

Metabolic syndrome: what are the acknowledged markers, and how reliable are they?

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Insulin resistance and its cluster of associated abnormalities, defined as the metabolic syndrome, are important coronary heart disease (CHD) risk factors. The report of the Adult Treatment Panel–III (ATP III) serves as a formal recognition of this, and the fact that approximately 25% of Western populations may be suffering from the untoward consequences of insulin resistance emphasizes the magnitude of the clinical problem. The aim of the definition of the metabolic syndrome based on ATP III criteria is to provide a tool able to identify insulin-resistant individuals, and it offers a pragmatic approach to the early identification of individuals at risk for CHD, with the potential benefit of a more aggressive lifestyle intervention and a more focused follow-up.

Keywords: metabolic syndrome; insulin resistance; coronary heart disease risk factor

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This article will provide a few comments rather than an answer to the question: “What are the acknowledged markers of the metabolic syndrome?” With the definition of metabolic syndrome, cardiologists have formally recognized the important role played by the defect in insulin action and associated abnormalities in increasing cardiovascular disease (CVD) risk.

DEFINITION OF THE METABOLIC SYNDROME AND INSULIN-RESISTANCE SYNDROME

The Adult Treatment Panel–III (ATP III) has stressed the importance in terms of coronary heart disease

(CHD) risk factors of a “constellation of lipid and nonlipid risk factors of metabolic origin,” defining this cluster of abnormalities as “the metabolic syndrome,” and pointing out that “this syndrome is closely linked to insulin resistance.”¹

Table I (page 162) lists the 5 criteria selected by the ATP III to identify individuals with the metabolic syndrome (abdominal obesity, elevated blood pressure, impaired fasting glucose, and elevated triglycerides (TG), and low high-density lipoprotein cholesterol (HDL-C). All of these abnormalities are related to insulin resistance, and the presence of only 3 of these criteria is required to make a diagnosis of metabolic syndrome. A recent report, evaluating the database of the Third National Health And Nutrition Examination Survey (NHANES III) in terms of these criteria, estimated that 1 out of 4 adults living in the USA deserved the diagnosis of metabolic syndrome.²

Insulin resistance syndrome and metabolic syndrome are not synonymous, but are closely related: resistance to insulin-mediated glucose disposal greatly increases the probability of developing one or more of the related abnormalities belonging to the metabolic

SELECTED ABBREVIATIONS AND ACRONYMS

ATP III	Adult Treatment Panel–III
CHD	coronary heart disease
CVD	cardiovascular disease
DECODE	Diabetes Epidemiology, Collaborative analysis Of Diagnostic criteria in Europe
FPG	fasting plasma glucose
HDL-C	high-density lipoprotein cholesterol
NCEP	National Cholesterol Education Panel
NHANES III	Third National Health And Nutrition Survey
TG	triglyceride

1. Abdominal obesity (waist circumference)	
• Men	>102 cm
• Women	>88 cm
2. Triglycerides	
	>150 mg/dl
3. HDL cholesterol	
• Men	<40 mg/dL
• Women	<50 mg/dL
4. Blood pressure	
	>130 / >85 mm Hg
5. Fasting glucose	
	>110 mg/dL

Table I. Adult Treatment Panel III (ATP III) diagnostic criteria for the metabolic syndrome. The presence of ≥ 3 criteria is required to make the diagnosis.

syndrome. Insulin resistance is characterized by decreased tissue sensitivity to the action of insulin, leading to a compensatory increase in insulin secretion.³ Insulin-mediated glucose disposal varies widely in the general population. When insulin-resistant individuals fail to provide the degree of hyperinsulinemia needed to maintain an adequate insulin secretion able to overcome the resistance, type 2 diabetes devel-

ops.^{4,5} However, even when insulin-resistant individuals secrete enough insulin to maintain glucose homeostasis, they remain at increased risk of developing a cluster of abnormalities⁶ that have been collectively described as the insulin resistance syndrome. This denomination highlights the central role of insulin resistance and compensatory hyperinsulinemia in the development of the cluster of the associated abnor-

malities, and thus in the pathogenesis of the syndrome. The insulin resistance syndrome, with its related abnormalities, is an umbrella under which all of the abnormalities related to insulin resistance with compensatory hyperinsulinemia can be collected (*Figure 1*), and predicts the risk of developing type 2 diabetes, hypertension, CHD, and stroke.^{7,8}

COMPONENTS OF THE INSULIN-RESISTANCE SYNDROME

Table II gives the abnormalities currently considered to be components of the insulin resistance syndrome, because of their relationship with insulin resistance and hyperinsulinemia:

Glucose tolerance

The majority of persons with the insulin resistance syndrome have a “normal” fasting plasma glucose (FPG) concentration (<110 mg/dL).

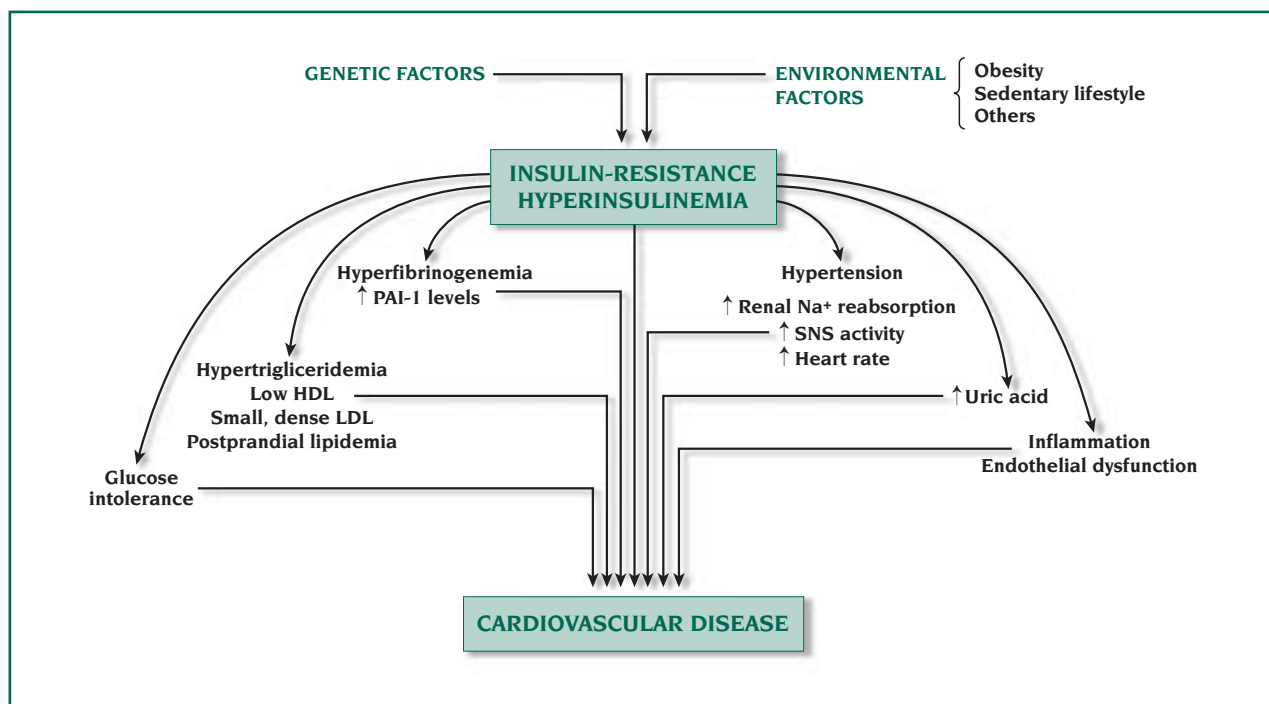


Figure 1. The insulin-resistance/hyperinsulinemia “umbrella.” HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAI-1, plasminogen-activator inhibitor-1; SNS, sympathetic nervous system.



However, individuals with either "impaired fasting glucose" (FPG concentration >110 and <126 mg/dL) or "impaired glucose tolerance" (FPG concentration <126 mg/dL, and a plasma glucose concentration >140 mg/dL and <200 mg/dL 120 min after a 75-g oral glucose challenge) are most likely insulin-resistant.

Dyslipidemia

Elevated plasma triglycerides (TG) and low plasma HDL-C are common findings in insulin-resistant/hyperinsulinemic persons. This characteristic dyslipidemia is also associated with the presence of small, dense low-density lipoprotein (LDL) particles, and an increase in the postprandial accumulation of TG-rich remnant lipoproteins.^{9,10} These abnormalities are highly atherogenic and provide the most well-established mechanistic link between the insulin resistance syndrome and CVD.^{11,12}

Hemodynamics

The increased sympathetic nervous system activity and renal sodium retention documented in the insulin resistance syndrome¹³⁻¹⁵ are likely the link that might explain why approximately 50% of patients with essential hypertension are insulin-resistant/hyperinsulinemic.¹⁶ The insulin-resistant/hyperinsulinemic subset of patients with essential hypertension also often shows the characteristic dyslipidemia of the insulin-resistance syndrome, and these individuals have a higher CVD risk.¹⁶

Uric acid metabolism

Plasma uric acid concentrations are higher in insulin-resistant individuals, and this is associated with a decrease in uric acid renal clearance.¹⁷ However, plasma uric acid is not a

very sensitive predictor of insulin resistance. Thus, though an elevated plasma uric acid concentration increases the probability that an individual is insulin-resistant, a normal concentration does not mean that an individual is insulin-sensitive.

Hemostasis

Plasma concentrations of plasminogen activator inhibitor-1 (PAI-1) are frequently increased in insulin-resistant/hyperinsulinemic individuals¹⁸ and may reflect the acute-phase reaction associated with the inflammation of the vascular wall.

Inflammation

There is evidence that other markers of inflammation are present in the insulin resistance syndrome, eg, C-reactive protein and higher white cell counts.¹⁹

Endothelial dysfunction

Functionally, endothelium-dependent vasodilatation is reduced in insulin-resistant/hyperinsulinemic individuals.²⁰ Mononuclear cells isolated from insulin-resistant/hyperinsulinemic individuals show greater adherence to cultured endo-

1. Some degree of glucose intolerance

- Impaired fasting glucose
- Impaired glucose tolerance

2. Dyslipidemia

- ↑ Triglycerides
- ↓ HDL-cholesterol
- ↓ LDL-particle diameter
- ↑ Postprandial lipemia

3. Hemodynamic

- ↑ Sympathetic nervous system activity
- ↑ Renal sodium retention
- ↑ Blood pressure (≈50% of patients with hypertension are insulin-resistant)

4. Abnormal uric acid metabolism

- ↑ Plasma uric acid concentration
- ↓ Renal uric acid clearance

5. Hemostasis

- ↑ Plasminogen-activator inhibitor-1 (PAI-1)
- ↑ Fibrinogen

6. Inflammation

- ↑ White cell count
- ↑ C-reactive protein

7. Endothelial dysfunction

- ↑ Mononuclear cell adhesion
- ↑ Plasma concentration of cell adhesion molecules
- ↓ Endothelial-dependent vasodilatation

Table II. Abnormalities associated with insulin-resistance/hyperinsulinemia.

thelium, associated with increases in plasma concentrations of cellular adhesion molecules.¹⁹

ATP III DIAGNOSTIC CRITERIA AND DIAGNOSIS OF THE METABOLIC SYNDROME

The clinical consequences of insulin resistance and compensatory hyperinsulinemia, (the insulin resistance syndrome), are increasingly considered as a major public health problem. The insulin resistance syndrome predisposes individuals to developing several clinical outcomes, which include type 2 diabetes, atherosclerotic CVD, hypertension, nonalcoholic steatohepatitis, polycystic ovary syndrome, and the list continues to expand. Despite the recognition of the importance of this syndrome, identifying individuals who have the insulin resistance syndrome is difficult, as there is no simple clinically available test to diagnose it.

The appropriate diagnostic approach to the insulin resistance syndrome is the measurement of insulin sensitivity, but there is no single definitive test for insulin resistance available for use in clinical practice and standardized assays for plasma insulin, a surrogate measure of insulin resistance, are not available for routine use. The National Cholesterol Education Panel (NCEP) has made a major contribution by publishing the Adult Treatment Panel III (ATP III) diagnostic criteria for the metabolic syndrome. Its goal was to provide a tool able to identify insulin-resistant individuals at increased risk of developing CVD.

The variables listed in *Table I* were selected because they tend to cluster together as well as being more commonly associated with insulin resistance. The numerical values of the 5 components are arbitrary,

not validated by hard data; however, abnormalities in all of them have been found to be associated with increased CHD risk. Use of the ATP III diagnostic criteria calls for the following comments.

Obesity

Waist circumference as a measure of obesity was included among the criteria for the diagnosis of the metabolic syndrome. However, obesity should be viewed as a condition that has an adverse effect on insulin resistance and increases the likelihood that abnormalities associated with insulin resistance might also be present. Therefore, obesity and waist circumference (which is a measure of excess adiposity), are risk factors for the insulin resistance syndrome, but not a diagnostic criterion for the insulin resistance syndrome. Obesity, indeed, may be a cause of insulin resistance, and not a consequence. Not all overweight/obese individuals are insulin-resistant, and not all insulin-resistant individuals are overweight/obese.²¹

However, this does not minimize the important role that the current epidemic of obesity plays in the increase in the prevalence of the metabolic syndrome. Therefore, since obesity is able to cause an insulin resistance syndrome similar to that of the primary nonobese syndrome, and given the fact that primary insulin resistance is rare while obesity is highly prevalent in the population, it is understandable why they are not kept separate and why obesity is considered a major criterion for the diagnosis of the metabolic syndrome.

Plasma glucose

Fasting plasma glucose is the variable with the greatest positive predictive value, and a concentration

between 110 and 126 mg/dL is highly predictive of insulin resistance/hyperinsulinemia. However, it is not a sensitive indicator, and the vast majority of insulin-resistant/hyperinsulinemic individuals have a fasting glucose concentration <110 mg/dL.

The Diabetes Epidemiology, Collaborative analysis Of Diagnostic criteria in Europe (DECODE) Study Group showed that post glucose challenge plasma glucose concentrations were better than fasting value in predicting CVD, and that more than 25% of subjects with normal glucose tolerance were in the most insulin-resistant tertile.²²

Therefore, a significant number of individuals with normal glucose tolerance are insulin-resistant and at increased CVD risk.

Blood pressure

Although hyperinsulinemia, a surrogate measure of insulin resistance, predicts the development of hypertension, no more than 50% of patients with essential hypertension are insulin-resistant.¹⁶ If patients with essential hypertension do not meet the criteria for hyperglycemia and dyslipidemia shown in *Table I*, it is possible that they are not insulin-resistant/hyperinsulinemic. Therefore, it may be more important to focus on whether or not an increase in blood pressure is associated with any of the manifestations of the insulin-resistance syndrome than simply consider the presence of hypertension.

Dyslipidemia

The ATP III criteria are most likely able to identify insulin-resistant/hyperinsulinemic individuals on the basis of plasma TG and HDL-C values. The TG/HDL-C concentration ratio is a powerful predictor of both



insulin resistance and CHD risk. The relationship between the TG/HDL-C concentration ratio and a specific measure of insulin-mediated glucose disposal has been found to have a correlation coefficient almost identical to that between insulin resistance and fasting plasma insulin concentration (a commonly used surrogate measure of insulin resistance). In addition, the TG/HDL-C concentration ratio provides an independent estimate of CHD risk. There is strong evidence that the dyslipidemic criteria proposed by the ATP III are characteristic of insulin-resistant/hyperinsulinemic subjects, highly predictive of CHD risk, and that treatment of dyslipidemia reduces the incidence of CVD.

ADVANTAGES OF THE ATP III DIAGNOSTIC APPROACH

The terms insulin resistance syndrome and metabolic syndrome are often used interchangeably to refer to the clinical consequences of insulin resistance and the compensatory mechanisms that develop to maintain homeostasis. However, the two terms are different and have different implications. The major point is that insulin resistance is not a disease, but a physiological change that increases the risk of developing one or more of the abnormalities listed in *Table II*. The more insulin-resistant an individual, the greater the degree of compensatory hyperinsulinemia, and the likelier the risk of developing one or more of the abnormalities listed in *Table II*. Conversely, the more abnormalities there are, the greater the chances are that the individual is insulin-resistant. Not all insulin-resistant individuals develop these abnormalities, nor is their appearance confined to insulin-resistant individuals. On the other hand, the presence of any one of them indicates that the

individual may be insulin-resistant, and increases the possibility that the other abnormalities may also be present.

The greatest benefit of the ATP III approach to the diagnosis of metabolic syndrome is the recognition that insulin resistance/hyperinsulinemia, and the consequences of these defects on insulin metabolism, must be taken into account in efforts aimed at decreasing CHD risk. The ATP III criteria do not have a pathophysiological value, but offer a pragmatic approach to improving the clinical outcome through implementation of lifestyle changes to decrease CVD risk. These criteria very probably reliably identify insulin-resistant/hyperinsulinemic individuals; however, they are based on arbitrary numerical scoring systems and are not validated by data.

CONCLUSION

Despite the limitations discussed above, the ATP III criteria should be considered as a useful tool, in the absence of better indicators, and their use is justified by the effort to enable early identification of individuals at risk of CHD, with the potential benefit of a more aggressive lifestyle intervention and a more focused follow-up.

The fact that approximately 25% of Western populations may be suffering from the consequences of insulin resistance emphasizes the magnitude of the clinical problem and the potential relevance of the metabolic syndrome.

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Metabolic syndrome: what are the acknowledged markers? - Zavaroni and others

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