

# The Metabolic Syndrome

Jointly sponsored by The Dulaney Foundation and *Diabetic Microvascular Complications Today*.

Release Date: October 2004. Expiration Date: October 31, 2005.

This continuing medical education activity is supported by an unrestricted educational grant from Eli Lilly and Company.

**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;

and

- 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

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: (1) the existence of any financial interest or

other relationships with the manufacturers of any commercial products/devices, or providers of commercial services, that relate to the content of their presentation/material or the commercial contributors of this activity; and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

### FACULTY DISCLOSURE DECLARATIONS

The physician faculty whose material appears in this program have a financial interest, relationship or affiliation in the following forms:

Serge A. Jabbour, MD, is a member of the speaker's bureau for Pfizer Inc. (New York).

Jeffrey L. Miller, MD, is a member of the speaker's bureau for GlaxoSmithKline (Research Triangle Park, NC).

Conni Koury, Editor of Diabetic Microvascular Complications Today has no commercial relationships to disclose.

### FACULTY CREDENTIALS

Drs. Serge A. Jabbour and Jeffrey L. Miller are from the Division of Endocrinology, Diabetes & Metabolic Diseases in the Department of Medicine, at Thomas Jefferson University Hospital in Philadelphia.

Address all correspondence to: Serge Jabbour, MD, or Jeffrey Miller, MD, 211 South Ninth Street, Suite 600 Philadelphia, PA 19107; 215-955-5564; fax: 215-928-3160; or e-mail: serge.jabbour@jefferson.edu or jeffrey.miller@jefferson.edu.

### INTRODUCTION

The quintet of abdominal obesity, hypertension, dyslipidemia, abnormal glucose metabolism and coagulopathy is known as the metabolic syndrome.<sup>1,2</sup> 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.<sup>3-5</sup>

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.<sup>6</sup> Even before becoming overweight or obese, recent surveys<sup>6a</sup> 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<sup>7</sup> causing pancreatic beta-cells

to secrete increased insulin to maintain euglycemia. With time this results in impaired glucose tolerance and eventually type 2 diabetes.<sup>8</sup> 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.<sup>9</sup> 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.<sup>10,11</sup>

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

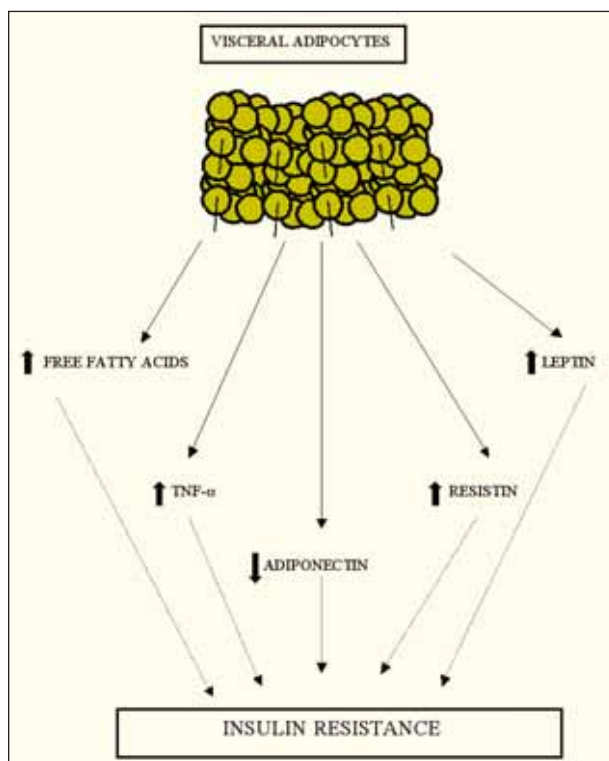
**TABLE 1. THREE OF THE FOLLOWING CLINICALLY IDENTIFY METABOLIC SYNDROME**

RISK FACTOR	DEFINING LEVEL
Abdominal obesity <sup>†</sup>	Waist circumference <sup>††</sup>
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130 mm Hg/85 mm Hg
Fasting glucose	≥110 mg/dL <sup>§</sup>

<sup>†</sup>The presence of abdominal obesity is more highly correlated with metabolic risk factors than is an elevated body mass index.

<sup>††</sup>Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased (37 in to 39 in).

<sup>§</sup>The new guidelines for impaired fasting glucose are now ≥100 mg/dL according to the American Diabetes Association



**Figure 1. Visceral obesity and insulin resistance: Released free fatty acids can directly block insulin-signaling pathways leading to insulin resistance.**

established.<sup>12</sup>

At least 25% of adults in the United States aged 20 to 70 years have metabolic syndrome,<sup>13</sup> and it occurs more frequently in those with impaired glucose tolerance and type 2 diabetes.<sup>14</sup> Metabolic syndrome increases with age<sup>13</sup> 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).<sup>12</sup>

### 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.<sup>15</sup> 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.<sup>16</sup> The released free fatty acids can directly block insulin-signaling pathways,<sup>17</sup> 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.<sup>18</sup> 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).<sup>19,20</sup>

Overexpressed TNF-alpha increases free fatty acid secretion.<sup>21</sup> Adiponectin may enhance insulin action; as obesity increases, adiponectin concentration in the blood decreases and insulin resistance increases.<sup>22</sup> Resistin is associated with insulin resistance,<sup>23</sup> 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.<sup>24</sup>

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.<sup>25</sup>

### HYPERGLYCEMIA

Several pathophysiologic changes precede the development of hyperglycemia in type 2 diabetes.<sup>18</sup> 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.<sup>8</sup> In the presence of functional defects in glucose-stimulated insulin secretion in the beta-cells, hyperglycemia ensues.<sup>18,26</sup>

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.<sup>26a</sup> 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.<sup>26a</sup>

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.<sup>18</sup>

An early defect is a relative insulin deficiency leading

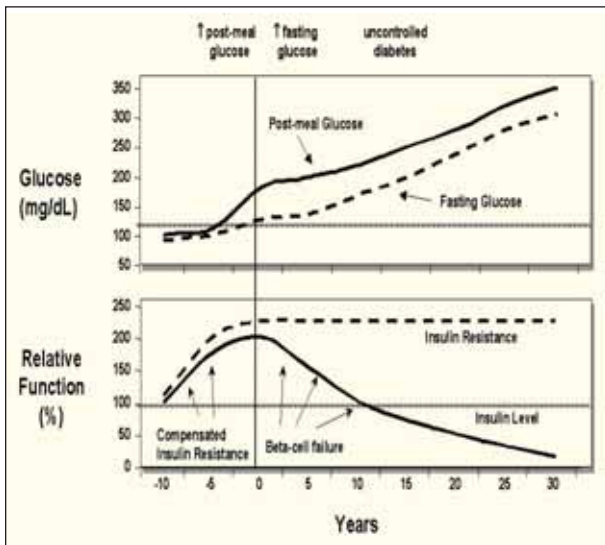


Figure 2. The natural history of diabetes is shown, depicting the increasing blood glucose with progressive beta-cell dysfunction.

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<sup>27</sup> (Figure 4). 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.<sup>28</sup> 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.<sup>6,28</sup>

### 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.<sup>4</sup>

### 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.<sup>29,30</sup> Elevated triglycerides, low levels of HDL, and the presence of small, dense LDL are independent risk factors for CVD,<sup>12,31,32</sup> representing a set of lipoprotein abnormalities that promote atherosclerosis.<sup>33</sup>

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.<sup>34</sup> 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

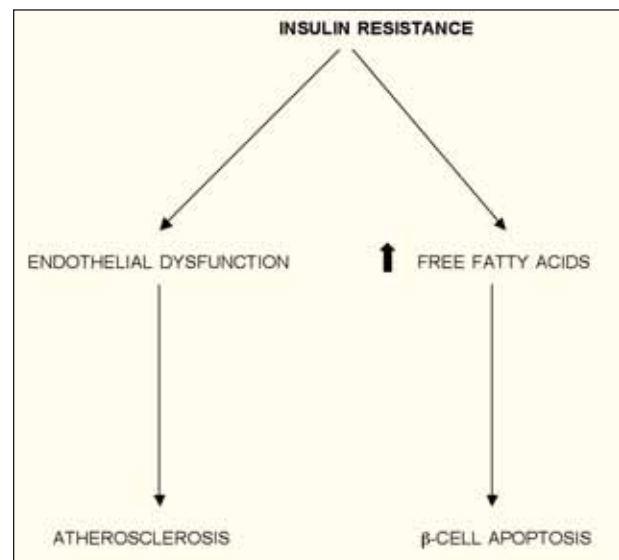


Figure 3. Dual defects of insulin resistance are shown.

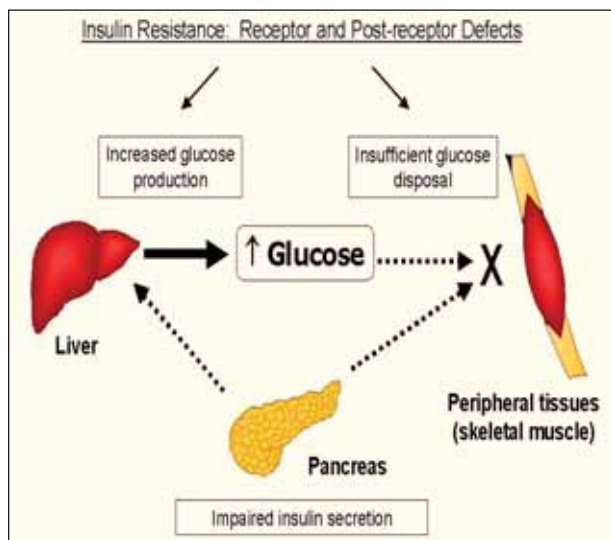


Figure 4. Sites of three major pathogenic defects that lead to type 2 diabetes. Insulin resistance in the muscle causes reduced glucose disposal from the bloodstream, and insulin resistance in the liver causes increased glucose production. Impaired insulin secretion by the pancreas is a critical feature that leads to hyperglycemia when the amount of insulin secreted and the timing of the insulin response are defective.

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.<sup>35</sup>

Patients who are insulin-resistant or have type 2 diabetes uncommonly have elevated total LDL cholesterol levels,<sup>34</sup> 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.<sup>32,34,35</sup>

### 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.<sup>33,36</sup> 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.<sup>37,38</sup>

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.<sup>39</sup>

### 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.<sup>40</sup> 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 and microalbuminuria.<sup>41</sup> 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.<sup>41a</sup> TZDs have been shown to relocate visceral to subcutaneous fat and have anti-inflammatory properties in the vascular endothelium.<sup>41b</sup>

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. ■

- Reaven GM. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595-1607.
- Reaven GM. Role of insulin resistance in human disease (syndrome X): An expanded definition. *Annu Rev Med*. 1993;44:121-131.
- DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;14:173-194.
- Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities - The role of insulin resistance and the sympathoadrenal system. *N Engl J Med*. 1996;334:374-381.
- Williams B. Insulin resistance: The shape of things to come. *Lancet*. 1994;344:521-524.
- Goldstein BJ. Insulin resistance as the core defect in type 2 diabetes mellitus. *Am J Cardiol*. 2002;90(suppl):3G-10G.
- St-Onge MP, Janssen I, Heymsfield SB. Metabolic syndrome in normal-weight Americans. *Diabetes Care*. 2004;27:2222-28.
- Reaven GM. Pathophysiology of insulin resistance in human disease. *Physiol Rev*. 1995;75:473-486.
- DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM: a balanced overview. *Diabetes Care*. 1992;15:318-368.
- Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. *JAMA*. 1999;281:1291-1297.
- Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. *Am J Cardiol*. 1995;75:894-903.
- UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-97.
- Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. *JAMA*. 2002;287:356-359.
- Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24:683-689.
- Carey DG, Jenkins AB, Campbell LV, et al. Abdominal fat and insulin resistance in normal and overweight women: direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. *Diabetes*. 1996;45:633-638.
- Zierath JR, Livingston JN, Thorne A, et al. Regional difference in insulin inhibition of non-esterified fatty acid release from human adipocytes: relation to insulin receptor phosphorylation and intracellular signalling through the insulin receptor substrate-1 pathway. *Diabetologia*. 1998;41:1343-1354.
- Dresner A, Laurent D, Marcucci M, et al. Effects of free fatty acids on glucose transport and IRS-1-associated phosphatidylinositol 3-kinase activity. *J Clin Invest*. 1999;103:253-259.
- Lebovitz HE. Type 2 diabetes: an overview. *Clin Chem*. 1999;45:1339-1345.
- Montague CT, O'Rahilly S. The perils of portliness: causes and consequences of visceral obesity. *Diabetes*. 2000;49:883-888.
- Yamauchi T, Karion J, Wahi H, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nat Med*. 2001;7:941-946.
- Hotamisligil GS. Mechanisms of TNF-alpha-induced insulin resistance. *Exp Clin Endocrinol Diabetes*. 1999;107:119-1125.
- Matsuzawa Y, Funahashi T, Nakamura T. Molecular mechanisms of metabolic syndrome X: contributions of adipocytokines. *Ann NY Acad Sci*. 1999;892:146-154.
- Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. *Nature*. 2001;409:307-312.
- Steppan CM, Brown EJ, Wright CM, et al. A family of tissue-specific resistin-like molecules. *Proc Natl Acad Sci USA*. 2001;98:502-06.
- DeCourten M, Zimmet P, Hodge A, et al. Hyperleptinaemia: the missing link in the metabolic syndrome? *Diabet Med*. 1997;14:200-208.
- Kahn BB. Type 2 diabetes: when insulin secretion fails to compensate for insulin resistance. *Cell*. 1998;92:593-596.
- Stumvoll M, Gerich J. Clinical features of insulin resistance and beta-cell dysfunction and the relationship to type 2 diabetes. *Clinics in Laboratory Medicine*. 2001;21:31-51.
- Jabbour SA, Goldstein BJ. Improving disease management with new treatments for type 2 diabetes mellitus. *Clinical Geriatrics* (special issue). 2001;9:57-68.
- Lebovitz HE. Insulin secretagogues: old and new. *Diabetes Rev*. 1999;7:139-53.
- Davidson MB. Clinical implications of insulin resistance syndrome. *Am J Med*. 1995;99:420-426.
- Parulkar AA, Pendergrass ML, Granda-Ayala R, et al. Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med*. 2001;134:61-71.
- Fontbonne A, Eschwege E, Cambien F, et al. Hypertriglyceridemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes: results from the 11-year follow-up of the Paris Prospective Study. *Diabetologia*. 1989;32:300-304.
- Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men: prospective results from the Quebec Cardiovascular Study. *Circulation*. 1997;95:69-75.
- Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation*. 1999;100:1134-1146.
- Ginsberg HN. Insulin resistance and cardiovascular disease. *J Clin Invest*. 2000;106:453-458.
- Reusch JEB. Current concepts in insulin resistance, type 2 diabetes mellitus, and the metabolic syndrome. *Am J Cardiol*. 2002;90(suppl):19G-26G.
- Meigs JB, Mittleman MA, Nathan DM, et al. Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham offspring study. *JAMA*. 2000;283:221-228.
- Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24:683-689.
- Lebovitz HE. Rationale for and role of thiazolidinediones in type 2 diabetes mellitus. *Am J Cardiol*. 2002;90(suppl):34G-41G.
- Haffner SM, Stern MP, Hazuda HP, et al. Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA*. 1990;263:2893-2898.
- Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.
- Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383-93.
- Yang L, An HX, Deng XL, et al. Rosiglitazone reverses insulin secretion altered by chronic exposure to free fatty acid via IRS-2-associated phosphatidylinositol 3-kinase pathway. *Acta Pharmacologica Sinica*. 2003;24(5):429-434.
- Parulkar AA, Pendergrass ML, Granda-Ayala R, et al. Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med*. 2001;134:61-71.

## 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  $\geq$ 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.

1. A B C D E      2. A B C D E      3. A B C D E      4. A B C D E      5. A B C D E  
 6. A B C D E      7. A B C D      8. A B C D E      9. A B C D      10. A B C D E

**REGISTRATION FORM**

First name \_\_\_\_\_ Last name \_\_\_\_\_ Degree (MD, PhD) \_\_\_\_\_  
 Specialty \_\_\_\_\_  
 Institution or practice name \_\_\_\_\_  
 Address \_\_\_\_\_  
 City \_\_\_\_\_ State \_\_\_\_\_ Zip Code \_\_\_\_\_ Country \_\_\_\_\_  
 Telephone \_\_\_\_\_ Fax \_\_\_\_\_ E-mail address \_\_\_\_\_

The processing fee has been underwritten by an unrestricted educational grant from Eli Lilly and Company.

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.

*The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. Please assist us in evaluating the effectiveness of this activity and make recommendations for future educational offerings by completing this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Please note: CME credit letters and long-term credit retention information will only be issued upon receipt of this completed evaluation. Thank you for your cooperation!*

**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: \_\_\_\_\_