The Metabolic Syndrome

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BY SERGE A. JABBOUR, MD; AND JEFFREY L. MILLER, MD

STATEMENT OF NEED
The combination of abdominal obesity, hypertension, dyslipidemia, abnormal glucose metabolism and coagulopathy is known as the metabolic syndrome. This combination leads to atherosclerosis and subsequent coronary artery disease and its associated conditions. Insulin resistance plays a major role in the development of type 2 diabetes and in the metabolic abnormalities seen with the condition. Insulin resistance goes hand in hand with obesity, which is growing in epidemic proportions worldwide. Recent studies have shown that people who are in the upper normal weight range — not even yet obese — are at risk for metabolic syndrome. Physicians who treat those with prediabetes and diabetes need to be able to identify those at risk for developing the metabolic syndrome and its clinical implications.

TARGET AUDIENCE
This activity is designed for primary care physicians, endocrinologists and cardiologists.

LEARNING OBJECTIVES
After successful completion of this program, the participant should be able to:
• discuss many of the implications of the metabolic syndrome;
• list the criteria for diagnosis and the clinical spectrum of the metabolic syndrome;
• review the pathogenesis of the metabolic syndrome;
• describe the cardiovascular implications of insulin resistance.

METHOD OF INSTRUCTION
Participants should read the learning objectives and CME program in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions.
Upon completing this activity as designed and achieving a passing score of 70% or higher on the self-assessment test, participants will receive a CME credit letter awarding AMA/PRA category 1 credit and the test’s answer key 4 weeks after the registration and evaluation materials are received.
The estimated time to complete this activity as designed is 1 hour.

ACCREDITATION
This activity has been planned and implemented in accordance with the essentials and standards of the ACCME through the joint sponsorship of The Dulaney Foundation and Diabetic Microvascular Complications Today.

DISCLOSURE
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- Serge A. Jabbour, MD, is a member of the speaker’s bureau for Pfizer Inc. (New York).
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- Conni Koury, Editor of Diabetic Microvascular Complications Today has no commercial relationships to disclose.

**FACULTY CREDENTIALS**

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**INTRODUCTION**

The quintet of abdominal obesity, hypertension, dyslipidemia, abnormal glucose metabolism and coagulopathy is known as the metabolic syndrome.\(^1\,^2\) This combination has also been called the insulin resistance syndrome, the obesity dyslipidemia syndrome and the deadly quartet, the end result being atherosclerosis which leads to coronary artery disease and its sequelae.\(^3\,^4\)

Insulin resistance plays a major role in the pathogenesis of type 2 diabetes and in associated metabolic abnormalities. Insulin resistance is strongly linked to obesity, which is growing in major proportions within the developed world, especially the United States.\(^6\) Even before becoming overweight or obese, recent surveys\(^6:\) showed that patients in the upper-normal weight range and those slightly overweight are at increased risk of developing metabolic syndrome.

Type 2 diabetes is caused by a dual defect of insulin resistance and beta-cell failure. Insulin resistance is a state in which a given concentration of insulin is associated with a subnormal glucose response\(^7\) causing pancreatic beta-cells to secrete increased insulin to maintain euglycemia. With time this results in impaired glucose tolerance and eventually type 2 diabetes.\(^8\) Insulin resistance and compensatory hyperinsulinemia also play a role in other metabolic abnormalities.

**MICRO AND MACRO COMPLICATIONS**

Cardiovascular complications associated with type 2 diabetes have attracted increasing attention. Macrovascular complications account for 80% of mortality in patients with type 2 diabetes.\(^9\) Although aggressive glycemic control can delay or prevent the microvascular complications of the disease, which may eventually lead to renal failure, blindness, and neuropathy, there is no concrete data linking glycemic control to macrovascular complications.\(^10\,^11\)

Cardiovascular disease (CVD) that accompanies diabetes is multifactorial. In 2001, the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program recognized diabetes as a cardiovascular risk equivalent, and a new definition for the metabolic syndrome as a treatment target in at-risk patients was

### Table 1. Three of the following clinically identify metabolic syndrome

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference(^\dagger)</td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130 mm Hg/85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

\(^\dagger\)The presence of abdominal obesity is more highly correlated with metabolic risk factors than is an elevated body mass index.

\(^\dagger\)Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased (37 in to 39 in).

\(\dagger\)The new guidelines for impaired fasting glucose are now ≥100 mg/dL according to the American Diabetes Association.
established.\textsuperscript{12}

At least 25\% of adults in the United States aged 20 to 70 years have metabolic syndrome,\textsuperscript{13} and it occurs more frequently in those with impaired glucose tolerance and type 2 diabetes.\textsuperscript{14} Metabolic syndrome increases with age\textsuperscript{13} and Mexican-Americans have the highest age-adjusted prevalence. Among African-Americans and Mexican-Americans, prevalence is higher in women. The importance of appropriate lifestyle intervention should be underscored.

The ATP III defines five clinically determined characteristics of metabolic syndrome and notes that the presence of any three is sufficient to confirm diagnosis (Table 1).\textsuperscript{12}

**CLINICAL SPECTRUM: OBESITY**

Obese patients are often insulin-resistant and hyperinsulinemic, three factors characteristic of prediabetes. Obesity, particularly increased central or abdominal obesity, is negatively correlated with insulin sensitivity.\textsuperscript{15} Several mechanisms explain how visceral obesity leads to insulin resistance and contributes to CVD. Visceral adipocytes are more metabolically active than subcutaneous adipocytes. Lipolysis from visceral fat is more pronounced than from subcutaneous fat, and visceral fat cells are less sensitive to suppression of lipolysis by insulin.\textsuperscript{16} The released free fatty acids can directly block insulin-signaling pathways,\textsuperscript{17} leading to insulin resistance.

Visceral fat also has direct access to portal circulation. Increased free fatty acids released into the portal circulation may impair metabolism and action of insulin, as well as increase gluconeogenesis in the liver.\textsuperscript{18} Different mediators secreted by the adipocytes have been implicated in the pathogenesis of insulin resistance associated with obesity. These mediators, known as adipocytokines, include tumor necrosis factor (TNF)-alpha, adiponectin, resistin and leptin (Figure 1).\textsuperscript{19,20}

Overexpressed TNF-alpha increases free fatty acid secretion.\textsuperscript{21} Adiponectin may enhance insulin action; as obesity increases, adiponectin concentration in the blood decreases and insulin resistance increases.\textsuperscript{22} Resistin is associated with insulin resistance,\textsuperscript{23} and recent work shows that although it appears to be limited in expression to rodents, there is a family of related molecules expressed in human fat tissue that may have similar effects.\textsuperscript{24}

Leptin is another adipose-specific hormone that contributes to appetite regulation and has been proposed to affect insulin sensitivity. Some investigators have suggested that hyperleptinemia plays a crucial role in insulin resistance.\textsuperscript{25}

**HYPERGLYCEMIA**

Several pathophysiologic changes precede the development of hyperglycemia in type 2 diabetes.\textsuperscript{18} One essential factor is insulin resistance impairing the utilization of glucose by peripheral tissues. Insulin resistance can worsen due to a variety of factors, including increases in body mass, sedentary lifestyle, age and glucocorticoids. To compensate, the pancreas increases insulin secretion with subsequent hyperinsulinemia.\textsuperscript{8} In the presence of functional defects in glucose-stimulated insulin secretion in the beta-cells, hyperglycemia ensues.\textsuperscript{18,26}

Insulin resistance and hyperinsulinemia may last for a decade or more, but ultimately insulin secretion decreases because of beta-cell failure (Figure 2). Free fatty acids not only seem to interfere with insulin action but also with insulin secretion.\textsuperscript{26a} It has been suggested that alterations in the expression of metabolic enzymes by free fatty acids may account for beta-cell insensitivity to glucose or for alterations in insulin secretion.\textsuperscript{26a}

At least part of the reason behind beta-cell failure is insulin resistance leading to elevated free fatty acids which result in beta-cell apoptosis (Figure 3). Hyperglycemia and type 2 diabetes develop when these two defects are present.\textsuperscript{18}

An early defect is a relative insulin deficiency leading
to increased postmeal glucose levels, due to decrease in glucose utilization. A later effect is an increase in glucose production by the liver, especially in the fasting state, due to insufficient insulin action in the liver. Patients with type 2 diabetes have three major pathophysiologic features that provide a useful framework on which to design the basis of a stepped therapeutic approach: insulin resistance with defective glucose disposal after meals in muscle and fat tissue, insulin resistance with increased glucose output by the liver and impaired beta-cell function. During the development of type 2 diabetes, beta-cell function is progressively lost.

At the time of the diagnosis of diabetes, up to 50% of beta-cell function has already been lost. It declines progressively over time at about 4% per year. The degree of beta-cell function is critical, because therapeutic approaches to prevent or treat diabetes are more effective earlier in the disease when beta-cell response is more robust.

HYPERTENSION

Insulin resistance and subsequent hyperinsulinemia cause exaggerated responses in tissues that remain sensitive to insulin, underlying many of the pathophysiologic features of the insulin resistance syndrome, such as hypertension. Insulin resistance and hypertension are associated, although not as strongly as insulin resistance and dyslipidemia. Patients with type 2 diabetes are almost twice as likely to have hypertension as patients without diabetes, and approximately 50% of patients with hypertension are insulin-resistant and hyperinsulinemic.

DYSLIPIDEMIA

A central component of the insulin resistance syndrome is a characteristic pattern of lipid abnormalities, including elevated triglycerides and decreased high-density lipoprotein (HDL) cholesterol. Although levels of low-density lipoprotein (LDL) cholesterol may not differ from those in normal patients, there is an increase in small, dense LDL particles in patients with insulin resistance. Elevated triglycerides, low levels of HDL, and the presence of small, dense LDL are independent risk factors for CVD, representing a set of lipoprotein abnormalities that promote atherosclerosis.

The resistance of adipose cells to the effects of insulin may initiate the dyslipidemia associated with insulin resistance. The inability of insulin-resistant fat cells to store triglycerides results in hydrolysis of triglycerides and release of fatty acids. The resulting availability of free fatty acids to the liver leads to increased hepatic synthesis and release of triglycerides and very low-density lipoprotein (VLDL) cholesterol. Exchange of cholesterol esters from HDL and LDL to VLDL for triglyceride molecules renders HDL unavailable to remove cholesterol from peripheral cells. Hypertriglyceridemia leads to low levels of HDL. Triglyceride-enriched LDL is readily converted to small, dense LDL, which has greater atherogenic potential, because it is more readily oxidized. Oxidized LDL is more readily scavenged by vascular scavenger LDL receptors and has a longer residence time in the vascular...
matrix. This leads to enhanced lipid deposition in the arterial wall. Oxidized LDL cholesterol is toxic to endothelial cells, leading to decreased nitric oxide release and enhanced expression of cytokines and adhesion molecules. These effects lead to vascular inflammation.35

Patients who are insulin-resistant or have type 2 diabetes uncommonly have elevated total LDL cholesterol levels,34 which suggests that the increased atherogenicity associated with diabetes is related to specific aspects of the LDL cholesterol lipid profile. The elevation in small, dense LDL composition is associated with increased triglycerides and reduced HDL cholesterol, all of which are risk factors for development of heart disease.32,34,35

IMPAIRED HEMOSTASIS

A more recently recognized component of the insulin resistance syndrome is a prothrombotic state. Patients with insulin resistance often have evidence of alterations in coagulation that predispose to arterial thrombosis.33,36 One of these alterations is increased levels of plasminogen activator inhibitor type 1. Thus, insulin resistance and hyperinsulinemia may increase the risk of CVD by impairing hemostatic function and enhancing the potential for acute thrombosis.

Although many of the individual components of the metabolic syndrome predict increased risk for CVD, presence of the metabolic syndrome is clearly associated with a high relative risk for coronary artery disease (CAD) (2.96), myocardial infarction (2.63), and stroke (2.27). This risk is greater than the risk associated with any of the individual components of the metabolic syndrome. For example, the relative risks for CAD for obesity, hypertension or dyslipidemia are 1.44, 1.57 and 1.73 respectively.37,38

Impaired glucose tolerance and type 2 diabetes are associated with increased risk for cardiovascular morbidity and mortality. The increased risk of macrovascular complications likely begins years before the development of clinical type 2 diabetes, when insulin resistance and hyperinsulinemia are present. Prediabetic subjects usually have hyperinsulinemia and a more atherogenic pattern of cardiovascular risk factors compared with subjects who do not develop diabetes.39

THERAPEUTIC IMPLICATIONS

Because the metabolic syndrome is associated with significant morbidity and mortality, early diagnosis and aggressive treatment are critical, especially in type 2 diabetes where complications often are present years before diagnosis. Adverse sequelae are easier to prevent than to reverse, and preservation of beta-cell function may slow progression of the disease.

In metabolic syndrome, the cornerstone for management is to reduce the underlying cause, mainly obesity. For most patients, weight reduction and increased physical activity will improve insulin resistance, hyperglycemia, hypertension and dyslipidemia, as well as reduce the risk of CVD. Even as little as a 7% loss of initial body weight can have a significant impact.40 If weight loss is not achieved, therapies should be targeted at the different components of the syndrome for the individual patient.

EARLY AGGRESSIVE TREATMENT

As CVD is the major cause of morbidity and mortality, and as these complications are established well before development of type 2 diabetes, early aggressive treatment aimed at reduction of visceral adiposity, glucose lowering, attention to blood pressure, dyslipidemia and the prothrombotic state are essential. As the common soil hypothesis between glycemia, hypertension, dyslipidemia and atherosclerosis is inflammation, early aggressive treatment with insulin sensitizers, statins, tissue-specific ACE inhibitors and aspirin favors these agents as specifically anti-inflammatory.

The benefit of a multiple risk factor intervention to reduce coronary risk in type 2 diabetes has been demonstrated in clinical trials of patients with type 2 diabetes.
diabetes and microalbuminuria.\textsuperscript{41} Significant reductions were also seen in progression of nephropathy, retinopathy and autonomic neuropathy.

**COMBINATION THERAPY**

Because diabetic patients often need more than one agent to control their glycemia, early combination therapy targeting multiple defects is recommended in order to achieve a sustained HbA1c of <7%. The combination should include an early intervention with a thiazolidinedione (TZD), where appropriate, because TZDs directly improves insulin resistance and may stabilize the decline in beta-cell function by reducing both lipid accumulation in the islets and chronically elevated free fatty acids that are characteristic of diabetes.\textsuperscript{41a} TZDs have been shown to relocate viscera to subcutaneous fat and have anti-inflammatory properties in the vascular endothelium.\textsuperscript{41b}

As macrovascular disease is the major cause of morbidity and mortality in diabetics, and as its complications can be well established before development of type 2 diabetes, early aggressive treatment aimed at reducing visceral adiposity, glucose lowering, blood pressure control, dyslipidemia, smoking and prothrombotic state are essential.  

6. Goldstein BJ. Insulin resistance as the core defect in type 2 diabetes mellitus. Am J Cardiol. 2002;90(suppl):30-10G.
35. Reusch JE. Current concepts in insulin resistance, type 2 diabetes mellitus, and the metabolic syndrome. Am J Cardiol. 2002;90(suppl):190-26G.
38. Lebovitz HE. Rationale for and role of thiazolidinediones in type 2 diabetes mellitus. Am J Cardiol. 2002;90(suppl):34G-41G.
## CME QUESTIONS

Circle the most appropriate answer in the "ANSWER SECTION" on the following page.

1. According to ATP-III guidelines, which of the following is a characteristic of the metabolic syndrome?
   a. Men with waist circumference >40 inches
   b. Triglycerides >200 mg/dL
   c. Men with HDL <35 mg/dL
   d. Blood pressure >140/90 mm Hg
   e. Fasting glucose ≥126 mg/dL

2. One of the mechanisms explaining the insulin resistance resulting from visceral obesity is:
   a. Amino acids
   b. Free fatty acids
   c. Cortisol
   d. Growth hormone
   e. Epinephrine

3. The dyslipidemia characteristic of the metabolic syndrome consists of:
   a. Increased triglycerides, normal HDL and increased large, fluffy LDL
   b. Normal triglycerides, decreased HDL and increased small, dense LDL
   c. Increased triglycerides, decreased HDL and increased large, fluffy LDL
   d. Increased triglycerides, decreased HDL and increased small, dense LDL
   e. Normal triglycerides, normal HDL and increased small, dense LDL

4. The impaired hemostasis in the metabolic syndrome is due to one of the following:
   a. Increased platelet count
   b. Low levels of tPA
   c. High levels of PAI-1
   d. Increased coagulation factors VIII and IX
   e. Leptin

5. Which of the following adipocytokines enhances insulin action?
   a. TNF-alpha
   b. free fatty acids
   c. Adiponectin
   d. Leptin
   e. Resistin

6. At the time of diagnosis of type 2 diabetes, up to what percentage of beta-cell function has already been lost?
   a. 0%
   b. 10%
   c. 30%
   d. 50%
   e. 100%

7. Oxidized LDL cholesterol can lead to:
   a. Increased nitric oxide release
   b. Suppression of cytokines production
   c. Decreased vascular inflammation
   d. Enhanced suppression of adhesion molecules

8. What is the least amount of weight needed to lose to prevent type 2 diabetes (according to the DPP).
   a. 7%
   b. 15%
   c. 25%
   d. 35%
   e. 55%

9. TZDs have been shown to:
   a. Increase free fatty acids
   b. Stabilize beta-cell function
   c. Relocate subcutaneous to visceral fat
   d. Enhance inflammation in the vascular endothelium

10. According to NHANES III data, the prevalence of the metabolic syndrome in the United States in adults between 20 and 70 years of age is at least:
    a. 10%
    b. 25%
    c. 50%
    d. 75%
    e. 90%
REGISTRATION/EVALUATION FORM

To obtain AMA/PRA category 1 credit, you must:
• Read the learning objectives and the CME article and complete the self-assessment test.
• Photocopy and complete this registration/evaluation form and record your test answers in the Answer Section below.
• Send the Registration/Evaluation form to The Dulaney Foundation, Post Office Box 25271, Tampa, FL 33622-5271, or fax to 813-258-8002.
• Retain a copy of your test answers. Your answer sheet will be graded, and if you achieve a passing score of 70% or better, you will receive a CME credit letter awarding AMA/PRA category 1 credit as well as the test answer key by mail within 4 weeks. If you do not achieve a passing score, you will be notified and offered the opportunity to complete the activity again.

ANSWER SECTION

Circle the best answer for each question on page 48.


REGISTRATION FORM

First name _________________________  Last name _________________________  Degree (MD, PhD) _____________

Specialty _________________________________________________________________________________________

Institution or practice name ___________________________________________________________________________

Address __________________________________________________________________________________________

City _______________________________  State _______  Zip Code _______  Country __________________________

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I attest that I have completed this activity as designed and I am claiming ____ (up to 1 credit) AMA/PRA category 1 credit.
Signature __________________________________________________________  Date _________________________

Credit for this activity is available until October 31, 2005.

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OBJECTIVES

After successful completion of this program, you should be able to:
• Discuss many of the implications of the metabolic syndrome. 5 4 3 2 1
• List the criteria for diagnosis and the clinical spectrum of the metabolic syndrome. 5 4 3 2 1
• Review the pathogenesis of the metabolic syndrome. 5 4 3 2 1
• Describe the cardiovascular implications of insulin resistance. 5 4 3 2 1

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

OVERALL EVALUATION

• The information presented increased my awareness/understanding of the subject. 5 4 3 2 1
• The information presented will influence how I practice. 5 4 3 2 1
• The information presented will help me improve patient care. 5 4 3 2 1
• The faculty demonstrated current knowledge of the subject. 5 4 3 2 1
• The program was educationally sound and scientifically balanced. 5 4 3 2 1
• The program avoided commercial bias or influence. 5 4 3 2 1
• Overall, the program met my expectations. 5 4 3 2 1
• I would recommend this program to my colleagues. 5 4 3 2 1

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

• If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide a brief description of how you plan to do so: ________________________________

• Please provide any additional comments pertaining to this activity (positive and negative) and suggestions for improvements: ________________________________

• Please list any topics you would like to see addressed in future educational activities: ________________________________