1. Title Page/Sponsorship
   Page i

2. Faculty List
   Page iv

3. CME Information
   Page v

4. Introduction
   Pages S1-S2
   Jr, Sidney C. Smith

5. Multiple Risk Factors for Cardiovascular Disease and Diabetes Mellitus
   Pages S3-S11
   Jr., Sidney C. Smith

6. Effect of Insulin Resistance, Dyslipidemia, and Intra-abdominal Adiposity on the Development of Cardiovascular Disease and Diabetes Mellitus
   Pages S12-S18
   Daniel J. Rader

7. Role of the Endocannabinoid System in Regulating Cardiovascular and Metabolic Risk Factors
   Pages S19-S25
   Stephen C. Woods
8. Therapeutic Options for Modifying Cardiometabolic Risk Factors
   Pages S26-S34
   Louis J. Aronne

9. CME-back
   Pages S37, S39-S42
Modifying Cardiovascular and Metabolic Risk Factors: The Role of the Endocannabinoid System and Cannabinoid Receptors

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Modifying Cardiovascular and Metabolic Risk Factors: The Role of the Endocannabinoid System and Cannabinoid Receptors

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Overview

Many patients have ≥1 cardiovascular or metabolic risk factor, including dyslipidemia, insulin resistance, hypertension, and intra-abdominal adiposity, and are at risk for cardiovascular disease and for metabolic disorders such as diabetes mellitus. Recent evidence suggests that a newly described physiologic system, the endocannabinoid (EC) system, is involved in lipid and glucose metabolism, and that overactivity of this system is associated with risk factor development. Blockade of cannabinoid (CB) receptors, however, has been shown to modify several of these risk factors. The articles contained in this supplement describe the pathophysiology and clinical relevance of the EC system and CB receptors, explain their role in the development of cardiovascular and metabolic risk factors, and offer strategies for risk reduction.

Educational Objectives

After completing this activity, participants should be able to:

• Identify excessive abdominal adiposity as a determinant of metabolic and cardiovascular risk in overweight patients

• Describe the role of CB receptors on metabolic abnormalities such as insulin resistance and dyslipidemia

• Evaluate the effectiveness of current strategies for modifying cardiovascular and metabolic risk factors in overweight patients

• Examine the potential role of new therapies in improving cardiovascular and metabolic risk factors in overweight patients

Target Audience

This CME activity is designed for primary care physicians, cardiologists, endocrinologists, and other interested healthcare professionals.

Accreditation and Designation of Credit

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Introduction

By the mid 1990s, the prevalence of both obesity and diabetes mellitus was increasing to epidemic proportions in the United States.\(^1\)\(^2\) By 2000, >55% of US adults were overweight (body mass index [BMI] ≥25), nearly 20% were obese (BMI ≥30), and 7.3% had diabetes.\(^1\)\(^3\) Abdominal obesity is a major factor in the constellation of interrelated cardiometabolic risk factors known as the metabolic syndrome, which is associated with a heightened risk for diabetes and cardiovascular disease (CVD).\(^4\) As defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the presence of ≥3 of the following 5 risk factors is diagnostic of the metabolic syndrome: (1) abdominal obesity, (2) elevated levels of triglycerides, (3) low high-density lipoprotein (HDL) cholesterol levels, (4) hypertension, and (5) elevated fasting glucose levels.\(^4\)\(^5\) Yet, even when they present with obvious signs of the metabolic syndrome—such as hypertension, dyslipidemia, and abdominal adiposity—many of these patients do not receive adequate care. For example, only 43% of obese individuals are advised to lose weight during routine checkups.\(^1\)

Optimally, the management of patients with the metabolic syndrome should begin early, before the development of diabetes and CVD, and probably even before ≥3 risk factors develop. From a clinical standpoint, the presence of the metabolic syndrome identifies patients at increased risk for diabetes and/or CVD; these individuals otherwise might not be identified as candidates for early preventive therapies, because they may not present with traditional risk factors for CVD, such as elevated low-density lipoprotein (LDL) cholesterol levels.\(^6\) However, atherogenic dyslipidemia, which is characteristic of the metabolic syndrome and type 2 diabetes, involves a clustering of lipoprotein abnormalities that include elevated triglycerides and apolipoprotein B; an increased number of small, dense LDL cholesterol particles; and a low HDL cholesterol level.\(^4\)\(^5\) Additional novel diagnostic markers not yet included in the diagnostic criteria for the metabolic syndrome, but shown to be strongly correlated with the metabolic syndrome, CVD, and insulin resistance/diabetes, include high-sensitivity C-reactive protein, an inflammatory marker;\(^7\) low plasma adiponectin levels;\(^8\) and elevated liver function tests, which are indicative of fatty liver disease.\(^9\) The presence of any of these novel cardiometabolic risk factors in association with the ATP III diagnostic criteria for the metabolic syndrome should further raise concern and prompt clinicians to implement primary prevention strategies directed toward lowering risk for diabetes and CVD.

Although the issue of whether the metabolic syndrome is caused by a specific etiology\(^10\) or a clustering of risk factors\(^4\)\(^11\) is debatable, opinion leaders concur that lifestyle changes (i.e., weight loss, physical activity, behavioral counseling) comprise the first-line approach to its management. Data from the Diabetes Prevention Program (DPP) indicate that, compared with metformin drug therapy, lifestyle intervention effects a greater reduction in the incidence of type 2 diabetes.\(^12\) However, for patients who fail to modify their cardiometabolic risk status through lifestyle modification alone, pharmacotherapy is a viable adjunct: Drug therapy is tailored to address the specific risk factors present in each patient and is added to lifestyle modification to achieve therapeutic goals. For example, abdominal obesity, a chronic and relapsing condition common in patients with the metabolic syndrome, may require drug therapy with either sibutramine or orlistat, both of which are approved for long-term use. Hypertension should be treated with monotherapy or, when unresponsive, with combined antihypertensive agents. Once a patient’s LDL cholesterol target goal has been met, the presence of a low HDL cholesterol level and a high triglyceride level may require treatment with a fibric acid derivative. Insulin-sensitizing agents are used to manage prediabetic states characterized by elevated fasting glucose levels.

Treatment options for patients with the metabolic syndrome may be expanding. Recent evidence suggests that a newly delineated physiologic system, the endocannabinoid (EC) system, regulates several components of the metabolic syndrome (e.g., weight, lipid and glucose metabolism) and that hyperactivity of this system promotes risk factor development.\(^13\)–\(^17\) In clinical trials, blockade of cannabinoid\(_1\) (CB\(_1\)) receptors with rimonabant reduced weight and waist circumference and improved various cardiometabolic risk factors.\(^14\)–\(^17\)
Effective treatment with lifestyle intervention and/or pharmacotherapy can modify cardiometabolic risk, particularly if initiated early in the cascade of risk factor development. Therefore, to intervene before the onset of diabetes and/or CVD, it is imperative that physicians recognize cardiometabolic risk factors and be familiar with the recommended treatment strategies.

The articles in this supplement to The American Journal of Medicine are based on an educational program held in April 2006 during the 14th American College of Physicians Annual Meeting in Philadelphia, Pennsylvania. They address the issues involved in modifying cardiometabolic risk in patients treated in the primary care setting.

Because an estimated 47 million adults in the United States currently have the metabolic syndrome, physicians can expect to manage increasing numbers of patients at high cardiovascular and metabolic risk. In the first article, I address the epidemiology of the metabolic syndrome and the importance of early identification and treatment of patients at high cardiovascular and metabolic risk. Next, Dr. Daniel J. Rader discusses the relation of obesity to the development of insulin resistance and the metabolic syndrome, and reviews the approaches that effectively reduce risk in patients treated in the primary care setting.

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In the third article, Dr. Stephen C. Woods describes the basic science behind the physiologic function of the EC system in the central and peripheral regulation of food intake and metabolism, and the impact of CB1 antagonists on this system in animal models and humans. In the final article, Dr. Louis J. Aronne focuses on the pharmacologic and nonpharmacologic options for modifying CVD risk through weight loss, and reviews recent clinical trial data suggesting that CB1 blockade with rimonabant modulates multiple cardiometabolic risk factors, both independently and through its impact on body weight.

The authors believe that the information in this supplement will help physicians intervene early in the identification and management of patients at high cardiovascular and metabolic risk and enhance their understanding of investigative therapeutic strategies that may be approved in the future for the treatment of patients. In light of the increasing prevalence of obesity and diabetes, it is imperative that physicians target the metabolic syndrome with aggressive and effective strategies at the patient, community, and national level.

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References


Multiple Risk Factors for Cardiovascular Disease and Diabetes Mellitus

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ABSTRACT

In the past 25 years, obesity and diabetes mellitus have overtaken cigarette smoking, dyslipidemia, and hypertension as risk factors for coronary heart disease. Data from a Centers for Disease Control and Prevention (CDC) survey of 50 states revealed that, in 2000, the prevalence of obesity among US adults was approximately 20%, a 61% increase from the 1991 prevalence rate. Currently, most adults (≥56%) are overweight, approximately 1 in 5 is obese, and 7.3% have diabetes. Overweight and obesity increase the risk for hospitalization and death from cardiovascular disease (CVD) and type 2 diabetes at all levels of risk and independently of other risk factors. In particular, abdominal obesity (assessed indirectly by measuring waist circumference) may be associated with clustering of cardiovascular and metabolic risk factors (i.e., hypertriglyceridemia, low high-density lipoprotein [HDL] cholesterol levels, high blood pressure, and elevated levels of fasting glucose) known as the metabolic syndrome. Patients with even minimal abnormalities in any 3 of the 5 risk factors for the metabolic syndrome are at heightened risk for CVD or diabetes. It is estimated that 47 million US adults, 25% of the population, have ≥3 metabolic syndrome components. Abdominal obesity is the most common, followed by low HDL cholesterol levels, high blood pressure, and high levels of triglycerides. The risk for disease increases over time as the number of metabolic syndrome characteristics accumulates; therefore, early intervention is warranted. Given the prevalence and potentially deadly consequences of the metabolic syndrome, it is imperative for physicians to recognize the presence of these risk factors in their patients and to familiarize themselves with the recommended treatment strategies. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Cardiovascular risk; Metabolic syndrome; Obesity; Type 2 diabetes mellitus

In the past 25 years, the prevalence of the so-called traditional risk factors for cardiovascular disease (CVD) (i.e., cigarette smoking, dyslipidemia, hypertension) has gradually declined in the United States. The area in which the greatest progress has been made is smoking cessation. In 1960, nearly 50% of the US population smoked, a prevalence rate that decreased to about 23% by 2000 (Figure 1).

The reduction in the prevalence of these risk factors is at least in part attributable to the broader application of medical therapies to treat dyslipidemia and hypertension, and to aggressive advocacy and public policy programs to limit smoking in public places, ban cigarette advertising, and restrict the sale of tobacco to minors.

Unfortunately, as smoking declined, the prevalence of obesity and diabetes mellitus dramatically increased. Data from the American Obesity Association (AOA) indicate that an estimated 127 million adults in the United States are overweight and 60 million are obese. The reasons for the increase in obesity appear to be multifactorial and are associated with a more sedentary lifestyle, a higher dietary intake of simple carbohydrates, and the emergence of insulin resistance. Currently, surging rates of obesity and diabetes threaten to offset the hard-won survival benefits associated with the reduction in traditional risk factors. It also has been speculated that poor diet and physical inactivity may soon overtake tobacco as the leading cause of death in the United States and that the consequences of obesity may
lead to a decline in life expectancy in the United States in the 21st century. These trends are not limited to the United States but appear to be occurring worldwide in association with changes in lifestyle that involve “supersized” dietary intake and decreased physical activity.

The current pandemics of obesity and diabetes in the United States and worldwide will undoubtedly increase the risk for CVD. Healthcare professionals are ideally positioned to assume a proactive role in counseling patients on weight and lifestyle issues and in advocating for public policies designed to promote healthy lifestyle choices (e.g., school and workplace cafeterias that offer healthy meal choices, transportation alternatives that facilitate walking and bicycling, and programs that encourage physical activity in schools and workplaces). The same strategies used by healthcare providers and public health officials that have proved successful in reducing the prevalence of traditional risk factors, such as smoking, should be applied to the reduction of nontraditional risk factors for type 2 diabetes and CVD.

**EPIDEMIOLOGIC TRENDS IN OBESITY, METABOLIC AND CARDIOVASCULAR RISK**

Population-based data from the United States and the United Kingdom document a trend toward an explosive increase in obesity and type 2 diabetes that parallels the decline in traditional coronary heart disease (CHD) risk factors and threatens to erode CHD survival gains.

**United States**

In the United States, the prevalence rates of obesity and diabetes reached near-epidemic proportions between 1991 and 2000, as documented by the Behavioral Risk Factor Surveillance System (BRFSS). The BRFSS was organized by the Centers for Disease Control and Prevention (CDC) to provide state-specific estimates of behaviors that relate to the leading causes of death. Data were collected through a cross-sectional standardized telephone survey of noninstitutionalized adults aged ≥18 years. The data on weight and diagnosed diabetes were self-reported and, therefore, probably underestimate the true prevalence of obesity and diabetes, particularly because individuals tend to underestimate their weight and overestimate their height, and many persons with diabetes remain undiagnosed. The 2000 BRFSS was based on responses from 184,450 participants in 50 states and was compared with data from previous surveys.

Data from the BRFSS revealed that, in 2000, the prevalence of obesity had reached 19.8% among US adults, which reflects a 61% increase from the 1991 prevalence rate. In just 1 year (1998 to 1999), the prevalence of obesity increased from 17.9% to 18.9%, an increase of 5.6%, and 57% from 1991. For every kilogram increase in self-reported weight, diabetes increased by approximately 9%. It seems that not only are Americans growing fatter every year, but they are also increasing their risk for diabetes and CVD. The prevalence of diabetes increased to 6.9% in 1999, a 6% increase in 1 year. Obesity begets diabetes, as illustrated by the close parallel between rising rates of obesity and type 2 diabetes during the 1990s (Figure 2).

These staggering rates of obesity and diabetes are not confined to isolated geographic pockets. Every US region is in the grip of a twin epidemic of obesity and diabetes. In 1991, only 4 of the participating states had obesity rates of ≥15%, whereas by 2000, all participating states except Colorado had rates of obesity >15%. The prevalence of obesity continues to climb each year, with rates of ≥20% becoming common. In 1991, no states had obesity rates of ≥20%; however, by 2000, 22 states had obesity rates that reached this level.

The increased prevalence of type 2 diabetes paralleled that of obesity. The prevalence of self-reported diagnosed diabetes increased from 4.9% in 1990 to 7.3% in 2000. In 1990, 4 states had diabetes rates of ≥6%, whereas by 2000, 43 of 50 states had such rates. In 2000, Mississippi had the highest rates of obesity (24.3% of the population) and of diabetes (8.8%).

The nation was sedentary throughout the decade, with rates of physical inactivity that remained unchanged. In 1991, 1998, and 2000, 28.4%, 28.2%, and 28.2% of participants, respectively, did not engage in physical activity on a regular basis.

These findings indicate that, within a 9-year period during the 1990s, there was a steady increase in obesity and diabetes throughout the United States. Currently most adults (>56%) are overweight, approximately 1 in 5 is obese, and 7.3% have type 2 diabetes. If these trends continue at the present rate, it will place an enormous strain on existing healthcare resources at the state and national levels. Although both obesity and diabetes are preventable, only 42.8% of obese participants who were trying to lose weight had been advised to do so by a healthcare professional; only 15.6% of overweight participants had received such advice.

**United Kingdom**

Using the previously validated and updated IMPACT mortality model to combine and analyze data on utilization and effectiveness of cardiology treatments and risk factor trends, a group of British researchers sought to explain the reasons for the decline in CHD mortality observed in England and Wales between 1981 and 2000. The model incorporated data for men and women 25 to 84 years old that included (1) CHD patient numbers, (2) utilization of specific medical and surgical treatments, (3) population trends in major cardiovascular risk factors, (4) effectiveness of specific cardiology treatments, and (5) effectiveness of specific risk factor reductions.

The results showed that, during this period, CHD mortality rates decreased by 62% in men and by 45% in women, resulting in 68,230 fewer deaths in 2000. Approximately 40% of the decrease in CHD risk was due to the combined
effects of modern cardiologic treatments and almost 60% to reductions in major risk factors, primarily smoking. Medical and surgical interventions accounted for 42% of the decrease. The role of specific interventions in decreasing risk was as follows: secondary prevention (11%), various heart failure treatments (13%), initial treatments of acute myocardial infarction (MI) (8%), and hypertension (3%). However, the largest contribution to risk factor reduction was attributable to smoking cessation, which decreased risk by 48%, followed by decreases in blood pressure (9.5%) and total serum cholesterol (9.6%). Clearly, physician efforts to implement primary and secondary prevention strategies had succeeded in reducing traditional risk factors for CHD mortality.

However, the good news about control of traditional risk factors was blunted by a disturbing trend toward the emergence of obesity, physical inactivity, and diabetes as increasingly prevalent CHD risk factors. The combination of these risk factors caused an additional 7,650 CHD deaths. The prevalence of obesity increased by 186%, resulting in an estimated additional 2,095 CHD deaths. Simultaneously, diabetes prevalence increased by 66%, causing an additional 2,888 CHD deaths, and indirect evidence suggested a 30% decrease in physical activity was responsible for 2,662 additional deaths. Overall, the triple threat of obesity, diabetes, and physical inactivity contributed to about 8,000 additional deaths in 2000, and the increase in these risk factors “canceled out 2 decades of improvement in cholesterol.”

Figure 1  Prevalence of cardiovascular disease risk factors in US adults (1961–2000). Hypertension is defined as blood pressure ≥140/90 mm Hg or current use of antihypertensive medication; high total cholesterol is defined as ≥240 mg/dL (≥6.21 mmol/L); and overweight is defined as body mass index ≥25 (kg/m²). (Reprinted with permission from NHLBI/NIH Fact Book for Fiscal Year 2002, p. 50).

Figure 2  The parallel between worsening trends of diabetes mellitus and obesity in the United States. (Adapted from JAMA and Diabetes Care.)
Clinical Implications of Obesity

In the individual case, as opposed to on the population level, the long-term outlook for overweight and obese patients is discouraging and, therefore, mandates early intervention on the part of healthcare providers to prevent such common complications as CHD, CVD, and diabetes. Recently published data from the Chicago Heart Association Detection Project in Industry study established that obesity in middle age increases the risk for hospitalization and mortality from CHD, CVD, and diabetes in older age (≥65 years). This prospective study examined the relation of body mass index (BMI) earlier in life to morbidity and mortality in older age among individuals with and without other risk factors. The study population of 17,643 men and women aged 31 to 64 years was recruited from 1967 to 1973 and was followed for a mean of 32 years. Participants were stratified into 5 baseline CVD risk categories (low, moderate, intermediate, elevated, and high) and 3 weight groups (normal, BMI 18.5 to 24.9 [kg/m²]; overweight, BMI 25.0 to 29.9; and obese, BMI ≥30.0).

The results showed that overweight and obesity greatly compromised health status at all levels of risk. Multivariate analyses adjusted for systolic blood pressure and total cholesterol level showed the odds ratio (95% confidence interval) for CHD death for obese participants compared with those of normal weight in the same risk category was 1.43 (0.33–6.25) for low risk and 2.07 (1.29–3.31) for moderate risk. For CHD hospitalization, the corresponding results were 4.25 (1.57–11.5) for low risk and 2.04 (1.29–3.24) for moderate risk. The results were similar for other risk groups and for CVD but stronger for diabetes (e.g., low risk 11.0 [2.21–54.5] for mortality and 7.84 [3.95–15.6] for hospitalization). Once again, a strong correlation was demonstrated between obesity and diabetes.

At every level of risk ranging from low to high, the presence of obesity increased the likelihood of mortality. The relative impact of obesity was stronger for individuals in the lower risk category compared with higher risk categories. Compared with CHD and CVD, the impact of overweight and obesity on diabetes was stronger and statistically significant for almost all risk categories (Figure 3). Obesity emerged as an independent risk factor in that elevated risk was present for individuals both with and without other major cardiovascular risk factors (i.e., smoking, high blood pressure, and/or high serum total cholesterol in young adulthood and middle age). Simply being obese increased an individual’s risk of dying from heart disease and/or diabetes. These results further underscore the fact that obesity is a major public health problem associated with a reduction in life expectancy similar in magnitude to that associated with smoking. Physicians should not accept weight gain in adulthood as a benign normal part of aging, even in the absence of other risk factors. Instead, overweight and obesity should prompt immediate clinical concern and aggressive evaluation for cardiovascular and metabolic risk.
Abdominal obesity was the most prevalent characteristic, occurring in 38.6% of those with the metabolic syndrome. Data analysis of 8,814 male and female participants in the Third National Health and Nutrition Examination Survey (NHANES III) showed that the prevalence of the metabolic syndrome ranged from 6.7% among those age 20 to 29 years to ≥42% in those >60 years. Using NCEP ATP III criteria, the prevalence of the various components of the metabolic syndrome among this representative sample of noninstitutionalized adults is delineated in Table 2. Estimates of high fasting glucose would have been higher than 13% if the modified cutoff ≥100 mg/dL had been used.

Abdominal obesity was the most prevalent characteristic, occurring in 38.6% of those with the metabolic syndrome. Low HDL cholesterol, high blood pressure (or medication use), and hypertriglyceridemia were also highly prevalent in 37.1%, 34.0%, and 30.0% of participants, respectively. Alarming, 71.2% of participants had ≥1 and 43.9% had ≥2 metabolic syndrome traits. This raises the question of
whether early intervention, when patients present with 1 or 2 risk factors, might prevent the development of the full-blown syndrome. For example, simply advising a patient with 1 trait, abdominal adiposity, to lose weight might prevent the development of insulin resistance, as well as other risk factors.

### PREDICTIVE VALUE OF THE METABOLIC SYNDROME

Studies have shown that the metabolic syndrome is a clinically reliable entity for predicting the risk for cardiac events and diabetes. In a multivariate analysis of 10,357 NHANES III participants, cardiovascular risk clustering was shown to increase the risk for MI to a substantially greater extent than any individual risk factor alone (Table 3). The individual components of the metabolic syndrome, insulin resistance (defined by the older cutoff of fasting glucose $\geq 110$ mg/dL), hypertriglyceridemia, and hypertension were independently and significantly related to MI and stroke. These findings suggest that the metabolic syndrome is a useful clinical entity for helping clinicians identify those patients at increased risk for MI and stroke and implement appropriate preventive strategies.

The West of Scotland Coronary Prevention Study (WOSCOPS) used a modified NCEP ATP III definition in which BMI was substituted for waist circumference. The results showed that men with 4 or 5 components of the metabolic syndrome had a 3.7-fold increase in CHD risk and a dramatic 24.5-fold increase in diabetes compared with men with none (both $P < 0.0001$). Thus, the metabolic syndrome is correlated even more strongly with diabetes risk than with CHD risk, particularly when 4 or 5 components are present. The sum of risk factors is greater than its individual parts, as the risk for each disease increases as the number of metabolic syndrome traits accumulates. Timely intervention is crucial because once impaired glucose tolerance manifests, the conversion rate to diabetes is so high that it may be too late for preventive management. Also, lowering the glucose cutoff improved the prediction of both CHD and diabetes risk, and identified a greater number of men with the metabolic syndrome. The value of waist circumference over BMI in predicting type 2 diabetes may require adjustment by ethnic group.

The risks associated with the metabolic syndrome appear to worsen over time. A prospective Finnish cohort study of 1,209 men aged 42 to 60 years at baseline and followed for approximately 11.4 years showed that the prevalence of $\geq$3 risk factors over 10 years significantly increased CVD mortality (Figure 4). These findings demonstrate that the metabolic syndrome is associated with increased mortality, even in its early phases before the development of CVD or diabetes. The strong correlation of metabolic syndrome with CVD and diabetes over time, coupled with the increase in mortality, supports the rationale for early identification, treatment, and prevention of metabolic syndrome components, such as obesity.

### EXPANDING THE CLINICAL DEFINITION OF METABOLIC SYNDROME

The addition of proinflammatory and prothrombotic biomarkers to the current metabolic syndrome criteria might help to further define the population at high risk for CVD and diabetes.

High sensitivity C-reactive protein (hs-CRP), an easily measurable biomarker of inflammation, adds to the prognostic value of the metabolic syndrome at all levels of severity. An 8-year follow-up study of 14,719 initially healthy women revealed that, in those with $\geq$3 metabolic syndrome components, elevated hs-CRP ($>3$ mg/L) was associated with even greater risk ($P < 0.001$) (Figure 5). Among the 24% of women with the metabolic syndrome at baseline, age-adjusted incidence rates of future CVD events per 1,000 person-years of exposure were 3.4 for those with normal hs-CRP levels ($<3.0$ mg/dL) compared with 5.9 for those with elevated hs-CRP levels ($>3$ mg/L). In WOSCOPS, hs-CRP levels were also higher ($P < 0.0001$) in men with the metabolic syndrome compared with men with-
Thus, hs-CRP measurement appears to add important prognostic information.

A prothrombotic state, characterized by increased plasminogen activator inhibitor–1 (PAI-1) and fibrinogen, is also associated with the metabolic syndrome. Excess adipose tissue generates PAI-1, as well as other factors (e.g., cytokines, nonesterified fatty acids, adiponectin) that promote metabolic risk. Fibrinogen, an acute-phase reactant like hs-CRP, increases in response to cytokine production. Metabolically, prothrombotic and proinflammatory states may be interrelated. In lieu of specific drugs that target PAI-1 and fibrinogen, antiplatelet therapy with low-dose aspirin is generally recommended.

Cardiovascular and Metabolic Risk Assessment and Management

A recently issued statement from the ADA and the American Heart Association (AHA) called for a joint effort from...
members of both organizations to identify and treat cardiovascular and metabolic risk factors (prediabetes, hypertension, dyslipidemia, and obesity). Several algorithms for estimating CVD risk have been proposed. However, most have not been validated outside the specific study populations on which they were based. A notable exception (and one recommended in the ADA/AHA statement) is a risk assessment tool (accessible at no cost on the Internet at http://www.diabetes.org/diabetesphd) that has been validated across multiple and diverse clinical trials and includes every known risk factor. Although providers should routinely assess patients for CVD and diabetes risk, few do so using risk assessment algorithms. Yet, even identifying easily quantifiable risk factors such as blood glucose level, blood pressure, LDL cholesterol level, tobacco use, and obesity may be enough to facilitate appropriate preventive management of diabetes and CVD risk.

Finally, risk factor management through therapeutic lifestyle intervention (i.e., weight reduction and moderate physical activity) may be implemented and monitored in clinical practice. Obesity, in particular, is an obvious biomarker of underlying risk that should be addressed as a serious rather than merely cosmetic problem. Risk factor assessment and management is effective. If cardiovascular and metabolic risk factors are recognized in its early stages, lifestyle modification alone may be sufficient to prevent disease progression. In the later stages, pharmacotherapy (often involving polypharmacy) is indicated. Clearly, a concerted multispecialty effort is required to prevent the increasing prevalence of diabetes and obesity from eroding the hard-won survival gains of past decades.

SUMMARY

Population-based data show a trend toward an epidemic increase in obesity and diabetes, which parallels the decline in cigarette smoking and other traditional risk factors (i.e., dyslipidemia, hypertension for CHD). In 2000, the prevalence of obesity among US adults reached 20%, with 22 of the 50 states surveyed reporting obesity rates at this level and 43 reporting diabetes rates of >6%. Obesity increases the risk for hospitalization and death from CVD at all levels of CVD risk and independent of other risk factors. In particular, abdominal obesity acts as the driving force for insulin resistance and risk factor clustering, known as the metabolic syndrome.

An estimated 47 million US adults have the metabolic syndrome. If the current trends continue, the costs of treating end-stage cardiovascular and metabolic disease will place an enormous strain on the healthcare system. Efforts are under way to define the optimal combination of behavioral and medical therapies for these patients; early intervention appears warranted. Research is also being conducted to better understand the mechanism by which visceral adiposity may contribute to the occurrence of clustered risk factors and the subsequent development of CVD or diabetes. Given the expanding dimensions of the epidemic of obesity and the widespread occurrence of cardiovascular and metabolic risk, it is imperative that the practicing physician be alert to the presence of these risk factors among patients and become familiar with the recommended treatment strategies.

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Effect of Insulin Resistance, Dyslipidemia, and Intra-abdominal Adiposity on the Development of Cardiovascular Disease and Diabetes Mellitus

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ABSTRACT

Abdominal obesity contributes to insulin resistance, a metabolic abnormality linked to the development of type 2 diabetes mellitus and cardiovascular disease (CVD). Insulin resistance generally precedes the development of type 2 diabetes. Currently, an estimated 10 million US adults have diabetes and another 25 million have impaired glucose tolerance (IGT), an intermediate step between insulin resistance and diabetes. The pathophysiologic mechanisms known to increase CVD risk in individuals with insulin resistance include formation of advanced glycation end products, hypertension, proinflammatory and prothrombotic states, and dyslipidemia (i.e., low levels of high-density lipoprotein cholesterol, increased levels of triglycerides, small, dense low-density lipoprotein cholesterol particles, apoplipoprotein B, and inflammation). The increased flux of free fatty acids from adipose tissue to the liver promotes dyslipidemia. Insulin resistance and impaired glucose tolerance are associated with increased CVD risk. Individuals with coexisting metabolic syndrome and diabetes have the highest prevalence rates of CVD. The Nurses' Health Study showed that CVD risk was elevated even before the development of diabetes compared with women who never developed diabetes. Lifestyle modification is recommended as the first-line treatment for obesity and its metabolic sequelae. Pharmacotherapy may be useful in patients for whom nonpharmacologic approaches alone are ineffective or insufficient. Primary care physicians play a critical role in the early identification and treatment of patients at increased risk for the development of type 2 diabetes and CVD because of their obesity and associated complications. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Cardiovascular disease; Impaired glucose tolerance; Insulin resistance; Metabolic syndrome; Type 2 diabetes mellitus

The prevalence of obesity, type 2 diabetes mellitus, and the metabolic syndrome has increased dramatically in the past 2 decades. Obesity, specifically visceral abdominal obesity, contributes to the development of insulin resistance, which may underlie a number of the manifestations and cardiovascular complications of diabetes and the metabolic syndrome. Insulin resistance is associated with increased cardiovascular risk as well as the risk for developing overt diabetes. Therefore, early intervention to treat insulin resistance is an important preventive health strategy.

PATHOPHYSIOLOGY OF INSULIN RESISTANCE

Although it is recognized that insulin resistance increases the risk for type 2 diabetes, it is not as well known that it also increases the risk for cardiovascular disease (CVD). A number of factors increase the risk for insulin resistance, including genetic predisposition, obesity and inactivity, aging, medications, polycystic ovary syndrome, and rare disorders such as partial lipodystrophy. Concomitant conditions that are associated with insulin resistance include type 2 diabetes, hypertension, dyslipidemia, atherosclerosis, and polycystic ovarian syndrome (Figure 1).
Obesity drives the development of insulin resistance, which in turn promotes the development of CVD (Figure 2). Insulin resistance is itself a risk factor for CVD. It affects CVD risk through several pathophysiologic mechanisms as follows:

- Glucose intolerance and hyperglycemia facilitate the accelerated formation of advanced glycation end products (AGEs), which interact with AGE-binding receptors to promote atherosclerosis directly through changes in the function of endothelial, macrophage, and smooth muscle cells.
- Increased apolipoprotein (apo)-B concentrations, an increased proportion of small, dense low-density lipoprotein (LDL) cholesterol particles, decreased high-density lipoprotein (HDL) cholesterol, and hypertriglyceridemia characterize the dyslipidemia of visceral obesity and insulin resistance, and directly contribute to CVD.
- Insulin resistance blunts vascular production of nitric oxide, a factor crucial to the normal vasodilatory response and endothelial function.
- Insulin resistance contributes to the development of hypertension, a well-established risk factor for CVD.
- Insulin resistance most likely impairs thrombolysis through a mechanism that involves increased levels of plasminogen activator inhibitor–1 (PAI-1).

**Figure 1** Causes and associated conditions of insulin resistance. PCOS = polycystic ovarian syndrome.

**Figure 2** Association of insulin resistance with cardiovascular risk factors and atherosclerosis. AGES = advanced glycation end products; CRP = C-reactive protein; HDL = high-density lipoprotein; IL-6 = interleukin-6; LDL = low-density lipoprotein; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor–1; tPA = tissue plasminogen activator; VCAM = vascular cell adhesion molecule; ↑ = increased; ↓ = decreased. (Adapted from J Clin Endocrinol Metab.)
• Insulin resistance itself is a proinflammatory state characterized by elevated levels of inflammatory markers. The link between insulin resistance and inflammation is quite provocative, especially because a growing body of data suggests that adipose tissue is an inflammatory milieu that directly produces inflammatory mediators of CVD.

PREVALENCE OF GLYCEMIC ABNORMALITIES

The prevalence of glycemic abnormalities (i.e., insulin resistance, impaired glucose tolerance [IGT], diabetes) in the US population represents a serious public health concern of enormous magnitude. CVD risk begins to increase considerably before the onset of diabetes or even impaired fasting glucose. Data from the Centers for Disease Control and Prevention (CDC) indicate that approximately 20 million US adults have diabetes—14 million have diagnosed diabetes, and 6 million have undiagnosed diabetes. An additional 16 million individuals have IGT, an intermediate stage on the path from insulin resistance to diabetes. 

CVD risk (which is universally acknowledged to be substantially elevated in overt diabetes) begins to increase early in the progression from insulin resistance to diabetes (Figure 3). In fact, the risk for CVD increases as an individual progresses from insulin resistance to IGT to impaired fasting glucose to diabetes. Thus, identifying patients early in the process, before the onset of impaired fasting glucose, is an extremely important step in preventing and mitigating the consequences of CVD risk through lifestyle modification and medical intervention.

THE IMPACT OF PREDIABETIC STATES ON CARDIOVASCULAR DISEASE RISK

Accumulating evidence from clinical trials indicates that prediabetic states adversely affect the risk for CVD. In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, the investigators clearly established that IGT increased the risk for CVD mortality. This large database comprised 18,048 men and 7,316 women from 13 European prospective cohorts. The DECODE study compared the American Diabetes Association (ADA) fasting glucose criteria with the World Health Organization (WHO) 2-hour postchallenge glucose criteria in predicting CVD mortality. The ADA criteria define diabetes as a fasting plasma glucose concentration of 7.0 mmol/L (126 mg/dL) obtained with the use of the oral glucose tolerance test (OGTT). By contrast, WHO recommends the use of the OGTT only if the blood glucose concentration is within the questionable range of 5.5 (99 mg/dL) to 11.1 mmol/L (199.8 mg/dL). WHO defines diabetes using the same fasting glucose concentration as the ADA in combination with a 2-hour glucose concentration of ≥11.1 mmol/L (≥199.8 mg/dL).

Using the WHO criteria for 2-hour glucose classification, the investigators showed that individuals with diabetes had a significantly greater likelihood of dying over the follow-up period of up to 10 years (mean, 7.3 years) compared with persons who had normal glucose tolerance. Fasting blood glucose was not as accurate as 2-hour blood glucose in predicting mortality. Thus, these results confirm that, when used as the sole screening modality, abnormalities in 2-hour glucose concentrations predict mortality with greater accuracy compared with fasting glucose. The largest number of excess deaths was observed in the group with IGT that had “normal” fasting glucose concentrations of 6.0 mmol/L (108 mg/dL) or lower. Therefore, in clinical practice, the fasting glucose test alone will not identify all those at heightened risk. By contrast, IGT, based on the 2-hour glucose test, identifies patients at an intermediate stage between normal glucose tolerance and diabetes who are at substantially higher risk of dying from CVD over the next decade.

Not surprisingly, the metabolic syndrome has been shown to further increase the degree of coronary heart disease (CHD) risk, regardless of diabetes status. The presence of the metabolic syndrome, with or without diabetes, correlates with an increased prevalence of CHD, although the combination of the metabolic syndrome with diabetes confers the highest degree of risk. Using data from the Third National Health and Nutrition Examination Survey (NHANES III), researchers categorized adults >50 years into 4 groups by the presence/absence of the metabolic syndrome (as defined by the National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III]), with or without diabetes. The metabolic syndrome was shown to increase CHD risk. Individuals with the metabolic syndrome and diabetes had the highest CHD prevalence rate (19.2%). Notably, the metabolic syndrome, even without diabetes, was associated with a significantly increased prevalence rate (13.9%) of CHD. Those without the metabolic syndrome, regardless of their diabetes status, had the lowest rate of CHD prevalence. Thus, the presence of the metabolic syndrome, even in individuals without diabetes, was shown to markedly increase CHD risk.

The Nurses’ Health Study assessed the effect of prediabetic states on CVD risk in a population of 117,629 female nurses, aged 30 to 55 years, who did not have CVD at study entry and who were followed for 20 years. A total of 1,508 subjects had diagnosed type 2 diabetes at baseline and 5,894 subjects developed diabetes over the course of the study. During 2,238,288 person-years of follow-up, the investigators documented 1,556 new cases of myocardial infarction (MI) and 1,405 strokes. Figure 5 depicts the risk for MI or stroke by diabetes status and the risk for MI or stroke by time before diagnosis of diabetes. Compared with nondiabetic subjects, those who developed diabetes during follow-up had an age-adjusted increased relative risk for MI or stroke of 2.82 before diabetes diagnosis and 3.71 after diabetes diagnosis. Subjects who had diabetes at baseline had the highest risk, 5 times greater, of MI or stroke.
Among the subjects who were free of diabetes at baseline, the relative risk for CVD was 2.4 at ≥15 years before diabetes onset; 10 to 15 years before onset, the relative risk increased to 3.19; and at <10 years before onset, it increased to 3.64 (Figure 5). Clearly, the closer these individuals were to the onset of diabetes, the greater their CVD risk. The investigators concluded that their findings validated the “ticking clock” hypothesis that “it may be necessary to intervene before the onset of clinical diabetes, since the clock has already begun to tick.” Thus, the Nurses’ Health Study showed that prediabetes increases CVD risk, specifically MI or stroke. Because CVD risk begins to increase long before the onset of diabetes, high-risk patients should be aggressively screened and managed, with glucose tolerance tests included as a routine part of the diagnostic work-up.

The San Antonio Heart Study, a population-based study of 2,569 individuals followed for 8 years, assessed the relation of insulin resistance to CVD risk. Insulin resistance was measured using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). The HOMA-IR index is defined as fasting insulin (in microunits per milliliter) times fasting glucose (in millimoles per liter) divided by 22.5. In this study, logistic regression analysis showed that the risk for CVD (i.e., death, MI, bypass surgery, angina) increased across quintiles of HOMA-IR after adjustment for age, sex, and ethnicity (P for trend <0.0001). Individuals in the highest HOMA-IR quintiles...
for insulin resistance had the greatest CVD risk, ranging from 2.47 to 4.80 for quintile 4 and 4.80 to 41.7 for quintile 5, compared with persons in the lowest quintile (risk range, 0 to 1.02).19

In summary, accumulating evidence suggests that CVD risk begins with insulin resistance, a silent condition that occurs long before overt diabetes. Therefore, proactive and aggressive clinical management of high-risk patients with insulin resistance should begin well before the onset of diabetes or even impaired fasting glucose to prevent diabetes and CVD. In this regard, the metabolic syndrome provides useful and easily applicable clinical criteria for identifying patients with insulin resistance who are at increased CVD risk.

A CLINICAL CHALLENGE: THE DYSLIPIDEMIA OF INSULIN RESISTANCE

Abnormalities in lipid and lipoprotein metabolism are among the major risk factors for CVD in insulin resistance.23 One of the major mechanisms behind the dyslipidemia (i.e., low HDL cholesterol levels, small, dense LDL cholesterol particles, and hypertriglyceridemia) of insulin-resistant states is the increased flux of free fatty acids from adipose tissue to the liver. As illustrated in Figure 6, free fatty acids promote increased triglyceride synthesis in the liver, which can lead to the secretion of very-low-density lipoprotein. The accumulation of intracellular lipid metabolites in the liver appears to cause hepatic insulin resistance. Interestingly, even small degrees of weight loss increase hepatic insulin sensitivity in patients with type 2 diabetes and correspond with significant reduction in intrahepatic fat without any changes in circulating adipokines.24 In addition, insulin resistance increases production of apo-CIII, a protein that blocks uptake of remnant lipoprotein particles.

A low HDL cholesterol level is even more common in patients with insulin resistance than is hypertriglyceridemia. In insulin-resistant states, the following mechanisms lower HDL cholesterol: (1) cholesterol ester transfer protein mediates the transfer of cholesterol from HDL to the apo-B-containing lipoproteins; and (2) enzymes, such as hepatic lipase and endothelial lipase, are upregulated in the insulin-resistant state and, therefore, promote hypercatabolism of HDL.

TREATMENT OF DYSLIPIDEMIA IN INSULIN RESISTANCE

The ADA recommends aggressive targets for lipid management in patients with type 2 diabetes (Table 1).25 Given the adverse prognostic implications of prediabetic states, it might be prudent to extend these lipid targets to patients with the metabolic syndrome and insulin resistance. For many patients, these goals can be met with lifestyle modification and, if necessary, adjunctive pharmacotherapy.

Lifestyle modification is the first-line approach to the management of patients with the metabolic syndrome and insulin resistance. Several studies have shown that diet and exercise can prevent or delay the onset of diabetes in patients with IGT.26–28 In the Diabetes Prevention Program (DPP), lifestyle modification was almost twice as effective as metformin in preventing diabetes (relative reduction, 58% vs. 31%).27 The ADA recommends moderate weight loss (5% to 10% of body weight) and moderate physical exercise (30 minutes daily).25

Many patients require adjunctive pharmacologic treatment of dyslipidemia to reduce CVD risk in insulin-resistant states. However, it can be difficult to achieve effective reduction of triglycerides and elevation of HDL cholesterol levels with existing therapies. In fact, many patients require >1 drug to address the various individual components of the metabolic syndrome. This often results in therapy with a statin (to reduce LDL cholesterol) plus either niacin
or a fibrate (to reduce triglycerides and increase HDL cholesterol).

Ultimately, effective weight reduction, especially reduction in visceral adiposity, should improve insulin sensitivity and other manifestations of the insulin-resistant state and reduce the risk for type 2 diabetes and CVD. The optimal pharmacologic strategy for reducing CVD risk in insulin resistance and in the metabolic syndrome would be to target the dyslipidemia, hypercoagulable state, hypertension, insulin resistance, and obesity. However, the ADA cautions against the routine use of drug therapy to prevent diabetes until information from clinical trials establishes a clear rationale for its use.25

SUMMARY

Obesity frequently contributes to insulin resistance, which increases the risk for type 2 diabetes and CVD. Insulin-
resistant states are associated with a particular dyslipidemic profile characterized by hypertriglyceridemia, low levels of HDL cholesterol, and small, dense LDL cholesterol particles. The increased flux of free fatty acids from adipose tissue to the liver exacerbates hepatic insulin resistance and promotes all of these aspects of dyslipidemia. CVD risk increases markedly as glycemic abnormalities (i.e., insulin resistance and IGT) progress to overt diabetes.

Lifestyle modifications (diet and exercise) that target weight reduction, especially reduction in abdominal adiposity, comprise the first-line approach to treating glycemic abnormalities and reducing the risk for diabetes and CVD. Pharmacologic therapy is used adjunctively in patients at higher risk and those recalcitrant to lifestyle modification. Primary care physicians can play a major role in the early identification and preventive management of insulin-resistant states to help reduce progression to type 2 diabetes and decrease the risk for CVD.4

References

Role of the Endocannabinoid System in Regulating Cardiovascular and Metabolic Risk Factors

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ABSTRACT

Increased endocannabinoid (EC) system activity promotes excessive food intake and obesity in animals and humans. The EC system regulates food intake and hedonic reward through central mechanisms located within the hypothalamus and limbic forebrain. In rodent models, cannabinoid1 (CB1) receptor blockade reduces appetite and weight and prevents obesity and insulin resistance. The EC system also regulates food intake and metabolic factors through peripheral CB1 receptors located at multiple sites throughout the body, including adipose tissue, skeletal muscle, liver, and the gastrointestinal (GI) tract. In rodent models, CB1 receptor antagonists act in the liver to decrease lipogenesis, act in the GI tract to increase satiety, and function in adipose tissue to normalize adiponectin levels and reduce fat storage. The CB1 receptor antagonist rimonabant has been shown to reduce food intake and improve metabolic parameters, such as insulin resistance and fatty liver, in animal models of obesity. In preliminary human studies, upregulation of the EC system has been linked to obesity through mechanisms that include high-fat diet, insulin resistance, and genetic malfunction of an EC inactivation enzyme. Evidence suggests that CB1 receptor blockade is a novel therapeutic strategy that addresses the underlying mechanisms of both obesity and cardiometabolic risk. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Cannabinoid, receptor antagonists; Endocannabinoids; Fatty liver disease; Lipogenesis; Rimonabant

The endocannabinoid (EC) system is an intercellular signaling system that plays an important role in regulating cardiovascular risk factors associated with excess body weight and obesity.1 Increased EC system activity promotes excessive food intake and fat accumulation in animal models and humans.1,2 Little was known about the pharmacology or neurobiology of the EC system until the discovery of endogenous cannabinoids (ECs) and their receptors over the past 2 decades.3

THE ENDOCANNABINOID SYSTEM

The endogenous cannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), are phospholipid-derived precursor ligands of the 2 cannabinoid receptors, cannabinoid1 (CB1) and cannabinoid2 (CB2).4,5 (Figure 1). Both are 7-transmembrane, G-protein–coupled receptors, similar to receptors for many hormones and neurotransmitters; however, each of these receptors has its own unique structure.3,5

The ubiquitous CB1 receptor is found in numerous organs involved in the regulation of energy homeostasis, including the brain, adipose tissue, muscle, liver, and gastrointestinal (GI) tract.3 CB2 receptors are located predominantly in the immune system and are not discussed further in this review.

Unlike traditional hormones and neurotransmitters, which are preformed and stored in secretory vesicles until needed, the ECs are synthesized as needed from phospholipids upon activation of their synthetic enzymes. The phospholipid agonists, anandamide and 2-AG, activate cannabinoid receptors locally, in close proximity to the parent cell, and once activated, they are immediately metabolized and rapidly degraded.3 Within the brain, ECs act as retrograde neurotransmitters (or messengers) that inhibit synaptic ac-
tivity. Although ECs influence numerous behaviors, in general the net effect of ECs at diverse sites in the brain and throughout the body is anabolic, facilitating increased energy intake, decreased energy expenditure, and increased accumulation of body fat.2

NEUROMODULATING EFFECTS OF ENDOCANNABINOIDS

Neurotransmitters, such as norepinephrine, dopamine, γ-aminobutyric acid (GABA), and serotonin, transmit signals from neuron to neuron across synapses. The synapse itself consists of a presynaptic terminal containing presynthesized and packaged neurotransmitters, a postsynaptic terminal containing receptor sites for neurotransmitters, and a synaptic cleft between the presynaptic and postsynaptic membranes.

Traditional or canonical neurotransmitters activate receptors on postsynaptic neurons. Upon receiving a nerve impulse, the presynaptic neuron is activated, causing an increase in intracellular calcium which, in turn, results in the release of preformed neurotransmitters, such as serotonin. When serotonin interacts with receptors on the postsynaptic membrane, numerous events occur such as excitation or inhibition of the postsynaptic cell.6

The CB₁ receptor differs in that it is located primarily on presynaptic cell membranes, for example on presynaptic neurons that release the inhibitory neurotransmitter GABA. When these neurons release GABA into the synaptic cleft, the GABA inhibits activity in postsynaptic cells. However, when intracellular calcium levels become elevated in the postsynaptic neuron, enzymes that synthesize ECs are activated, causing the formation and release of endocannabinoids. These molecules then cross back in a retrograde fashion across the synaptic cleft, stimulating CB₁ receptors on the presynaptic membrane and thereby preventing increased calcium levels in the presynaptic cell. This has the effect of reducing the amount of neurotransmitter (i.e., GABA) release,6 a process known as retrograde suppression of neurotransmitter release.7 Stated more simply, the postsynaptic cell inhibits input from the presynaptic cell by activating ECs. In this example, GABA would normally act on a postsynaptic cell to halt an ongoing meal, i.e., to make an individual feel full. EC activation in the postsynaptic cell might occur in response to the sight or taste of a pleasing dessert, and the result would be attenuation of presynaptic GABA release and a tendency to keep eating. ECs therefore act in part by stimulating appetite and prolonging food intake during meals, resulting in fat accumulation over time.

CENTRAL MECHANISMS OF ENDOCANNABINOID ACTIVITY

The basic biologic activity of the EC system on food intake, body weight, and metabolic syndrome components has been described chiefly in animal models.1,8,9 The EC system modulates both the homeostatic (i.e., necessary for survival) and pleasurable aspects of eating through central mechanisms located within the hypothalamus and limbic forebrain, respectively.1

Because the hypothalamus regulates the quantity of food consumption, the injection of ECs directly into the
hypothalamus should promote increased food intake. This hypothesis was confirmed in a pioneering study, which showed that anandamide injection into the ventromedial hypothalamus of presatiated rats induced significant appetitive stimulation through stimulation of CB1 receptors. Conversely, when a CB1 receptor antagonist was injected 30 minutes before anandamide administration, it inhibited anandamide-induced food intake. The researchers concluded that cannabinoids modulate appetite by activating CB1 receptors located in the hypothalamus.

Kirkham and colleagues measured 2-AG levels in the hypothalamus and limbic forebrain of rats in relation to fasting, feeding, and satiation. They found that feeding decreased and food increased raised 2-AG levels. No changes were observed in satiated control animals (Figure 2). 2-AG robustly stimulated eating and appeared to regulate appetite and body weight through its activity on brain systems that mediate incentive and reward. This hypothesis was confirmed in another experiment in which the same investigators injected an EC into a different part of the brain, the nucleus accumbens of the limbic forebrain, which controls the hedonic or reward aspect of stimulants such as food. Injection of 2-AG significantly increased the amount of food eaten during the first hour after administration, whereas the injection of a CB1 receptor antagonist inhibited food intake.

The ability of CB1 receptor antagonism or deletion to blunt food intake after food deprivation was demonstrated in a study comparing CB1 receptor-deficient mice, in whom the CB1 receptor was genetically deleted or “knocked-out,” and wild-type control mice. The results showed that, following fasting, CB1 receptor-deficient mice ate less compared with their wild-type littermates. Further proof of concept was shown in the capability of the CB1 antagonist rimonabant to reduce food intake in wild-type mice but not knockout mice lacking the CB1 receptor. Additionally, the investigators found that increased hypothalamic levels of ECs contribute to the hyperphagia that promotes certain kinds of genetic obesity. Daily treatment of these obese mice with rimonabant resulted in a reduction in body weight, a finding indicative of the centrally mediated role played by ECs in the development of obesity.

In summary, studies have established that cannabinoids mediate food intake both in the hypothalamus, which controls energy homeostasis, and in the limbic system, which controls the pleasurable aspects of eating.

**CANNABINOID1 RECEPTOR BLOCKADE IN ANIMAL MODELS OF OBESITY**

Cannabinoids control food intake through centrally mediated mechanisms that involve interactions between feeding behavior and hedonic reward. The demonstration in animals that CB1 receptors control food intake and body weight, whereas CB1 receptor blockade reduces appetite and weight, has profound implications for the treatment of obesity in humans.

In an important study by Ravinet Trillou and colleagues, a population of CB1 receptor-deficient mice was compared with wild-type control mice to assess their response to standard and high-fat feeding regimens. Over the course of 11 weeks on a high-fat diet, the control mice became obese. By contrast, the mice lacking CB1 receptors remained as lean as they were on a standard diet. At the age of 20 weeks, the mean body weight and adiposity of the knockout mice were, respectively, 24% and 60% lower than those of the controls. In addition, CB1 receptor deletion reduced plasma insulin and leptin levels. Although the knockout mice preferred the high-fat diet, they did not become obese, and they maintained the same weight as normal control animals. Throughout the study, the knockout mice were lean and resistant to diet-induced obesity. In this animal model, the inability to activate the CB1 receptors prevented the development of obesity and insulin resistance.

In another study by Ravinet Trillou and colleagues, the effect of CB1 receptor blockade, as opposed to genetic deletion, was evaluated in a mouse model of diet-induced obesity. During a 5-week treatment period, rimonabant (10 mg/kg per day orally) induced a transient reduction in food intake of 48% in the first week and a significant and sustained reduction of body weight (–20%) and adiposity (–50%). Rimonabant also exerted favorable effects on metabolic parameters, correcting insulin resistance and lowering plasma leptin, insulin, and free fatty acid levels. After an initial sharp, but transient, reduction in food intake and weight, although the rats ate normally for the remainder of the study, they sustained their weight loss compared with controls, despite consuming a high-fat diet.

In summary, in animal models of obesity, CB1 receptor blockade with rimonabant transiently decreases high-fat dietary intake and persistently lowers body weight and insulin resistance.

**PERIPHERAL MECHANISMS OF ENDOCANNABINOID ACTIVITY IN OBESITY**

The EC system regulates food intake through peripheral as well as central mechanisms. CB1 receptors are located at multiple peripheral sites, including adipose tissue, muscle, the liver, and the GI tract (Figure 3). Ghrelin, a gut peptide, is a potent appetite stimulator. In addition to acting on the brain, it has important peripheral actions, including beneficial effects on the ischemic heart and increasing adipose tissue deposition; it also has direct effects on carbohydrate metabolism.

In the GI tract, cannabinoid and ghrelin levels increase in response to fasting and decrease on administration of a CB1 receptor antagonist. In a rat model, food deprivation increased anandamide content 7-fold in the small intestine, an effect that was reversed upon refeeding. The administration of rimonabant reduced food intake in both 24-hour food-deprived rats and partially satiated rats. In another study, intraperitoneal administration of rimonabant signifi-
Significantly decreased ghrelin levels and reduced food intake in rats whose ghrelin levels were elevated in response to a 24-hour fast. Because both ghrelin and anandamide increase food intake by reducing satiety signals from the GI tract, the implication is that endocannabinoids act in the GI tract, as they do in the brain, to favor increased energy intake.

In the liver and in adipose tissue, CB1 receptors are expressed and CB1 agonists facilitate the formation and storage of triglycerides, thus acting synergistically with actions in the brain (i.e., enhanced food intake) to favor weight gain. The fundamental role of hepatic EC system activation in diet-induced obesity in mice has been characterized by Osei-Hyiaman and colleagues. Specifically, activation of hepatic CB1 increases the activity of several lipogenic enzymes, causing the liver to synthesize more fat and thereby promoting both obesity and fatty liver disease. In wild-type control mice, CB1 receptors are located primarily in hepatocytes around the centrilobular veins and, as expected, were absent in CB1 knockout mice. Administration of a CB1 receptor agonist to wild-type mice increased hepatic gene expression of the lipogenic transcription factor SREBP-1c (sterol regulatory element–binding protein-1c) and its target enzymes, acetylcoenzyme-A carboxylase-1 and fatty acid synthase. The net result of this activity was to increase fatty acid synthesis. In this animal model, anandamide, 2-AG, and CB1 receptor levels were all elevated in diet-induced obesity, probably owing to a

Figure 2  Endocannabinoid levels in the hypothalamus and cerebellum of rats in relation to fasting, feeding, and satiation. Feeding lowers and food deprivation raises 2-arachidonoylglycerol (2-AG) levels in the hypothalamus but has no effect in the cerebellum, an area not directly involved in the control of food intake. *P <0.05. (Adapted with permission from Br J Pharmacol.)

Figure 3  Multisite location of cannabinoid1 (CB1) receptors, and effects of a CB1 antagonist on metabolism. GI = gastrointestinal; ↑ = increased; ↓ = decreased.

<table>
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<tr>
<th>Site of Action</th>
<th>Mechanism(s)</th>
<th>Enhances</th>
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<tr>
<td>Hypothalamus/Nucleus accumbens</td>
<td>↓ Food intake</td>
<td>Weight loss, reduced waist circumference</td>
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<tr>
<td>Adipose tissue</td>
<td>↑ Adiponectin</td>
<td>Reduced visceral fat</td>
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<td></td>
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<td>Muscle</td>
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<td>Liver</td>
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<td>GI tract</td>
<td>↑ Satiety</td>
<td>Weight loss</td>
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marked reduction in fatty acid amide hydrolase (FAAH). 15

Importantly, this study implicated CB1-mediated stimulation of fatty acid synthesis to fatty liver disease. Wild-type mice fed a high-fat diet for 3 weeks, though not yet obese, had a significant increase in the basal rate of hepatic fatty acid synthesis and the development of hepatic steatosis. 15 This deleteriously increased rate of hepatic fatty acid synthesis was inhibited by rimonabant in wild-type mice, but not in CB1 receptor knockout mice, implicating increased levels of anandamide and CB1 as the causative mechanisms. These findings strongly suggest that an early EC-mediated increase in de novo lipogenesis in the liver is a critical component in diet-induced obesity, and raise the possibility that CB1 antagonists may be effective not only as antiobesity agents but also in preventing or reversing the development of fatty liver. 15

Adipose tissue also expresses CB1 receptors, and the level is increased in obese animals. 9 In obese Zucker rats, cannabinoid administration increased the level of adipose tissue lipoprotein lipase, the enzyme that enables adipocytes to store fat, while rimonabant blocked this activity. Rimonabant exerted its activity in part by increasing expression of Acrp30 (adiponectin) messenger RNA (mRNA), a plasma protein that decreases hyperinsulinemia and weight. 9 Conversely, in adipose tissue of CB1 receptor knockout mice, rimonabant had no effect on Acrp30 mRNA expression, demonstrating a CB1 receptor-mediated effect. Thus, adipocyte CB1 receptor mRNA is upregulated in obesity and downregulated by CB1 receptor blockade, resulting in reduced hyperinsulinemia and suggesting that rimonabant regulates metabolism peripherally, as well as centrally, through mechanisms independent of weight loss alone. 9

In another study, CB1 receptor agonism induced adipocyte lipoprotein lipase activity in primary cultures of mouse adipocytes. 16 These findings suggest that the EC system modulates energy homeostasis through dual peripheral lipogenic and central orexigenic mechanisms and, therefore, that CB1 antagonists offer a novel approach to the treatment of both obesity and cardiometabolic risk. 16 Finally, rimonabant administration, but not pair feeding (where control animals receive the same amount of food voluntarily consumed by the rimonabant-treated animals), normalized plasma adiponectin in mice that were fed a high-fat diet. The effect of CB1 blockade with rimonabant normalized adiponectin, not only by reducing food intake but also by increasing levels of adiponectin, which increases insulin sensitivity.

In summary, the EC system regulates food intake through peripheral and central mechanisms located at multiple peripheral sites. CB1 receptor antagonists act in the liver to decrease lipogenesis, act in the GI tract to increase satiety, and function in adipose tissue to normalize adiponectin levels and reduce insulin sensitivity. In animal models, the CB1 receptor antagonist rimonabant reduces food intake and improves metabolic parameters, such as insulin resistance and fatty liver.

CANNABINOID1 BLOCKADE IN HUMAN OBESITY

Preliminary data in humans indicate that higher levels of cannabinoids are present in obese individuals. In a recent study, Engeli and associates 2 found that circulating levels of anandamide and 2-AG were significantly increased (35% and 52%, respectively, in obese compared with lean women) (Figure 4). 2 In addition, some forms of human obesity are associated with a mutation in FAAH, the enzyme that degrades ECs. In the Engeli group’s study, obese women had a reduction in adipose tissue FAAH gene expression of 59% compared with lean women (see Figure 4). 2

Related to this, Sipe and colleagues 17 observed that an FAAH gene mutation was associated with overweight and obesity in both white and black subjects (P = 0.05). In whites, genetically defective FAAH expression was correlated with increasing body mass index (BMI) and obesity, and a similar trend was observed in black subjects. 2 These data suggest that a genetic defect in FAAH, the enzyme that inactivates ECs, renders some individuals more susceptible to obesity and supports the use of CB1 blockade as a therapeutic strategy.

Important questions remain regarding the use of CB1 receptor antagonists to treat cardiometabolic risks. For example, since none of the clinical data published to date have included patients being treated for depression, it is unknown how rimonabant may interact with antipsychotic therapeutics such as some selective serotonin reuptake inhibitors that tend to cause weight gain. Likewise, there are no data yet on possible interactions of rimonabant with specific dietary nutrients, such as low-fat diets, or the consumption of omega-3 fats; and studies combining rimonabant with exercise have not yet been reported.

In summary, the hyperactivity of the EC system in obesity involves several factors, including a high-fat diet, insulin resistance, and genetic malfunctioning of EC inactivation mechanisms. CB1 receptor blockade appears to represent a viable therapeutic strategy that addresses the underlying mechanisms of obesity.

SUMMARY

Obese animals and humans have elevated levels of endogenous cannabinoids. The EC system exerts its effect through a synergistic interaction between central and peripheral mechanisms at multiple sites, thereby promoting dysregulation in metabolic and energy homeostasis, which culminates in a net anabolic effect. Administration of CB1 agonists, such as anandamide and 2-AG, increases food intake and body weight, whereas administration of CB1 antagonists reduces food intake and body weight and improves blood glucose and lipid profiles.

Evidence suggests that CB1 receptor antagonists act centrally in the brain to reduce food intake and peripherally in
adipose tissue to increase adiponectin and in the liver to decrease lipogenesis. Preliminary evidence indicates that CB1 blockade increases glucose uptake and oxygen consumption in muscle, decreases lipogenesis in the liver, and increases satiety in the GI tract. The subject of EC action is a timely one because CB1 antagonists have shown promise in clinical trials as novel therapeutic tools for the treatment of obesity and its associated cardiometabolic risk factors.

References

12. Ravinet Trillou C, Delgorge C, Menet C, Arnone M, Soubrie P. CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to


Therapeutic Options for Modifying Cardiometabolic Risk Factors

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ABSTRACT

Excessive adipose tissue is associated with increased expression or suppression of cytokines and hormones, leading to inflammation and chronic disease. In particular, abdominal adiposity, as evidenced by a high waist circumference, is a component of the metabolic syndrome, a constellation of risk factors (e.g., high waist circumference, high blood pressure, elevated triglycerides, low high-density lipoprotein cholesterol, elevated fasting glucose) that increases the risk for type 2 diabetes and cardiovascular disease. Lifestyle modification is the first-line approach to the management of obesity and the metabolic syndrome. However, for patients who cannot achieve a reduction in weight (5% to 10% of initial body weight) and cardiometabolic risk factors with lifestyle modification alone, physicians should consider adjunctive long-term pharmacotherapy. A variety of approved and investigational pharmacologic agents have been shown to reduce weight and modify metabolic syndrome components, including sibutramine, orlistat, metformin, and rimonabant. Data from four phase 3 trials suggest that rimonabant, the first cannabinoid receptor inhibitor, modulates cardiometabolic risk factors, both through its impact on body weight and through direct pathways that are not related to weight loss. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Metabolic syndrome; Metformin; Obesity; Orlistat; Rimonabant; Sibutramine

Obesity is a chronic and common metabolic disorder that affects approximately one third (32.2%) of adults in the United States.1 Primary care physicians manage health complications of obesity in large numbers of overweight and obese patients in the office setting. Obesity predisposes individuals to numerous comorbidities, including type 2 diabetes mellitus, gallbladder disease, hypertension, heart disease, osteoarthritis, sleep apnea, and certain forms of cancer.2 In particular, abdominal obesity, assessed indirectly by a high waist circumference, is one of a constellation of risk factors associated with insulin resistance and increases the risk of developing cardiovascular disease (CVD) and diabetes 1.5- to 2-fold.2

Recent evidence suggests that an increased body fat mass, especially when located predominantly centrally, is associated with excessive amounts of inflammatory cytokines (i.e., interleukin-6 and tumor necrosis factor–α) and adipose tissue hormones (i.e., lipase, estrogen, adiponectin, and insulin).3 The excessive hormone levels associated with increased fat stores assault various organ systems, thereby mediating disease states. For example, increased adipose tissue mass produces higher levels of insulin, estrogen, and inflammatory hormones, all of which are associated with an increase in breast cancer risk. The accumulation of excess adipose tissue also promotes adaptations and alterations in cardiac structure and/or function that can lead to numerous cardiac complications, including coronary heart disease (CHD), heart failure, and sudden death.3

The management of obesity and its complications is clinically challenging. The standard treatment paradigm focuses on managing clinically relevant obesity-related complications (i.e., dyslipidemia, hypertension, type 2 diabetes, and CVD). By contrast, preemptive weight management directed toward reducing body mass index (BMI [kg/m²]) and abdominal fat before serious health complications...
emerge addresses the underlying etiology of the complications and represents a reasonable early preventive intervention before, not after, the development of chronic disease. Current evidence-based guidelines from the National Institutes of Health (NIH) recommend weight loss interventions in overweight and obese patients with ≥2 risk factors for obesity-related comorbidities.4

CLINICAL GUIDELINES FOR WEIGHT LOSS

Weight loss through lifestyle change is the first-line approach to the management of overweight or obesity in patients at high cardiometabolic risk. According to the guidelines, a combination of low-calorie diet, increased physical activity, and behavior therapy provides the most successful intervention for weight loss and weight maintenance.4 Patients who adhere to these recommendations may lose as much as 10% of their initial body weight within 6 months.4

Following a low-calorie diet, obese patients can lose 1 to 2 lb [0.45 to 90 kg] per week by reducing their caloric intake 500 to 1,000 kcal/day [2,100 to 4,200 kJ/day] below that required to maintain their initial body weight. Increasing physical activity enhances weight loss efforts and facilitates weight maintenance, as well as reducing CHD risk and decreasing body fat while maintaining muscle mass. The long-term goal is to work up to ≥30 minutes of moderate-intensity physical activity on most, and preferably all, days of the week. Behavior therapy and strategies can improve adherence. Given its effectiveness, lifestyle therapy consisting of combined diet, physical activity, and behavior therapy is indicated for all individuals who are overweight or obese if they have ≥2 comorbidities and a BMI of 25 to 29.9 or a high waist circumference, and for all of those with a BMI of ≥30, regardless of comorbidities (Table 1).4

Obesity-related comorbidities that confer a high absolute risk of mortality include established CHD, other atherosclerotic diseases, type 2 diabetes, and sleep apnea.4

Non–life-threatening obesity-related comorbidities that increase risk include osteoarthritis, gallstones, stress incontinence, and gynecologic abnormalities (e.g., amenorrhea and menorrhagia).4

Obesity is a chronic and relapsing disease and, therefore, many patients find it difficult to lose weight and maintain weight loss with lifestyle therapy alone. Long-term pharmacotherapy, in conjunction with continued lifestyle-modification efforts, should be considered for patients with a BMI of 27 to 29.9 if they have comorbidities and have failed to lose 1 lb/wk [0.45 kg/wk] after 6 months of combined lifestyle therapy. Pharmacotherapy is indicated for all those with BMI of ≥30 (see Table 1).4

Bariatric surgical treatments, such as gastric bypass or gastric banding, are widely used and extremely effective in inducing long-term weight loss.5 However, bariatric procedures are appropriate only for 2 categories of patients: (1) selected severely obese patients with a BMI of 35 to 39.9 along with obesity-related comorbidities, and (2) all severely obese patients with a BMI ≥40.4 Approaches that are less invasive than, but as effective as, surgery are clearly needed. Optimally, early intervention with aggressive and effective nonpharmacologic and pharmacologic approaches in the primary care setting will prevent patients from ever needing bariatric surgery.

NONPHARMACOLOGIC APPROACHES

Traditionally, treatment of cardiovascular and metabolic risk has addressed the management of individual risk factors, such as hypertension, type 2 diabetes, hypertriglyceridemia, and low high-density lipoprotein (HDL) cholesterol. Because obesity sets the stage for cardiometabolic risk, weight control through therapeutic lifestyle change is the first-line approach to cardiometabolic risk modification.4,6 Studies have shown that intensive lifestyle intervention is as effective as, or more effective than, drug therapy in reducing weight and cardiometabolic risk.7,8

The value of combined lifestyle intervention (i.e., diet, exercise, and behavioral therapy) in reducing weight, preventing or delaying diabetes onset, and preventing and treating the metabolic syndrome was illustrated in 2 analyses from the Diabetes Prevention Program (DPP).7,8 The DPP population database comprised 3,234 nondiabetic individuals with impaired glucose tolerance. Participants were randomly assigned to receive metformin 850 mg twice daily (n = 1,073), lifestyle modification (n = 1,079), or placebo (n = 1,082).7 The initial study was designed to assess the effect of pharmacologic versus nonpharmacologic intervention on diabetes prevention, whereas the later study assessed their impact on metabolic syndrome prevalence, prevention, and treatment.

The goals for participants assigned to the intensive lifestyle intervention group were to achieve and maintain a weight reduction of ≥7% of initial body weight through a low-calorie, low-fat diet and to engage in moderately intense physical activity, such as brisk walking, for ≥150 min/wk.7,8 During the first 6 months of the study, subjects participated in 16 individual counseling sessions with case managers and registered dietitians. During months 7 to 36, subjects participated in individual counseling sessions (usually monthly) with a registered dietitian, group sessions with case managers, and additional individual support sessions as needed. The focus of these sessions was to review food and activity records and to discuss problem-solving difficulties. Notably, participants received positive reinforcement in the form of praise from staff for meeting their goals, as opposed to criticism for slip-ups or lack of progress.7

In the initial analysis, the DPP investigators reported that the intensive lifestyle modification group outperformed the other 2 groups by a significant margin. The incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 years in the placebo, metformin, and lifestyle-modification groups, respectively.7 The incidence of diabetes was reduced by 58% in the lifestyle-modification group and 31% in the met-
formin group compared with placebo. Participants in the lifestyle-modification group lost considerably more weight and kept it off, probably owing to intensive weight maintenance counseling. The average weight loss was 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle-modification groups, respectively (P < 0.001). Significantly, participants in the intensive lifestyle-modification group not only achieved a 7% weight loss over a 1-year period but also were able to maintain a 4% weight loss over a 4-year period.

In the second analysis, Orchard and colleagues resolved the issue of whether the benefits of lifestyle intervention extended to the prevention of the metabolic syndrome. The metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) as the presence of ≥3 of the following components: high waist circumference, hypertriglyceridemia, low HDL cholesterol levels, hypertension, and impaired fasting glucose levels. At baseline, 53% of subjects had the metabolic syndrome. By 3 years, 53% of those in the placebo group had acquired the metabolic syndrome compared with 47% in the metformin group and 38% in the lifestyle-modification group (Figure 1). Lifestyle intervention proved considerably more effective than drug therapy in preventing the metabolic syndrome. The incidence of the metabolic syndrome was reduced by 41% in the lifestyle group (P < 0.001) and by 17% in the metformin group (P = 0.03) compared with placebo. Lifestyle intervention had a dramatic effect in preventing new cases of the metabolic syndrome and reducing waist circumference and blood pressure, but not in reducing abnormalities in HDL cholesterol and triglycerides.

In summary, the DPP established that lifestyle modification is an effective intervention in achieving weight

<table>
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<th>Table 1</th>
<th>National Institutes of Health (NIH) treatment guidelines for overweight or obese patients*</th>
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<td>Treatment</td>
<td>BMI Category*</td>
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BMI = body mass index.
*Yes alone indicates that the treatment is indicated regardless of the presence or absence of comorbidities. The solid arrow signifies the point at which therapy is initiated.

Adapted from The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.
loss, preventing or delaying diabetes, and preventing and treating metabolic syndrome. However, it should be noted that a great deal of behavioral-counseling resources were required to implement this approach successfully in both the acute and maintenance phases of weight loss. Nonetheless, with proper implementation and adherence, lifestyle modification alone can reduce weight and cardiometabolic risk in high-risk patients with impaired glucose tolerance.

**PHARMACOLOGIC APPROACHES**

Obesity is a chronic and relapsing disease and, as such, requires long-term management. In an effort to overcome the weight regain that typically follows weight loss, drug therapy in conjunction with continuing lifestyle intervention can be used for the long term.

The choice of appropriate drug is limited by the fact that few drugs are available in the United States for long-term use. Agents approved by the US Food and Drug Administration (FDA) fall into 2 broad categories: appetite suppressants and nutrient absorption inhibitors. Appetite suppressants act on neurotransmitters (i.e., norepinephrine, serotonin, and dopamine) within the central nervous system (CNS), whereas drugs that inhibit nutrient absorption act locally on pancreatic enzymes to prevent conversion of dietary fat into absorbable free fatty acids.

At present, the only 2 drugs approved for long-term use in the treatment of obesity are sibutramine, a centrally acting appetite suppressant, and orlistat, a locally acting inhibitor of nutrient absorption. Although phentermine, a norepinephrine reuptake inhibitor, is the most widely prescribed weight-loss agent, because of an absence of long-term data from clinical trials, it is only approved for short-term use.

**Sibutramine**

Sibutramine acts on the CNS to inhibit the reuptake of norepinephrine and serotonin. The drug amplifies satiety signals and may induce a sensation of fullness.

A pooled analysis of data from six 12-month studies of sibutramine therapy versus controls (diet and exercise alone) showed that sibutramine (10 mg) was associated with a 3-fold improvement in weight loss in overweight and obese patients with comorbidities. During a 1-year period, 63% of sibutramine-treated patients achieved a ≥5% weight loss. The percentage of those achieving ≥10% weight loss was 31% for sibutramine responders compared with 8% for controls. Overall, two thirds of sibutramine-treated patients met the NIH goal of a 5% to 10% weight loss.

The Sibutramine Trial of Obesity Reduction and Maintenance (STORM) showed that sibutramine not only induced weight loss but also improved metabolic syndrome traits, such as triglycerides, HDL cholesterol, waist circumference, and insulin, over a 2-year period. In this European, multicenter, randomized, double-blind trial, obese patients (BMI 30 to 45) were treated with sibutramine (10 mg/day) and an individualized 600 kcal/day [2,520 kJ/day] diet for a 6-month period of acute weight loss. Then, 467 patients (77% of the 605 initially recruited) were randomized to receive sibutramine (n = 352) or placebo (n = 115) for a subsequent 18 months. If weight regain occurred, the dose of sibutramine was increased up to 20 mg/day (a dose higher than that approved for use); this occurred in 183 (52%) patients.

Of the 204 sibutramine-treated patients who completed the trial, 89 (43%) achieved the study end point and maintained ≥80% of their original weight loss compared with 9 (16%) of the 57 patients in the placebo group (odds ratio, 4.64; P <0.001). The trial demonstrated that almost all patients who adhered to the regimen were able to achieve ≥5% weight loss and over half managed a >10% weight loss within 6 months.

A major benefit of sibutramine treatment was its favorable effect on metabolic syndrome components. Patients in the sibutramine group had a significantly greater decrease in waist circumference and waist–hip ratio compared with those in the placebo group. In the first 6 months of the trial, all patients had substantial decreases in triglycerides, very-low-density lipoprotein cholesterol, insulin, C-peptide, and uric acid, but not low-density lipoprotein (LDL) cholesterol. However, following randomization, these changes were sustained in the sibutramine group but not in the placebo group. Over the 2-year period, HDL cholesterol concentration in the sibutramine group increased 20.7% versus 11.7% in the placebo group.

Of note, the contribution of sibutramine to maintaining body weight and beneficial cardiometabolic change was confirmed by the observation that, once patients in the placebo group stopped taking the drug after 6 months of treatment, they experienced immediate and steady increases in weight and reversal of cardiometabolic improvement. This rebound response is similar to that seen in patients who stop treatment for hypertension or diabetes. Thus, once initiated, sibutramine therapy should be continued long term to achieve maximum and sustained efficacy.

In primary care practice, weight-loss drugs should not be viewed as a “magic bullet” capable of resolving weight and metabolic issues in the absence of lifestyle counseling. The importance of prescribing weight-loss medication in conjunction with, rather than instead of, lifestyle modification was confirmed in a 1-year randomized trial of sibutramine conducted in the primary care setting. Obese patients (N = 224) were randomized to receive 1 of 4 interventions: sibutramine (15 mg/day) alone, delivered in 8 primary care visits of 10 minutes each; intensive lifestyle-modification counseling alone (30 group sessions); sibutramine plus 30 group sessions of intensive lifestyle-modification counseling; or sibutramine plus brief lifestyle counseling (8 visits of 10 to 15 minutes). At 1 year, the patients who received sibutramine in combination with intensive lifestyle counseling lost a mean of 12.1 kg. By contrast, those who received sibutramine
alone, lifestyle modification alone, or sibutramine and brief lifestyle counseling lost much less weight (5.0 kg, 6.7 kg, and 7.5 kg, respectively) (Figure 2). These results underscore the necessity of combining pharmacotherapy with lifestyle-modification therapy, as recommended in the guidelines. The group receiving both interventions lost twice as much weight (12.1 kg) at 1 year compared with the group receiving sibutramine alone (5.0 kg) or lifestyle-modification therapy alone (6.7 kg). In addition, nearly twice as many patients in the intensive lifestyle modification plus sibutramine group lost 10% of their initial body weight. Thus, intensive lifestyle counseling plus sibutramine therapy had an additive effect in helping patients maximize their weight-loss goals.

The side effects of sibutramine reported in clinical trials, including modest increases in blood pressure and pulse rate, may be of concern in some patients at high cardiovascular risk. However, the potentially deleterious, but manageable, effects of sibutramine on blood pressure are offset by its beneficial effects on weight and cardiometabolic risk in the majority of patients.

Orlistat

Orlistat reduces fat absorption by binding to pancreatic lipases and partially inhibiting the hydrolysis of dietary fat (triglycerides) into absorbable free fatty acids and monoacylglycerols. Two multicenter studies of 2 years’ duration each—a US study and a European study—showed that patients treated with orlistat 120 mg three times daily, in conjunction with a low-calorie diet, lost 9% to 10% of initial body weight, respectively, within the first year compared with a 6% weight loss in the placebo-treated group.

Orlistat also helps patients maintain weight loss during the second year of use. In the European Multicentre Orlistat Study, patients who switched from orlistat to placebo gained weight, whereas those who switched from placebo to orlistat lost weight during the second year of treatment. Similarly, in the US trial, patients treated with orlistat 120 mg regained less weight during the second year compared with patients treated with orlistat 60 mg or placebo. Improvements in most cardiovascular risk factors, with the exception of triglycerides, were observed in both long-term studies.

The Orlistat Primary Care Study confirmed that orlistat (120 mg) was an effective long-term weight loss adjunct in the office setting. During the second year of this trial, 18.6% of patients in the orlistat 120-mg group, compared with 6.6% in the placebo group (P = 0.001), sustained a weight loss of ≥10% of initial body weight. Thus, clinical trials have shown that orlistat, in conjunction with diet, facilitates sustained weight loss over a 2-year period.

The side effects of orlistat relate to its mechanism of action. Patients take orlistat 120 mg with meals or up to 1 hour after meals and, subsequently, approximately one third of caloric and dietary fat intake is excreted in stools. The side effects of orlistat are gastrointestinal in nature, all of which typically decrease with continued treatment. The small decrease in fat-soluble vitamin associated with orlistat can be offset by daily administration of a multivitamin.

In summary, for patients who cannot control their weight and improve their cardiometabolic risk status through lifestyle modification alone, pharmacologic intervention focused on managing individual risk factors is an often-used and effective adjunct. Obesity pharmacotherapy, if successful, can improve multiple cardiometabolic risk factors. It is hoped that new agents in clinical development will expand the limited armamentarium of available long-term agents.

EFFECTS OF NEW ANTIHYPERGLYCEMIC AGENTS ON WEIGHT AND METABOLIC SYNDROME

Several antihyperglycemic agents (i.e., metformin, exenatide, and pramlintide) approved for the treatment of diabetes appear to have beneficial effects on obesity and other cardiometabolic risk factors that comprise the metabolic syndrome. These agents have shown promise in reducing weight and improving abnormal glucose metabolism and therefore may help to prevent diabetes and CVD.
**Metformin**

Metformin, an antihyperglycemic agent, appears to decrease adiposity and improve insulin resistance. The effects of metformin on body weight, insulin resistance, and other cardiometabolic risk factors are currently under investigation in overweight nondiabetic populations. One such study assessed the effects of metformin 850 mg twice daily in combination with a low-calorie, low-glycemic diet in 24 obese (BMI > 30) adolescents with hyperinsulinemia. After 8 weeks, the 12 patients randomized to the metformin group experienced a greater reduction in weight and body mass compared with the 12 patients in the placebo group. Results also showed that metformin enhanced insulin sensitivity and decreased hyperinsulinemia, leading to significant decreases in plasma leptin, cholesterol, triglycerides, and free fatty acid levels. This study clearly suggests that the antiobesity effect of metformin may exert beneficial metabolic effects on hyperinsulinemic states, thereby potentially preventing progression to diabetes. However, larger long-term studies are needed to confirm these preliminary findings.

**Exenatide**

Exenatide is a new injectable treatment for type 2 diabetes that mimics the actions of the pancreatic incretin hormone glucagon-like peptide–1, thereby enhancing insulin secretion. The effect of exenatide on glycemic control was investigated in a placebo-controlled, 82-site study. Of the 336 obese patients with diabetes (mean BMI, 34; mean weight, 100 kg) recruited, 272 completed the 30-week study. The patients, all of whom had failed to achieve adequate glycemic control with metformin, were randomized into 3 groups to receive exenatide (5 μg or 10 μg twice daily) or placebo in addition to metformin and without any specific dietary intervention. At week 30, hemoglobin A1C (HbA1C) changes from baseline for the twice-daily 5-μg and 10-μg exenatide dosage groups were −0.40 and −0.78, respectively, compared with +0.08 for placebo (P < 0.002). Of the evaluable patients, 46% in the 10-μg exenatide group and 32% in the 5-μg exenatide group achieved an HbA1C ≤ 7%. Exenatide-treated patients experienced a progressive dose-dependent weight loss of −2.8 kg in the 10-μg group and −1.6 in the 5-μg group. Generally well tolerated, exenatide reduced HbA1C and weight without increasing the incidence of hypoglycemia in these difficult-to-treat patients with metformin-recalcitrant type 2 diabetes.

**Pramlintide**

Pramlintide, an injectable antihyperglycemic agent, mimics the activity of the pancreatic hormone amylin, which, along with insulin, regulates postprandial glucose control. The drug is indicated for the treatment of type 1 or type 2 diabetes and may be prescribed in conjunction with insulin or metformin. In a pooled post hoc analysis that included overweight and obese insulin-treated patients with type 2 diabetes, pramlintide-treated (120 μg twice daily) patients had a body-weight reduction of −1.8 kg (P < 0.0001) compared with placebo-treated patients, and approximately 3 times the number of pramlintide patients experienced a ≥5% reduction of body weight compared with patients given placebo. A phase 2 dose-ranging study evaluating the safety and weight effects of pramlintide in obese patients has yielded positive results; however, data from this study have yet to be published.

**Cannabinoid1 Blockade: A Novel Pharmacologic Approach to Weight Loss and Cardiometabolic Risk**

The endocannabinoid (EC) system appears to play a role in the central and peripheral regulation of body weight and energy balance. Animal studies have demonstrated that administration of cannabinoid agonists increased food intake, whereas administration of a cannabinoid1 (CB1) receptor blocker decreased food intake. A recent study appears to document overactivity of the peripheral EC system. In obese versus lean women, circulating levels of 2 endogenous cannabinoids, anandamide and 1/2-arachidonoylglycerol, were increased by 35% and 52% (P < 0.05), respectively. In addition, fatty acid amide hydrolase (FAAH) gene expression in adipose tissue was reduced in the obese women and may contribute to the excess levels of circulating Ecs because FAAH is the primary enzyme involved in the degradation of anandamide. These markers of EC system activity were not affected by a 5% weight loss. These findings support the concept that activity of the ECs may be greater in obese women than in lean women.

In 4 pivotal phase 3 clinical trials, rimonabant, the first selective CB1 receptor blocker, was shown to reduce weight and waist circumference and improve numerous cardiovascular and metabolic risk factors in >6,000 patients. In all 4 of the Rimonabant In Obesity/Overweight (RIO) trials (the RIO–Europe Study, the RIO–North America Study, the RIO–Lipids Study, and the RIO–Diabetes Study), rimonabant was associated with an increased HDL cholesterol and decreased waist circumference and triglycerides (Figure 3). During the first year, the percentage of patients treated with rimonabant 20 mg who experienced a ≥5% weight loss was 48.6%, compared with 20% for patients given placebo, whereas the percentage achieving a ≥10% weight loss was 25.2%, compared with 8.5% for placebo-treated patients (P < 0.001). Levels of HDL cholesterol increased and levels of fasting insulin and triglycerides decreased in patients receiving rimonabant 20 mg.

Of importance, the trial also addressed the efficacy of rimonabant in preventing weight regain. Overweight or obese patients (N = 3,045) were randomized to receive...
rimonabant (5 mg or 20 mg) or placebo for 1 year and then rerandomized to receive either the same dose of rimonabant or placebo for an additional year. When patients initially treated with 5 mg or 20 mg of rimonabant for 1 year were switched to placebo in the second year of the trial, they regained most of the weight they had lost. By contrast, the patients who continued treatment with rimonabant 20 mg maintained a mean ± SEM weight loss from baseline of 7.4 ± 0.4 kg (Figure 4). The same pattern was observed for waist circumference.

Overall, a greater percentage of patients receiving rimonabant 20 mg for both years achieved a weight loss of ≥5% (40% vs. 19% of placebo-treated patients; $P < 0.001$) or ≥10% (17% vs. 8% of placebo-treated patients; $P < 0.001$). These findings reflect real-life clinical scenarios, in that they demonstrate that sustained weight loss and improved cardiometabolic risk status depends on continuous long-term treatment. As is the case with other chronic diseases (i.e., diabetes and hypertension), obesity treatment is effective only when patients receive continuing therapy.
The RIO–North America trial also showed rimonabant 20 mg in conjunction with a standard dietary intervention produced favorable changes in the prevalence of the NCEP ATP III–defined metabolic syndrome, which significantly declined from 34.8% to 21.2% in the rimonabant 20-mg group compared with a reduction of 31.7% to 29.2% in the placebo group ($P < 0.001$) (Figure 5).24 Results of the RIO-Diabetes trial, a multicenter, randomized, placebo-controlled, 1-year study, have recently been published.25 Overweight or obese patients with diabetes ($N = 1,045$), who were already receiving metformin or sulfonylurea, were randomized to receive rimonabant 5 mg or 20 mg once daily or placebo. Rimonabant 20 mg was associated with a dramatic reduction in body weight and waist circumference. Weight and waist circumference decreased by 5.3 kg and 5.2 cm, respectively, in patients treated with rimonabant 20 mg versus 1.4 kg and 1.9 cm, respectively, for placebo-treated patients ($P < 0.0001$).25 These reductions in weight and waist circumference are similar to those typically observed for diabetics in trials of weight-loss agents.

Rimonabant also exerted a beneficial effect on cardiometabolic and glycemic variables. Twice as many patients in the rimonabant 20-mg group (43%) achieved the target end point of $\text{HbA}_1\text{C} < 6.5\%$ compared with patients in the placebo group (21%) ($P < 0.0001$).25 Indeed, >50% of the improvement in $\text{HbA}_1\text{C}$ attributed to rimonabant was independent of the weight loss achieved. Rimonabant reduced the prevalence of the metabolic syndrome in the 20-mg group from 79% at baseline to 64% at the end of 1 year.25

The RIO-Lipids trial evaluated the effect of rimonabant in 1,036 overweight or obese patients with untreated dyslipidemia.26 Rimonabant was shown to improve several nontraditional cardiometabolic risk factors significantly. During the 1-year treatment period, triglycerides decreased 15.8% and HDL cholesterol increased 23.4% in the rimonabant 20-mg group ($P < 0.001$ for both).26 Of note, although no change in levels of LDL cholesterol was observed, the distribution of LDL cholesterol particles shifted toward larger size in the rimonabant 20-mg group compared with placebo, with a difference of 1.1 A in the peak size of LDL cholesterol particles ($P = 0.008$) and a 4.6% lower proportion of small LDL cholesterol particles ($P = 0.007$).26 Plasma adiponectin levels, which bear an inverse relation to weight gain, increased significantly ($P < 0.001$) in the rimonabant 20-mg group compared with placebo, an increase not attributable to weight loss alone. Additionally, plasma leptin and C-reactive protein levels decreased. Thus, in this high-risk population, the total impact of rimonabant on clinical variables, such as lipid and glucose metabolism, represented the beneficial effect of weight loss and also a direct effect on numerous components of metabolic risk, perhaps mediated by its impact on adiponectin secretion rather than body weight loss per se.26

In summary, the phase 3 RIO trials established that rimonabant induces weight loss and improves cardiometabolic risk status in obese or overweight patients, including high-risk patients with preexisting diabetes or dyslipidemia. Rimonabant acts through a unique mechanism to exert its effects on cardiometabolic risk independent of weight loss alone. The adverse events, which included depressed mood, nausea, anxiety, and dizziness, were mild to moderate and decreased over time. The proportions of patients who had treatment-related adverse events or serious adverse events were slightly higher in patients receiving rimonabant 5 mg and 20 mg than in those receiving placebo. However, the differences in adverse-event rates among the rimonabant versus the placebo groups tended to be more notable earlier in the treatment period.

Figure 5 The Rimonabant in Obesity/Overweight (RIO)–North America trial: Change from baseline in metabolic syndrome status at 1 year. ITT = intention to treat; LOCF = last observation carried forward. (Adapted from JAMA.24)
SUMMARY

The accumulation of excess adipose tissue causes increased expression or suppression of certain hormones, leading to inflammation and chronic disease. Lifestyle intervention is the first-line approach to the management of obesity and the metabolic syndrome. However, for patients who cannot achieve weight loss and favorable alterations in cardiometabolic risk factors with lifestyle modification alone, adjunctive long-term pharmacotherapy is indicated.

A variety of pharmacologic agents can help facilitate weight loss and are associated with improvements in several cardiometabolic risk factors. Data from the 4 RIO trials show that rimonabant significantly reduced metabolic syndrome parameters compared with placebo over and above the improvements expected from weight loss alone. In conclusion, pharmacotherapy can be used in conjunction with lifestyle intervention to sustain weight loss and reduce cardiometabolic risk factors.

References

Modifying Cardiovascular and Metabolic Risk Factors: The Role of the Endocannabinoid System and Cannabinoid Receptors

CME SECTION

ASSESSMENT TEST AND EVALUATION FORM

Sponsored by:
Network for Continuing Medical Education (NCME)

Release Date: March 2007
Expiration Date: March 2008
CME ASSESSMENT TEST

Modifying Cardiovascular and Metabolic Risk Factors: The Role of the Endocannabinoid System and Cannabinoid Receptors

Please circle the correct response to each question on the Answer Sheet provided. A passing score of ≥70% must be achieved to receive CME credit.

1. Approximately how many adults in the United States are estimated to have the metabolic syndrome?
   a. 75 million
   b. 56 million
   c. 47 million
   d. 15 million

2. Which of the following most closely correlates with the metabolic syndrome?
   a. High low-density lipoprotein (LDL) cholesterol levels
   b. Increased waist circumference
   c. Body mass index
   d. High high-density lipoprotein (HDL) cholesterol levels

3. According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), which of the following defines the current threshold for impaired fasting glucose?
   a. ≥120 mg/dL
   b. ≥110 mg/dL
   c. ≥100 mg/dL
   d. None of the above

4. According to NCEP ATP III, which of the following waist circumference measurements begins the cutpoint for excessive abdominal adiposity in men?
   a. >38 in
   b. >40 in
   c. >42 in
   d. None of the above

5. Which of the following increases a patient’s risk for insulin resistance?
   a. Inactivity
   b. Aging
   c. Medications
   d. All of the above

6. Approximately how many adults in the United States have impaired glucose tolerance?
   a. 10 million
   b. 24.6 million
   c. 26.2 million
   d. 30 million

7. Which of the following describes the relative risk for myocardial infarction or stroke among women in the Nurses’ Health Study (NHS) who had diabetes mellitus at baseline?
   a. 3.71
   b. 3.63
   c. 5.02
   d. 5.91

8. Which of the following is a potential mechanism of atherogenesis in insulin-resistant states?
   a. Vasodilation
   b. Hypoglycemia
   c. Smooth muscle cell proliferation
   d. None of the above

9. Which term best describes the overall effect of the endocannabinoid system on weight and cardiometabolic parameters?
   a. Catabolic
   b. Anabolic
   c. Satiating
   d. Reinforcing

10. Which best describes the effect of a high-fat diet on cannabinoid1 (CB1) receptor knockout mice?
    a. Obesity
    b. Weight maintenance
    c. Insulin resistance
    d. High leptin levels

11. Which of the following sites contains CB1 receptors?
    a. Liver
    b. Hypothalamus
    c. Adipose tissue
    d. All of the above

12. According to the National Institutes of Health (NIH) guidelines, how much weight can patients on a low-calorie diet (500 to 1,000 kcal/day) expect to lose each week?
    a. 1 to 2 lb
    b. 2 to 3 lb
    c. 2 lb
    d. 3 to 4 lb

13. Which of the following describes the percentage reduction in diabetes in patients treated with lifestyle modification alone in the Diabetes Prevention Program (DPP)?
    a. 23%
    b. 31%
    c. 52%
    d. 58%
14. Which of the following drugs is not approved by the US Food and Drug Administration (FDA) for long-term treatment of obesity?
   a. Orlistat
   b. Phentermine
   c. Sibutramine
   d. None of the above

15. Which of the following cardiometabolic risk factors were shown to improve in clinical trials of rimonabant?
   a. HDL cholesterol and triglycerides
   b. C-reactive protein and sleep apnea
   c. Waist circumference and LDL cholesterol
   d. All of the above
Modifying Cardiovascular and Metabolic Risk Factors: The Role of the Endocannabinoid System and Cannabinoid Receptors

Instructions: (1) Please read the entire CME activity carefully. (2) Complete the posttest by circling the correct answer to each question on the Answer Sheet below. Be sure to retain a copy of your answers for your files. (3) Answer all questions on the Evaluation Form, and return it with your Answer Sheet to the address below. Please note: a CME certificate will be issued only upon receipt of your completed Evaluation Form.

To receive your CME certificate, please return your completed Answer Sheet and Evaluation Form by mail or fax to:

NCME (Attn.: CME Department)
One Harmon Plaza
Secaucus, NJ 07094
Fax: (201) 867-2491

### ANSWER SHEET (circle the best answer to each question)

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### Credit Verification

☐ I participated in the entire activity and claim 2 credits.

☐ I participated in only part of the activity and only claim partial credit based on ___ hours of instruction. (e.g., 0.25, 0.5, 0.75 hours)

_I certify that the above is true and correct._

Signature

PLEASE PRINT CLEARLY

Name:

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Address:

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Phone:_________________________ Fax:_________________________

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Last 4 digits of your Social Security Number*:_________________________

*US residents; for credit-record purposes only.
The Network for Continuing Medical Education (NCME) is committed to excellence in continuing education. Your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please reflect carefully and complete this Evaluation Form.

**Effectiveness in Meeting Identified Needs**

Was the activity effective in meeting the educational needs as identified below? □ Yes □ No

Many patients have \( \geq 1 \) cardiovascular or metabolic risk factor, including dyslipidemia, insulin resistance, hypertension, and intra-abdominal adiposity, and are at risk for cardiovascular disease and for metabolic disorders such as diabetes mellitus. Recent evidence suggests that a newly described physiologic system, the endocannabinoid (EC) system, is involved in lipid and glucose metabolism, and that overactivity of this system is associated with risk factor development. Blockade of cannabinoid (CB) receptors, however, has been shown to modify several of these risk factors. This activity describes the pathophysiology and clinical relevance of the EC system and CB receptors, explains their role in the development of cardiovascular and metabolic risk factors, and offers strategies for risk reduction.

**Rating scale:** 5 = Outstanding; 4 = Good; 3 = Satisfactory; 2 = Fair; 1 = Poor

**Effectiveness of the Individual Faculty Members**

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Knowledge of subject matter</th>
<th>Appropriateness of teaching strategies</th>
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<tbody>
<tr>
<td>Louis J. Aronne, MD</td>
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<tr>
<td>Daniel J. Rader, MD</td>
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<td>Sidney C. Smith, Jr., MD</td>
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**Educational Objectives**

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<tr>
<th>Objective</th>
<th>Degree to which this presentation provided you with knowledge or skills to implement in your practice</th>
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<tr>
<td>Identify excessive abdominal adiposity as a determinant of metabolic and cardiovascular risk in overweight patients</td>
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<tr>
<td>Describe the role of CB receptors on metabolic abnormalities such as insulin resistance and dyslipidemia</td>
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<td>Evaluate the effectiveness of current strategies for modifying cardiovascular and metabolic risk factors in overweight patients</td>
<td>5 4 3 2 1</td>
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<tr>
<td>Examine the potential role of new therapies in improving cardiovascular and metabolic risk factors in overweight patients</td>
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**Learning Contract**

State 1 practice change you may make based on these objectives.

How certain are you that you will make this change?

□ 1%–20%  □ 21%–40%  □ 41%–60%  □ 61%–80%  □ 81%–99%  □ 100%

□ You have permission to contact me in approximately 3 months to determine whether I was able to implement a change in my practice as a result of this CME activity.

(Contact me by:  □ e-mail  □ fax)

**Future Educational Needs**

Please list any other topics that would be of interest to you for future educational activities: