiposity, comprise the first-line approach to treating glycemic abnormalities and reducing the risk for diabetes and CVD. Pharmacologic therapy is used adjunctively in patients at higher risk and those recalcitrant to lifestyle modification. Primary care physicians can play a major role in the early identification and preventive management of insulin-resistant states to help reduce progression to type 2 diabetes and decrease the risk for CVD.⁴

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