Lipid Abnormalities in Insulin Resistant States

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There are many metabolic consequences of insulin resistance and multiple conditions associated with insulin resistant states. The most obvious pathology associated with insulin resistance is type 2 diabetes mellitus, but other manifestations include hypertension, central obesity, a hypercoagulable state, and dyslipidemia. The atherogenic dyslipidemia associated with insulin resistant states is characterized by hypertriglyceridemia; an increase in very-low-density lipoprotein secretion from the liver; an increase in atherogenic small, dense low-density lipoprotein; and a decrease in high-density lipoprotein cholesterol. Each of these lipid abnormalities is an independent risk factor for coronary artery disease, and in concert, the cardiovascular risk is magnified. Therefore, insulin resistant states should be identified as early as possible in patients, and these lipid abnormalities should be assessed and treated.
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Key words: Insulin resistance • Lipoproteins • Metabolic syndrome

Recent evidence suggests that up to one-third of the American population is insulin resistant.[1] When insulin resistance, or reduced insulin sensitivity, exists, the body attempts to overcome this resistance by secreting more insulin from the pancreas. This compensatory state of hyperinsulinemia causes several metabolic abnormalities that occur together commonly enough to be thought of as a syndrome. These interrelated metabolic abnormalities have come to be known by a variety of names, including the insulin resistance syndrome, syndrome X, the "deadly quartet," and most recently, the metabolic syndrome,

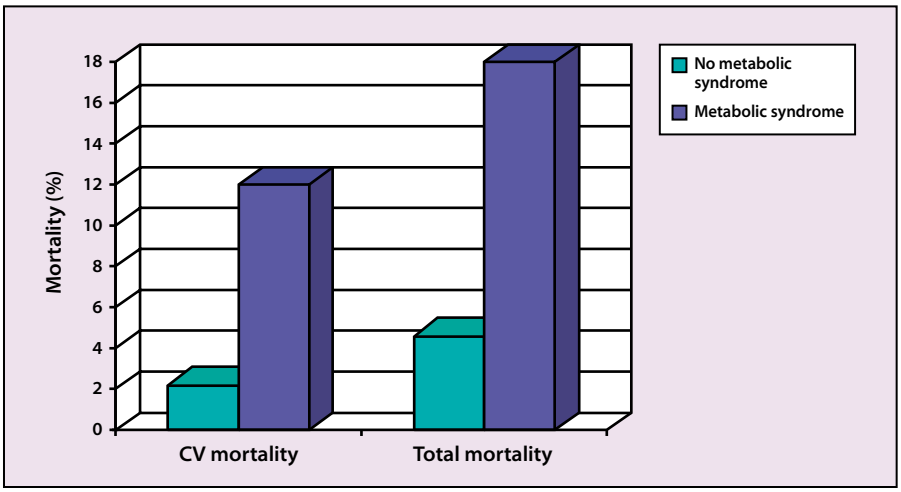


Figure 1. *Isomaa and colleagues studied 4483 subjects participating in a large family study of type 2 diabetes in Finland and Sweden. They defined the metabolic syndrome as the presence of at least two of the following risk factors: obesity, hypertension, dyslipidemia, and microalbuminuria. After a median follow-up of 6.9 years, cardiovascular (CV) and total mortality were assessed. The authors found that cardiovascular and total mortality were markedly increased in subjects with the metabolic syndrome. Data from Isomaa et al.*[5]

as highlighted in the recent report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).[2] Characteristic abnormalities of the insulin resistance syndrome include glucose intolerance, obesity, high blood pressure, a prothrombotic state, and dyslipidemia.[3] The metabolic abnormalities associated with insulin resistance have been associated individually with cardiovascular disease,[4] and the occurrence of these abnormalities together in the insulin resistance syndrome has been found to greatly increase cardiovascular mortality (Figure 1).[5] It is the dyslipidemia of the insulin resistance syndrome that is the focus of this review.

How Is Insulin Resistance Diagnosed?

The gold standard for diagnosis of insulin resistance is a test called the hyperinsulinemic euglycemic clamp study. This complicated test involves intravenous infusion of insulin and glucose at different doses to see what levels of insulin control different levels of glucose. Insulin resistance is diagnosed when a defined amount of insulin stimulates glucose uptake by peripheral tissues to a lesser degree than it does in normal (insulin-sensitive) individuals. Because of the impracticality of performing this test, other clues to the presence of insulin resistance must be sought. Typically, a clinical diagnosis is made using the criteria described in Figure 2, which shows the characteristic abnormalities of the insulin resistance syndrome as delineated in NCEP ATP III as the metabolic syndrome.[2] Since the diagnosis is based on a cluster of abnormalities that co-segregate, all components of the metabolic syndrome should be assessed in a patient presenting with any one of the metabolic abnormalities. Screening is particularly important in overweight patients.

Lipoprotein Abnormalities in Insulin Resistant States

The dyslipidemia associated with insulin resistant states is characterized by hypertriglyceridemia; an increase in very-low-density lipoprotein (VLDL) secretion from the liver; an increase in atherogenic small, dense low-density lipoprotein (LDL); and a decrease in high-density lipoprotein (HDL) cholesterol.[6,7] Not only are these characteristic changes ubiquitous, but abnormalities of triglyceride and HDL metabolism are an early manifestation of insulin resistance, often detectable even before the development of abnormal postprandial or fasting glucose levels.[8]

Figure 2. *The characteristic abnormalities of the insulin resistance syndrome as delineated in the National Cholesterol Education Program Adult Treatment Panel III as the metabolic syndrome. Though not all individuals who meet criteria for the metabolic syndrome are insulin resistant, these metabolic abnormalities can provide strong clues to the presence of insulin resistance. The metabolic syndrome is diagnosed when any 3 of these are present. HDL-C, high-density lipoprotein cholesterol. Data from the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.*[2]

Risk Factor	Defining Level
Abdominal obesity (waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglyceride level	>150 mg/dL
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥ 85 mm Hg
Fasting glucose	≥110 mg/dL

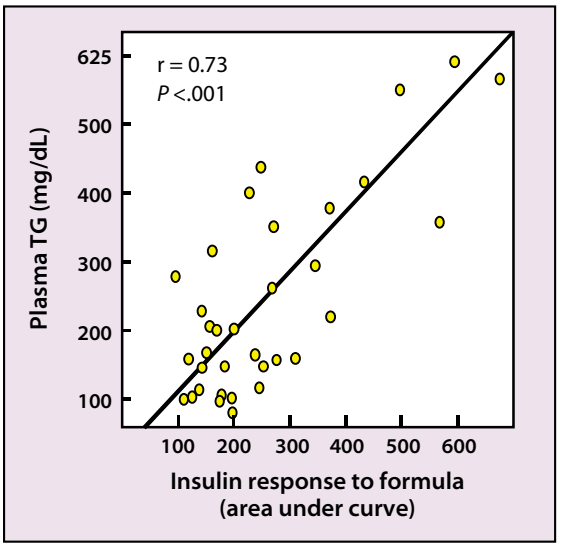


Figure 3. *Olefsky and colleagues found a strong correlation between insulin response to an oral glucose challenge and plasma triglyceride (TG) levels. This analysis reveals that much of the variability in plasma triglyceride levels in this cohort could be explained by insulin resistance as measured by the insulin response to oral glucose. Adapted with permission from Olefsky et al.*[9]

Relationship Between Insulin Resistance and Hypertriglyceridemia

Much of the atherogenic dyslipidemia of the insulin resistance syndrome begins with hypertriglyceridemia. A relationship between insulin resistance and hypertriglyceridemia has been suspected for some time. To verify this, Olefsky and colleagues studied 34 individuals with diabetes or high triglycerides. The subjects were kept in a metabolic ward and maintained on a liquid formula diet (15% protein, 43% carbohydrate, and 42% fat). After 4 days of metabolic stabilization, the researchers found a highly significant relationship between fasting plasma triglyceride concentration and insulin response to formula (Figure 3), highlighting insulin's role in the control of triglyceride metabolism.[9]

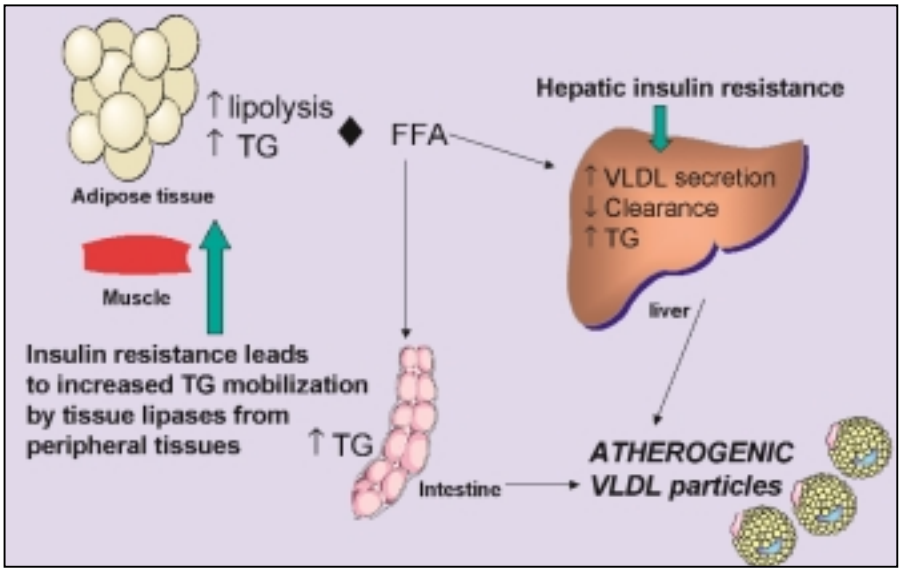
The predominant triglyceride-containing lipoprotein is VLDL. VLDL is synthesized by the liver, and its production is stimulated by increased delivery of free fatty acids (FFA) to the liver. Research describing how insulin regulates triglyceride levels has shown that in patients with normal insulin sensitivity, insulin acutely inhibits VLDL secretion from the liver.[10] When insulin resistance occurs, however, the chronically high insulin levels make the liver resistant to the inhibitory effects of insulin on VLDL secretion.[11] In addition, in insulin resistant states there appears to be defective clearance of VLDL cholesterol.[12,13] The insulin resistance syndrome also causes reduced FFA absorption and enhanced lipolysis by adipocytes, both resulting in increased circulating FFA levels. The increased FFA delivery to peripheral tissues (notably liver and intestine) in conjunction with insulin resistance leads to overproduction of both hepatically and intestinally derived triglyceride-rich lipoprotein particles (Figure 4).

Relationship Between Insulin Resistance and Low HDL Cholesterol

In a study by Reaven and colleagues, an association between hyperinsulinemia and low HDL cholesterol was found. In both nonobese and obese subjects, those who had insulin levels above the median had lower HDL cholesterol levels than did those with insulin levels below the median (Figure 5).[14] This association has since been verified by several investigators.

In the presence of increased plasma

Figure 4. *The insulin resistance syndrome causes reduced free fatty acid (FFA) absorption and enhanced lipolysis by peripheral tissues, both causing increased circulating FFA levels. The increased FFA delivery to liver and intestine in conjunction with insulin resistance leads to overproduction of both hepatically and intestinally derived triglyceride (TG)-rich lipoprotein particles. There is a further decrease in clearance of these particles by the liver, leading to the increased concentration of atherogenic very-low-density lipoprotein (VLDL) particles characteristic of insulin resistance.*



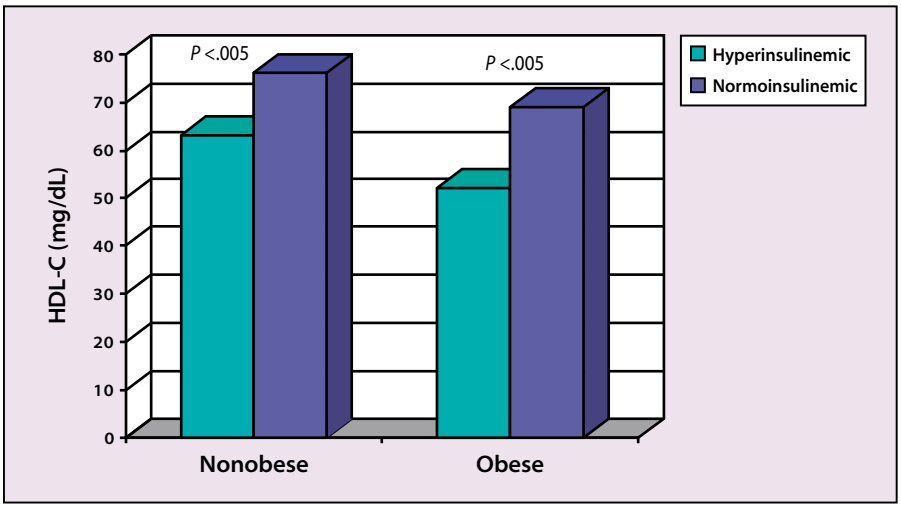


Figure 5. *Reaven and colleagues at Stanford University found an association between hyperinsulinemia and low high-density lipoprotein cholesterol (HDL-C). In both nonobese and obese subjects, those who had insulin levels above the median had lower HDL-C levels than did those with insulin levels below the median. Adapted with permission from Reaven et al.*[14]

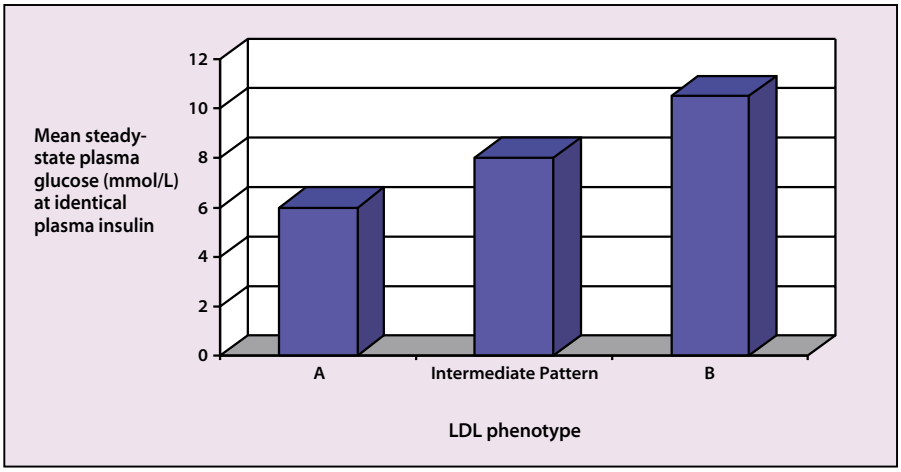
levels of VLDL, the plasma protein cholesteryl ester transfer protein (CETP) can facilitate the exchange of triglycerides in VLDL for cholesterol in HDL. In other words, a VLDL particle will give up a molecule of triglyceride, donating it to HDL, in exchange for one of the cholesteryl ester molecules from HDL. This causes two adverse outcomes. First, a cholesterol-rich VLDL particle (which is highly atherogenic) is formed. Second, a triglyceride-rich cholesterol-depleted HDL particle is formed. This triglyceride-rich HDL particle can undergo hydrolysis of its triglyceride and dissociation of its protein component, apolipoprotein (apo) A-I. The free apo A-I is cleared very rapidly, so not only is HDL cholesterol reduced, but the amount of circulating apo A-I (and therefore the number of HDL particles) is also reduced.

Relationship Between Insulin Resistance and Small, Dense LDL Particles

The LDL abnormality found in insulin resistant states typically does not show up on a standard lipoprotein profile. In insulin resistance, the LDL level is usually within normal limits or only mildly elevated; however, the LDL particle is often of abnormal composition. Insulin resistance has been found to be related to cholesterol-depleted and therefore smaller and denser LDL particles (Figure 6).[15] As patients become more insulin resistant and fasting glucose levels increase, the LDL phenotype is characterized by smaller, denser LDL particles (phenotype B) as opposed to the larger, more buoyant, cholesterol-rich LDL particles (phenotype A). Small, dense LDL particles have been found to be associated with a threefold increase in risk for coronary heart disease. The increased atherogenicity of these particles is attributed, at least in part, to their ability to enter vessel walls faster than larger LDL particles, their increased susceptibility to oxidation, and their increased uptake by macrophages.

The underlying abnormality causing small, dense LDL particles in insulin resistance is, again, hypertriglyceridemia, and the mechanism is similar to that which causes low HDL levels. Increased levels of VLDL triglyceride in the presence of CETP can promote the transfer of triglyceride into LDL in exchange for LDL cholesteryl ester. This triglyceride-rich LDL particle undergoes hydrolysis to remove triglyceride, which leads to a smaller, denser, lipid-depleted LDL particle. Hypertriglyceridemia is so intimately related to the LDL particle size that the LDL phenotype can often be determined simply by knowing the

Figure 6. *As patients become more insulin resistant and fasting glucose levels increase, the low-density lipoprotein (LDL) phenotype is characterized by smaller, denser, more atherogenic LDL particles (phenotype B) as opposed to the larger, more buoyant, less atherogenic LDL particles (phenotype A). Adapted with permission from Reaven et al.*[15]



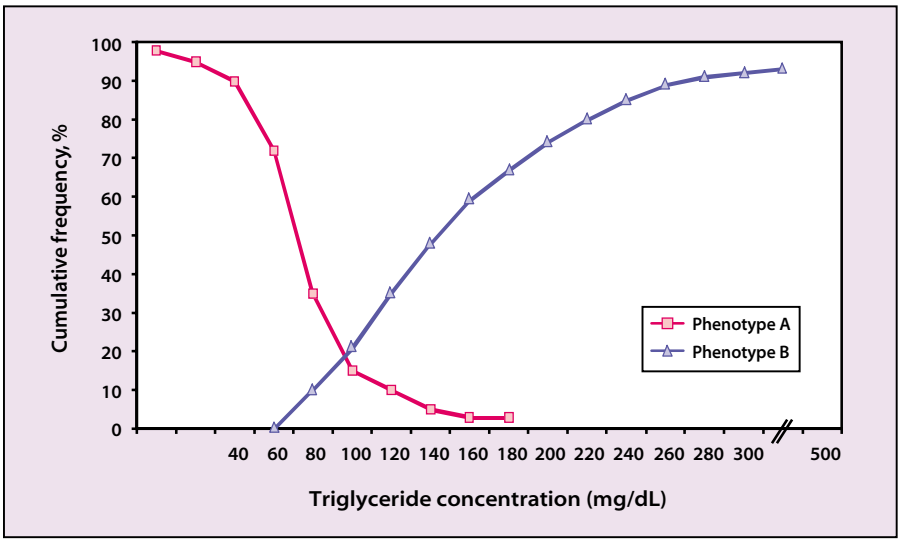


Figure 7. *Low-density lipoprotein (LDL) phenotype can often be determined by knowing the triglyceride concentration. With triglyceride levels less than approximately 70 mg/dL, nearly all individuals have large, buoyant LDL (phenotype A), but with triglyceride levels greater than approximately 150 mg/dL, small, dense LDL particles (phenotype B) predominate. Adapted with permission from Austin et al.*[16]

triglyceride concentration (Figure 7).[16] With triglyceride levels less than approximately 70 mg/dL, nearly all individuals have large, buoyant LDL (phenotype A), but with triglyceride levels greater than approximately 150 mg/dL, small, dense LDL particles (phenotype B) predominate.

Figure 8 summarizes the lipid abnormalities associated with insulin resistant states.[17] The insulin resistance syndrome is associated with increased VLDL concentrations and increased VLDL size; an increase in small, dense LDL particles; and a decrease in both HDL concentration and HDL size to a less protective HDL particle.

Treatment of Lipid Abnormalities Associated with Insulin Resistance

There are several nonpharmacologic and pharmacologic interventions that may increase sensitivity of insulin and therefore improve lipoprotein abnormalities.

Nonpharmacologic Treatment of Dyslipidemia Associated with Insulin Resistant States

Physical activity, weight control in overweight patients,[18] reduction in saturated fat, and carbohydrate moderation are recommended for patients with insulin resistance. Research has demonstrated that increased physical activity has an immediate effect on insulin sensitivity.[19] In addition, in a small study of smokers (N = 40), it was found that smoking cessation was associated with increased insulin sensitivity.[20]

Pharmacologic Treatment of Dyslipidemia Associated with Insulin Resistant States

Treatment strategies for the dyslipidemia of insulin resistance require treatment of lipid abnormalities in the presence of excess insulin. Pharmacologic agents that modify lipids in the insulin resistance syndrome fall into two categories: agents that improve insulin sensitivity and lipid lowering agents.

Agents that improve insulin sensitivity. There is currently no drug approved by the U.S. Food and Drug Administration for the treatment of insulin resistance. There are, however, some pharmacologic agents that may increase sensitivity to insulin.

The two types of insulin-sensitizing agents in clinical use are the thiazolidinediones (eg, rosiglitazone, pioglitazone) and the biguanide agent metformin. Although these agents are primarily intended as antidiabetic

The thiazolidinediones have been shown to lower triglycerides, raise HDL, and possibly increase LDL particle size.

Figure 8. *A summary of the characteristic lipoprotein changes of the insulin resistance syndrome. Insulin resistance is associated with increased very-low-density lipoprotein (VLDL) concentrations, a greater proportion of large VLDL particles and increased VLDL size. There is also an increase in small, dense low-density lipoprotein (LDL) particles and a decrease in mean LDL size. With insulin resistance, there is also a decrease in both high-density lipoprotein (HDL) concentration and HDL size to a presumably less protective HDL particle. TG, triglyceride; lg, large; sm, small; HDL-C, high-density lipoprotein cholesterol; Sens, sensitive; Res, resistant; DM, diabetes mellitus. Reprinted with permission from Waring et al.*[17]

Group	VLDL-TG (mg/dL)	lg VLDL (mg/dL)	VL DL size (nm)	sm LDL (mg/dL)	LDL size (nm)	HDL-C (mg/dL)	sm HDL (mg/dL)	HDL size (nm)
Insulin Sens	64	13	47.7	26	21.0	41	12.7	8.90
Insulin Res	89	32	51.6	41	20.7	37	14.8	8.70
DM	123	55	53.3	56	20.4	37	15.5	8.70

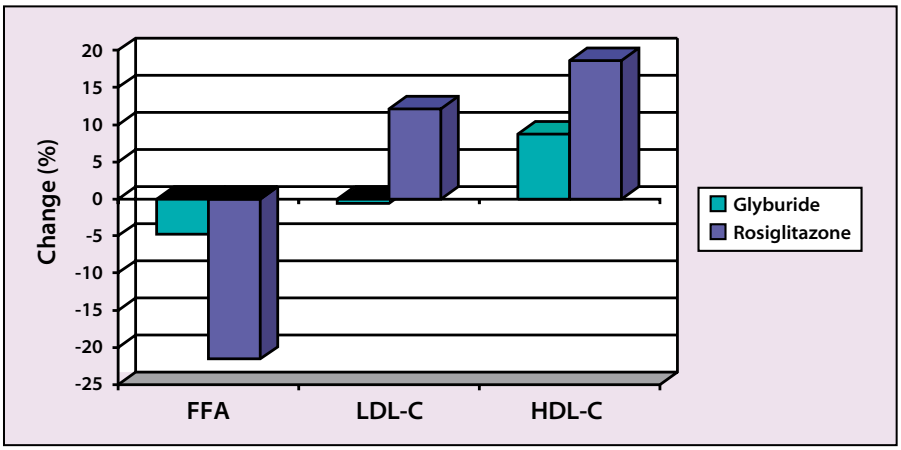


Figure 9. *Pooled data fom studies involving 2315 subjects with type 2 diabetes mellitus. The thiazolidinedione agent rosiglitazone was found to have beneficial effects on lipid levels as compared with the insulin secretagogue glyburide. Both agents controlled blood glucose levels but only the insulin-sensitizing agent improved blood lipids, suggesting that it is the improvement in insulin sensitivity rather than the control of blood glucose that is responsible for the beneficial lipid effects of the thiazolidinediones. FFA, free fatty acids; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. Data from Avandia® (rosiglitazone) package insert.*[21]

agents, both of these classes have been shown to have lipid-modifying effects as well.

The thiazolidinediones have been shown to lower triglycerides, raise HDL (Figure 9),[21] and possibly increase LDL particle size. Although treatment with thiazolidinediones is often associated with a small increase in LDL concentration, this effect may reflect an increase in LDL particle size to a less atherogenic particle.[22]

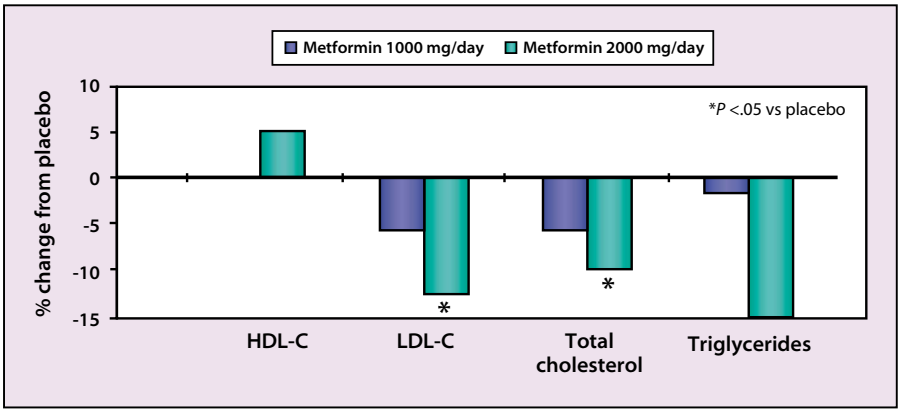
Metformin is an antidiabetic agent that both reduces hepatic glucose production and improves insulin sensitivity. It has been found to have beneficial lipid effects causing a reduction in total cholesterol, LDL, and triglycerides while increasing HDL (Figure 10).[23] Metformin does not appear to increase LDL particle size as do the thiazolidinediones.[24]

Lipid-lowering agents. Niacin and fibric acid derivatives (fibrates) have been shown to have specific effects on components of the atherogenic dyslipidemia of the insulin resistance syndrome. Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) have not been demonstrated to specifically affect components of atherogenic dyslipidemia; however, they have been demonstrated to strikingly improve cardiovascular outcomes in individuals with insulin resistance (Figure 11).[25]

Niacin therapy not only lowers triglycerides, lowers LDL, and raises HDL levels, it also shifts LDL particles from small and dense to larger, more buoyant LDL particles. Niacin works, in part, by reducing hepatic production of VLDL, which results in lower levels of VLDL and LDL. It also increases HDL levels. Because elevated VLDL and reduced HDL are the characteristic lipoprotein patterns found in insulin resistant states, niacin is a viable treatment option for the dyslipidemia of the insulin resistance syndrome. However, niacin has also been found to accentuate insulin resistance; thus, there has been concern over its use in insulin resistant states. The recent Arterial Disease Multiple Intervention Trial, however, found beneficial lipoprotein changes in diabetic subjects randomized to niacin, and this study demonstrated that glycemic control could be maintained in the face of niacin therapy by intensifying the use of hypoglycemic agents.[26]

Fibric acid derivatives, such as gemfibrozil and fenofibrate, lower triglycerides and raise HDL levels (Figure 12).[27] They have a variable effect on LDL levels, but there is evidence that these agents may also increase LDL particle size.[28] The

Figure 10. *Results from a 9-week double-blind, placebo-controlled, crossover study of 24 nondiabetic subjects who had characteristic dyslipidemia of the insulin resistance syndrome (mean high-density lipoprotein cholesterol [HDL-C], 43; mean triglycerides, 270). The subjects were randomized either to metformin 1000 mg/d, metformin 2000 mg/d, or placebo. The results of the metformin doses are shown below. There were statistically significant decreases in total cholesterol and low-density lipoprotein cholesterol (LDL-C) with the metformin 2000 mg per day dose as compared to placebo. HDL-C was also increased somewhat with the 2000 mg/d dose. There was no change in weight or blood glucose in these nondiabetic subjects. Thus, lipid changes were not related to improved glycemic control or weight loss. Data from Pentikainen et al.*[23]



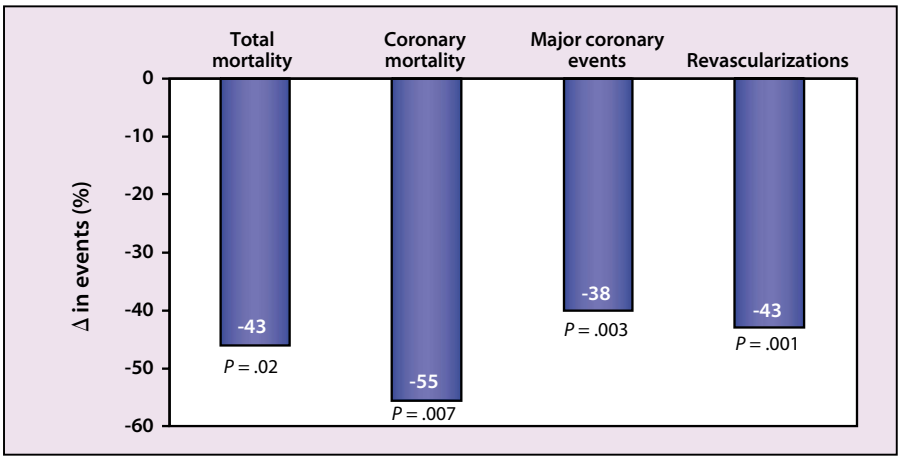


Figure 11. *In a post hoc analysis of the Scandinavian Simvastatin Survival Study, individuals with insulin resistance (as determined by fasting glucose levels between 110 and 125 mg/dL) who received simvastatin experienced significant reductions in coronary mortality (55%), major coronary events (38%), and need for revascularization (43%) as compared to insulin resistant individuals randomized to placebo. Data from Haffner et al.*[25]

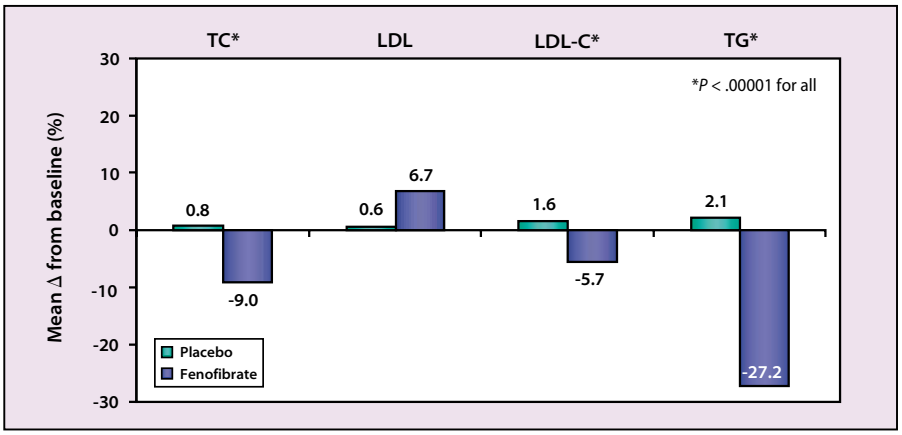


Figure 12. *In the Diabetes Atherosclerosis Intervention Study, fenofibrate improved lipid profiles in subjects with type 2 diabetes mellitus as compared to placebo. TC, total cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides. Adapted with permission from Diabetes Atherosclerosis Intervention Study.*[27]

	TZD	Metformin	Niacin	Fibrates	Statins
TC	↑	↓	↓	↓	↓↓
LDL-C	↑	↓	↓	+/–	↓↓↓
LDL size	↑	→	↑↑	↑	→
HDL-C	↑	→ or ↑	↑↑↑	↑↑	↑
TG	↓ or →	↓	↓↓↓	↓↓↓	↓↓
Insulin Sensitivity	↑	↑	↓	→	→
CV event reduction	No data	Yes (UKPDS)	Yes (CDP)	Yes (VA-HIT)	Yes (numerous trials)*

Figure 13. *Summary of the effect of various pharmacotherapies on the dyslipidemia of the insulin resistance syndrome. TZD, thiazolidinedione; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL, high-density lipoprotein; TG, triglycerides; CV, cardiovascular; UKPDS, United Kingdom Prospective Diabetes Study; CDP, Coronary Drug Project; VA-HIT, Veterans Administration-HDL Intervention Trial; →, no change; +/-, variable results. Data from UKPDS*[29]*, Berge KG and Canner PL*[30]*, VA-HIT*[31]*, and *Taskinen.*[32]

fibrates are peroxisome proliferator-activated-α agonists that function by activating genes important in triglyceride and HDL metabolism. The recent Diabetes Atherosclerosis Intervention Study found that treatment with fenofibrate reduces the angiographic progression of coronary-artery disease in type 2 diabetics and that this effect is related, at least partly, to the correction of lipoprotein abnormalities.[27]

Statins are lipid-lowering agents with powerful LDL-lowering capabilities, moderate triglyceride-lowering properties, and modest HDL-raising capabilities. Statins cannot shift LDL particle size; however, by dramatically reducing total LDL levels, they lower both small, dense LDL and large, buoyant LDL concentrations. Although statins have not been specifically studied in insulin resistant populations, subgroup analysis of statin trials have shown striking cardiovascular event reductions in patients with type 2 diabetes mellitus and patients with insulin resistance (Figure 11).[25]

Figure 13 summarizes the effect of various pharmacotherapies on the dyslipidemia of the insulin resistance syndrome.[29–32]

Conclusion

The insulin resistance syndrome encompasses numerous metabolic abnormalities, greatly increasing cardiovascular risk. Among the metabolic abnormalities is dyslipidemia (Figure 14). Elevated triglyceride levels, reduced levels of HDL, and an increased incidence of small, dense LDL particles characterize the dyslipidemia of insulin resistance. Each of these lipid abnormalities is an independent risk factor for coronary artery disease, and in concert, the cardiovascular risk is magnified. Therefore, insulin resistant states should be identified as early as pos-

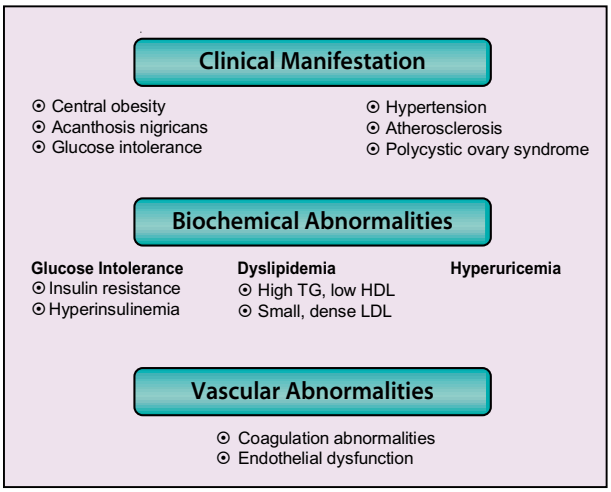


Figure 14. *Summary of the numerous metabolic abnormalities associated with the insulin resistance syndrome. These combined abnormalities greatly increase cardiovascular risk. TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.*

sible in patients, and these lipid abnormalities should be assessed and treated. ■

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Main Points

- The metabolic abnormalities associated with insulin resistance have been associated individually with cardiovascular disease, and the occurrence of these abnormalities together in the insulin resistance syndrome has been found to greatly increase cardiovascular mortality.
- The dyslipidemia associated with insulin resistant states is characterized by hypertriglyceridemia; an increase in very-low-density lipoprotein secretion from the liver; an increase in atherogenic small, dense low-density lipoprotein (LDL); and a decrease in high-density lipoprotein (HDL) cholesterol.
- After 4 days of metabolic stabilization, researchers found a highly significant relationship between fasting plasma triglyceride concentration and insulin response to formula, highlighting insulin's role in the control of triglyceride metabolism.
- In a study by Reaven and colleagues, an association between hyperinsulinemia and low HDL cholesterol was found. In both nonobese and obese subjects, those who had insulin levels above the median had lower HDL cholesterol levels than did those with insulin levels below the median.
- As patients become more insulin resistant and fasting glucose levels increase, the LDL phenotype is characterized by smaller, denser LDL particles as opposed to the larger, more buoyant, cholesterol-rich LDL particles. Small, dense LDL particles have been found to be associated with a threefold increase in risk for coronary heart disease.
- Physical activity, weight control in overweight patients, reduction in saturated fat, and carbohydrate moderation are recommended for patients with insulin resistance.
- The two types of insulin-sensitizing agents in clinical use are the thiazolidinediones (eg, rosiglitazone, pioglitazone) and the biguanide agent metformin.
- Niacin and fibric acid derivatives (fibrates) have been shown to have specific effects on components of the atherogenic dyslipidemia of the insulin resistance syndrome. Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) have not been demonstrated to specifically affect components of atherogenic dyslipidemia; however, they have been demonstrated to strikingly improve cardiovascular outcomes in individuals with insulin resistance.

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