

The Metabolic Basis of Atherogenic Dyslipidemia

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Atherogenic dyslipidemia is one of the major components of the metabolic syndrome, a complex cluster of several risk factors within a single patient that according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III includes at least 3 of the following: large waist circumference, elevated triglyceride levels, low levels of high-density lipoprotein cholesterol (HDL-C), hypertension, and elevated fasting glucose levels, which are directly related to the incidence of coronary heart disease. Atherogenic dyslipidemia clinically presents as elevated serum triglyceride levels, increased levels of small dense low-density lipoprotein (sdLDL) particles, and decreased levels of HDL-C. An important component of atherogenic dyslipidemia is central obesity, which is defined as increased waist circumference and has recently been identified as a chief predictor of the metabolic syndrome in certain patients. Another recent study found that both body mass index and waist circumference were highly predictive of eventual development of the metabolic syndrome. Because atherogenic dyslipidemia usually precedes the clinical manifestation of the metabolic syndrome, strategies to treat it are the focus of pharmacologic intervention. For example, the 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors, commonly known as statins, benefit hypercholesterolemic patients who have atherogenic dyslipidemia that is associated with the metabolic syndrome. Pioglitazone, an antidiabetic agent that acts primarily by decreasing insulin resistance, improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone improves glycemic control while reducing circulating insulin levels.

The investigational agent, rimonabant—a centrally and peripherally acting, selective cannabinoid type-1 receptor blocker—is the first therapy developed for managing several cardiovascular risk factors at one time. Rimonabant has shown promise in attacking atherogenic dyslipidemia from several vantage points by affecting glucose, HDL-C, triglycerides, and waist circumference in patients who are prone to atherogenic dyslipidemia. (*Clinical Cornerstone*. 2005;7[2/3]:27–35). Copyright © 2005 Excerpta Medica, Inc.

Atherogenic dyslipidemia is one of the major components of the metabolic syndrome, a complex cluster of several risk factors within a single patient that according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) includes at least 3 of the following: large waist circumference, elevated triglyceride levels, low levels of high-density lipoprotein cholesterol (HDL-C), hypertension, and elevated fasting glucose levels, which are directly related to the incidence of coronary heart disease.¹ Atherogenic dyslipidemia clinically presents as elevated serum triglyceride levels, increased small dense low-density lipoprotein (sdLDL) particles, and decreased levels of HDL-C. A more detailed analysis usu-

ally reveals other lipoprotein abnormalities, such as increased remnant lipoproteins, elevated apolipoprotein B, and small high-density lipoprotein particles^{2,3}; all of these abnormalities have been implicated as being independently atherogenic. The 3 abnormalities of elevated serum triglycerides, increased sdLDL particles, and low HDL-C have been termed the atherogenic lipoprotein phenotype⁴ or, more simply, the lipid triad. This multiplex array of lipid abnormalities is a powerful risk factor for coronary heart disease (CHD), defined as angina pectoris, unstable angina, myocardial infarction, or coronary death.

The lipid triad is not to be confused with elevated low-density lipoprotein cholesterol (LDL-C), which by

itself has been shown in the Framingham Offspring Study to be an independent risk factor for CHD.^{5,6} However, atherogenic dyslipidemia is more prevalent than isolated high LDL-C and often precedes the full clinical manifestation of the metabolic syndrome.⁷

CENTRAL OBESITY AS A PRIME PREDICTOR OF CORONARY HEART DISEASE

Central obesity, which is measured as increased waist circumference, is an important component of atherogenic dyslipidemia and has recently been identified as a chief predictor of the metabolic syndrome in certain patients. A 2005 study, The Genetic Epidemiology of Metabolic Syndrome Project, examined the frequency at which either familial or sporadic atherogenic dyslipidemia predicts the metabolic syndrome, according to the NCEP ATP III, in white patients.⁸ The ATP III clinical identification of the metabolic syndrome is presented in **Table I**.¹ Elevated triglycerides and concomitant low HDL-C levels were used to define the affection status of atherogenic dyslipid-

emia because they are: (1) primary features of this form of dyslipidemia; (2) associated with insulin resistance, detectable early in the development of the metabolic syndrome; (3) individually highly inherited; and (4) relatively simple to quantify. The results showed that the vast majority of patients aged >35 years who were affected with atherogenic dyslipidemia met the ATP III definition for the metabolic syndrome. Therefore, atherogenic dyslipidemia, whether familial or sporadic, is a strong identifier of predisposition for this syndrome. The strongest association was with abdominal obesity, whereas the weakest relationship was between dyslipidemia and systolic blood pressure. This finding agrees with other published reports that show blood pressure is not as distinct a factor in the metabolic syndrome,⁹ whereas obesity is often described as such.¹⁰

Recent findings have shown that intra-abdominal adiposity (measured as waist circumference) is a truer predictor of CHD than weight or body mass index (BMI).¹¹ Although obesity, as defined by increased BMI, has risen significantly in the last few decades, waist circumference has increased even more, with 37% of men and 55% of women currently having high-risk waist circumferences. This places them at higher risk for CHD even if their BMI is <30 kg/m².¹²

TABLE I. CLINICAL IDENTIFICATION OF THE METABOLIC SYNDROME ACCORDING TO THE NATIONAL CHOLESTEROL EDUCATION PROGRAM ADULT TREATMENT PANEL III (ATP III).*

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

HDL-C = high-density lipoprotein cholesterol.

*The ATP III panel did not find adequate evidence to recommend routine measurement of insulin resistance (eg, plasma insulin), the proinflammatory state (eg, highly sensitive C-reactive protein), or the prothrombotic state (eg, fibrinogen or plasminogen activator inhibitor-1) in the diagnosis of the metabolic syndrome.

†Some male individuals can develop multiple metabolic risk factors when the waist circumference is only marginally increased (eg, 94–102 cm [37–39 in]). Such persons may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

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KEY POINT

Recent findings have shown that intra-abdominal adiposity (measured as waist circumference) is a truer predictor of CHD than weight or BMI.

The San Antonio Heart Study was a population-based, longitudinal trial that assessed the development of the metabolic syndrome in a total of 1968 non-Hispanic white and Mexican American patients.¹³ After 8 years of follow-up, both BMI and waist circumference were shown to be highly predictive of eventual development of the metabolic syndrome. The study findings revealed that patients with baseline BMI ≥30 kg/m² or waist circumference ≥40 inches in men or ≥35 inches in women were 3- to 8-fold more likely to develop the metabolic syndrome than those with a lower BMI (<25 kg/m²) or small

waist circumference. Overall, ~33% of those with high BMI and increased waist circumference developed the metabolic syndrome compared with ~10% of those in the thinner group (Figure).

HOW IS CENTRAL OBESITY ASSOCIATED WITH ATHEROGENIC DYSLIPIDEMIA?

Obesity is a common factor that contributes to insulin resistance, which in turn plays a major role in the pathogenesis of cardiovascular disease (CVD) because of its tendency to promote atherogenic dyslipidemia.^{14,15} Obesity suppresses insulin sensitivity in several ways. One way is through excess lipolysis; that is, through the release of large amounts of nonesterified fatty acids (NEFAs) into the circulation. These high levels of NEFA suppress glucose uptake by muscle tissue.¹⁶ Obesity may impact insulin action via additional pathways as well (eg, through the release of abnormal amounts of other products from adipose tissue, particularly cytokines, leptin, tumor necrosis factor- α and interleukin-6 (IL-6), and reduced production of the insulin-sensitizing cytokine adiponectin).^{17,18} One manifestation of high levels of circulating cytokines often exhibited by obese persons is elevated plasma levels of C-reactive protein, which has been shown to be a predictor of CHD in healthy subjects.¹⁹

Upper-body obesity is recognized clinically as increased waist circumference and is the most recognized variant in adipose tissue distribution associated with

KEY POINT

Obesity is a common factor that contributes to insulin resistance, which plays a major role in the pathogenesis of CVD because of its tendency to promote atherogenic dyslipidemia.

the metabolic syndrome.²⁰ Upper-body obesity is usually accompanied by increases in adipose tissue in both truncal subcutaneous and intra-abdominal regions, compared with lower-body obesity, which is characterized by excess fat in the gluteofemoral region. The causes of upper-body obesity are multifactorial and may be influenced by heredity; its connections to the metabolic syndrome are not well understood. However, those persons with upper-body obesity typically have greater insulin resistance and more severe metabolic risk factors than those with lower-body obesity.

PHARMACOLOGIC CONTROL OF ATHEROGENIC DYSLIPIDEMIA

Because atherogenic dyslipidemia usually precedes the clinical manifestation of the metabolic syndrome, strategies to treat it are the focus of pharmacologic intervention.

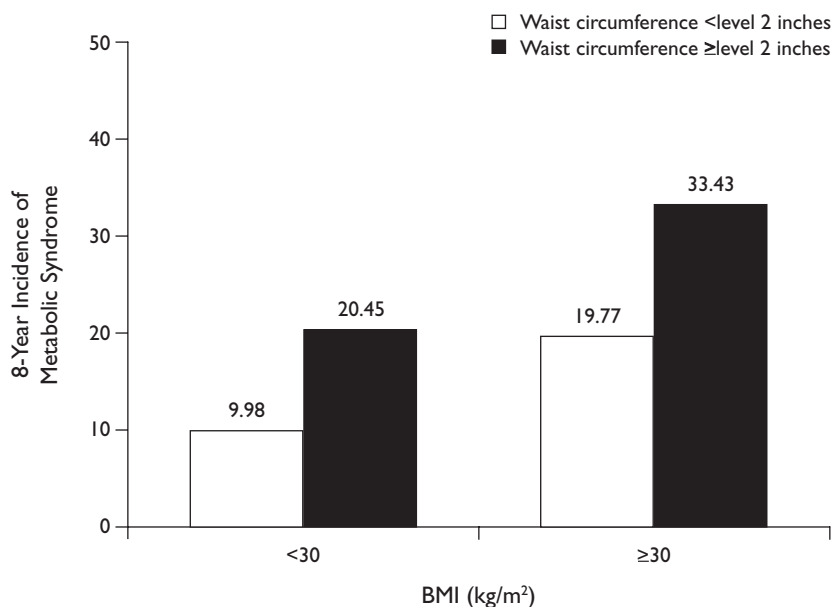


Figure. Eight-year incidence of the metabolic syndrome, as characterized by waist size versus body mass index (BMI). Level 2 = waist ≥ 40 inches in men or ≥ 35 inches in women. Adapted with permission.¹³

KEY POINT

Because atherogenic dyslipidemia usually precedes the clinical manifestation of the metabolic syndrome, strategies to treat it are the focus of pharmacologic intervention.

For example, the 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors, commonly known as statins, benefit hypercholesterolemic patients who have atherogenic dyslipidemia that is associated with the metabolic syndrome. In a recent study, Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR), the efficacy of different doses of rosuvastatin, atorvastatin, simvastatin, and pravastatin in lowering LDL-C were assessed. Treatment with statins was found to be as effective at reducing LDL-C in patients with the metabolic syndrome as in those without this disorder.²¹

Pioglitazone, an antidiabetic agent that acts primarily by decreasing insulin resistance, improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone improves glycemic control while reducing circulating insulin levels.²²

There were, however, large differences in potency. Another noteworthy finding was that modifications in HDL-C and triglycerides tended to be greater in patients with the metabolic syndrome than in patients without the disorder.

The investigational drug rimonabant is a centrally and peripherally acting, selective cannabinoid type-1 receptor blocker. It affects several cardiovascular risk factors at once, including intra-abdominal adiposity and its metabolic consequences. Its effects on glucose and atherogenic dyslipidemia are independent of weight loss.²¹

One-year data from the Rimonabant in Obesity-Europe (RIO-EUROPE) trial,²³ a large, multicenter, randomized, double-blind, Phase III trial, were recently reported. The trial was conducted to compare patients receiving rimonabant 5 mg, or 20 mg QD, in addition to a mild hypocaloric diet with patients receiving placebo. The primary efficacy end point was weight change from baseline after 1 year of treatment in the intention-to-treat population.

Sustained, clinically meaningful weight loss, as well as reduction in waist circumference and associated

improvements in several cardiovascular and metabolic risk factors, was achieved by those patients treated with rimonabant over 1 year.²³

Significantly more patients treated with rimonabant 20 mg than placebo achieved weight loss of $\geq 5\%$ ($P < 0.001$) and $\geq 10\%$ ($P < 0.001$). Improvements in waist circumference, HDL-C, triglycerides, insulin resistance, and prevalence of the metabolic syndrome were significantly greater in those patients receiving rimonabant 20 mg than those receiving placebo.

The results of the RIO-EUROPE trial²³ hold promise for the treatment of obesity and associated risk factors through modulating the activity of the endocannabinoid system.

Evolving Perspectives on the Definition of Metabolic Syndrome

In addition to the ATP III clinical identification of the metabolic syndrome (**Table I**), various organizations have set forth clinical criteria for its diagnosis.³ Although similar in many aspects to other guidelines, the World Health Organization (WHO) clinical criteria for the metabolic syndrome regards insulin resistance as a required component for diagnosis of the syndrome (**Table II**).^{3,24,25} WHO guidelines have defined insulin resistance as 1 of the following: type 2 diabetes mellitus (DM); impaired fasting glucose; impaired glucose tolerance, or a glucose uptake below the lowest quartile for background population under hyperinsulinemic, euglycemic conditions for individuals with normal fasting glucose values (defined as < 110 mg/dL). Furthermore, any 2 of 5 other risk factors are regarded as sufficient to meet the definition of metabolic syndrome. Requiring objective evidence of insulin resistance may provide a stronger prediction of type 2 DM than ATP III; however, consistent with ATP III findings, type 2 DM does not exclude a diagnosis of the metabolic syndrome.³

The American Diabetes Association (ADA) recently conducted an extensive review of the literature relating to the metabolic syndrome and uses the term *metabolic syndrome* to refer to “a clustering of specific CVD risk factors whose underlying pathophysiology is thought to be related to insulin resistance.”²⁶ The ADA acknowledges that certain CVD risk factors are prone to cluster. However, their recommendation is that further research is needed (including studies that investigate the pathogenesis of the metabolic syndrome) and that “clinicians should

TABLE II. WORLD HEALTH ORGANIZATION (WHO) CRITERIA FOR METABOLIC SYNDROME.^{3,22,23}

Insulin resistance, identified by 1 of the following:

- type 2 diabetes mellitus
- impaired fasting glucose
- impaired glucose tolerance
- or for those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions

Plus any 2 of the following:

- antihypertensive medication and/or high blood pressure (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic)
- plasma triglycerides ≥ 150 mg/dL (≥ 1.7 mmol/L)
- high-density lipoprotein cholesterol < 35 mg/dL (< 0.9 mmol/L) in men or < 39 mg/dL (1.0 mmol/L) in women
- body mass index > 30 kg/m² and/or waist:hip ratio > 0.9 in men or < 0.85 in women
- urinary albumin excretion rate ≥ 20 μ g/min or albumin:creatinine ratio ≥ 30 mg/g

Adapted with permission.³

evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for diagnosis of the metabolic syndrome.”²⁶ The ADA urges clinicians to evaluate their patients for CVD risk factors, emphasizing that all CVD risk factors should be individually and aggressively treated. Further studies and analyses relating to the clinical utility of various definitions of the metabolic syndrome are anticipated in the near future.

CONCLUSIONS

Atherogenic dyslipidemia is part of a complex cluster of abnormalities called the metabolic syndrome that are directly related to the incidence of CHD. Central—or intra-abdominal—obesity, as measured by waist circumference, appears to be the chief predictor of CHD and impacts both the glucose and lipid profiles of patients who have excessive abdominal fat. Because atherogenic dyslipidemia is generally the forerunner of the metabolic syndrome, pharmacologic strategies have focused on how to correct it. A new agent, rimonabant, is showing promise in attacking atherogenic dyslipidemia from several vantage points by affecting glucose HDL-C, triglycerides, and waist circumference in patients who are prone to atherogenic dyslipidemia.

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Dialogue Box

EDITORIAL BOARD

Please elaborate on the difference between small dense low-density lipoprotein (sdLDL) particles and large fluffy, or buoyant, LDL particles.

VINIK

LDL particles can be differentiated according to either their diameter or size or their phospholipid/protein ratio content. The sdLDL particles mixed in apolipoprotein B are the ones that are notoriously sensitive to the effects of hyperglycemia and oxidation. These particles are believed to be greatly atherogenic, getting into the subendothelial space where they are ingested by macrophages to form foam cells. The large fluffy variety of LDL particles, or the so-called “buoyant” LDL, are less likely to penetrate the endothelial barrier, are less subject to oxidation, and are not proatherogenic.

EDITORIAL BOARD

Why don't the current National Cholesterol Education Program (NCEP) guidelines make this distinction?

VINIK

Since standardization of the laboratory tests required for differentiating LDL particle size has not yet been achieved, NCEP guidelines cannot directly address this issue. The guidelines indirectly address it with their recommended serum triglyceride target of 150 mg/dL. This target is based, at least in part, on the phenotypic finding that the cutoff between patients with a predominance of sdLDL versus those with large buoyant LDL appears to be ~120 to 150 mg/dL. When the level is >150 mg/dL, a large proportion of LDL is in the small dense form, whereas at a level <150 mg/dL, the “large fluffy” form becomes more prevalent. NCEP guidelines indicate that as long as the triglyceride level can be reduced to <150 mg/dL, you will have a predominately nonatherogenic form of LDL particles circulating.

EDITORIAL BOARD

Why did the early triglyceride-lowering trials not show the same beneficial impact on the relative risk

of coronary disease as the LDL-lowering trials? Was it simply because triglyceride levels weren't reduced enough?

VINIK

A beneficial cardiovascular effect was demonstrated in the Veterans Administration High-Density Lipoprotein Intervention Trial (VA-HIT), which examined the use of gemfibrozil, a fibric acid derivative. In this study, a reduction of ~20% in serum triglycerides was associated with a 30% to 34% reduction in macrovascular events. This study has not been viewed as one supporting triglyceride reduction, however, because the authors attributed the beneficial effect to the concomitant 4% to 6% rise in HDL cholesterol (HDL-C). Another study supporting triglyceride lowering was the German Policeman Study; however, once again, whether the positive impact was due to the lowering of triglycerides or the concomitant rise in HDL-C can be debated. Until we have studies that use an agent exclusively for triglycerides, which lipid fraction is responsible for the reduction will remain open to debate.

EDITORIAL BOARD

Is subcutaneous fat in the upper body as bad as omental fat?

VINIK

I think we have been oriented for a long time to believe that omental fat is bad fat. This concept has been supported by studies demonstrating that simply removing abdominal or hip fat does not increase insulin sensitivity or reduce the risk for diabetes or a macrovascular event. On the other hand, reduction of omental fat following an omentectomy or gastric bypass procedure has been shown to reduce insulin resistance. Having said that, at least in Caucasians and African Americans, subcutaneous fat in the upper abdominal area appears to have the same implications as omental fat, producing similar inflammatory changes with macrophage infiltration and the release of inflammatory cytokines.

Dialogue Box

EDITORIAL BOARD

What about other ethnic groups?

VINIK

Asians with metabolic syndrome, including the Japanese, do not have the same measurements for abdominal obesity as Caucasians or African Americans do. When Asians accumulate fat, they tend to accumulate it not on the exterior, as we do, but more on the interior. Therefore, NCEP criteria must be modified, since waist circumference will vary for different populations.

EDITORIAL BOARD

What determines whether a person's fat is deposited in the lower body or upper body?

VINIK

I think it's predominately genetic. In some people, the polymorphism of the β -3 adrenergic gene appears to determine where their deposits go.

EDITORIAL BOARD

Wasn't this concept of upper-body and lower-body obesity referred to in the past as the apple and pear?

VINIK

Correct. I call it gut/butt, but you can call an apple a person with a high gut/butt ratio and a pear a person with a low gut/butt ratio.

EDITORIAL BOARD

Is the traditional concept that men tend to be more apple and women tend to be more pear still valid?

VINIK

Yes and no. In the normal situation, that is absolutely right. A man, as he grows older, tends to get the so-called "beer belly," gaining weight around the abdominal area above the umbilicus. A woman, as she grows older, tends to gain the weight below the umbilicus.

Unfortunately, over the last decade we have seen an explosion of metabolic syndrome in women due to large gains in women's weight around the waist. We're tending to see a change in that pattern and I'm not sure why. The old apple and pear distinction of men and women is changing. Women are now beginning to look more like men, in that they are accumulating fat in the upper part of the body, and they are now at greater risk of metabolic syndrome than men are.

EDITORIAL BOARD

A common strategy in managing patients with hypertriglyceridemia is simply to be more aggressive at LDL cholesterol (LDL-C) levels rather than directly targeting the triglyceride level. What are your thoughts about this strategy?

VINIK

Although recent studies support aiming for lower and lower LDL-C levels, we likely won't truly know the right answer until the results are in from the Losartan Intervention for Endpoint Reduction (LIFE) study, which is comparing the impact of lowering serum triglycerides to <150 mg/dL versus lowering LDL-C to ~70 mg/dL. I do think that the data from studies I mentioned earlier suggest that we should be targeting a triglyceride level of 150 mg/dL at the present time.

EDITORIAL BOARD

It sounds like you believe that regardless of how low you target LDL-C, the reduction of triglycerides may very well play an important adjunctive role.

VINIK

I like the way you have chosen the words because I think the primary target in anybody has to be LDL-C. Even in the person with diabetes who doesn't have an elevated LDL-C level, the primary target has to be LDL-C. When you have gotten the LDL-C to target and you still have elevated triglycerides, then you need to bring the triglyceride number down as well.

Dialogue Box

EDITORIAL BOARD

How concerned are you about rhabdomyolysis when adding a fibric acid derivative or niacin to a patient already on a statin?

VINIK

In clinical practice I have no hesitation to add a fibric acid derivative, in particular fenofibrate, to a statin once I've gotten the LDL-C level to goal. Similarly, I have no hesitation to prescribe niacin in a diabetic patient; both the flushing and any issue related to producing hyperglycemia with niacin are fairly easily handled.

EDITORIAL BOARD

How central a role does dyslipidemia play in the development of metabolic syndrome?

VINIK

One of my favorite papers is one published by Steve Haffner and Mike Stern in the *Lancet* some years ago based on the San Antonio Heart Study. In that paper, which was called "The Clock Starts Ticking," the authors showed that when one looks at evolution and the development of diabetes, long before the development of fasting or postprandial hyperglycemia, there is an elevation in triglycerides, with an increase in very low-density lipoprotein cholesterol (VLDL-C) and an increase in free fatty acids. I think what has escaped people's attention is that the natural history of atherogenesis is based not on hyperglycemia but on the metabolic abnormality that produces high levels of triglycerides and free fatty acids.