

Metabolic Syndrome: From Global Epidemiology to Individualized Medicine

JA Batsis¹, RE Nieto-Martinez^{2,3} and F Lopez-Jimenez⁴

The metabolic syndrome (MetS) encompasses a constellation of metabolic abnormalities that are thought to place patients at higher risk for the development of diabetes and cardiovascular (CV) disease. The underlying pathophysiology is still a point of contention among various professional organizations leading to inconsistencies in the manner in which MetS is defined. Each definition has its advantages and disadvantages. Nonetheless, there is an agreement that insulin resistance and obesity are likely the central contributing factors. Because the prevalence of obesity has been increasing at a frightening rate in the past few decades, MetS represents a major public health problem that should be identified clinically in individual patients. This review describes the changing epidemiology of obesity and of MetS and discusses its importance in CV disease. We outline the existing controversies that surround MetS and discuss the role of lifestyle, pharmacological, surgical, and novel approaches in its management.

HISTORICAL BACKGROUND

The recognition of the metabolic syndrome (MetS) can be dated to the 1920s when Kylin¹ recognized a triad of gout, hypertension, and hyperglycemia in his patients. Since then, studies have correlated complications of obesity to body fat, hypertriglyceridemia, hyperinsulinemia, and hypertension.²⁻⁴ Reaven's⁵ Banting lecture in 1988 defined syndrome X as metabolic complications of insulin resistance among obese and non-obese patients. Significant cardiovascular (CV) risk factors, including abdominal obesity, hypertension, hyperlipidemia, and hyperglycemia, were frequently observed and clustered together in patients with type 2 diabetes mellitus (T2DM) and impaired fasting glucose. Reaven proposed that insulin resistance and resultant compensatory hyperinsulinemia was the major underlying pathophysiological abnormality explaining most of this clustering phenomenon and possibly the underlying cause of CV disease. Interestingly, he failed to include obesity on his list of disorders that were primary manifestations of insulin resistance.

ONGOING CHANGES IN THE DEFINITION OF THE METABOLIC SYNDROME

Since Reaven's landmark lecture, the definition of MetS appears to be in an ever-changing flux. Various organizations

have proposed definitions of MetS. Although the general principles are similar among groups, cutoffs and thresholds for the variables all differ somewhat. For example, **Table 1** illustrates the major differences among existing definitions. The World Health Organization (WHO) required evidence of insulin resistance, believing that this was the major underlying abnormality in patients with MetS.⁶ Patients with T2DM are included. Microalbuminuria is a criterion for MetS using the WHO definition,⁶ but it is omitted by all other definitions.⁶⁻¹⁰ In 1999, the European Group for the Study of Insulin Resistance (EGIR)⁸ modified the WHO definition by excluding diabetes, as they presumed that insulin resistance preceded the development of diabetes. In addition, this group had specific parameters for classifying central obesity by using a waist circumference of ≥ 94 cm in men and ≥ 80 cm in women.

In 2001, the National Cholesterol Education Program—Adult Treatment Panel III (ATPIII) defined MetS as a constellation of metabolic abnormalities, including hypertension, dyslipidemia, and hyperglycemia associated with insulin resistance.⁹ Insulin resistance was excluded from their definition, as its measurement was difficult and not standardized.⁹ Their objective was to identify patients at high risk for developing CV disease, with the goal of implementing

¹Division of Primary Care Internal Medicine, Department of Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA; ²Department of Physiology, Universidad Centro-Occidental Lisando Alvarado, School of Medicine, Barquisimeto, Venezuela; ³Department of Internal Medicine, Metabolism and Nutrition Unit (UMENUTRI), Barquisimeto, Venezuela; ⁴Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA. Correspondence: F Lopez-Jimenez (lopez@mayo.edu)

Published online: 12 September 2007. doi:10.1038/sj.clpt.6100355

Table 1 Evolving definitions of the MetS 1998–2005

Criterion	Definition					
	WHO ⁶ 1998	EGIR ⁸ 1999	ATPIII ⁹ 2001	AACE ⁵ 2003	IDF ⁷ 2005	AHA/NHLBI ¹⁰ 2005
Measure of obesity	WHR Men: > 0.90 Women: > 0.85 and/or BMI > 30 kg/m ²	Waist circumference Men: ≥94 cm Women: ≥80 cm Specifically, BMI should not be included	Waist circumference Men: > 102 cm Women: > 88 cm	—	Waist circumference— ethnicity specific (see Table 2)	Waist circumference Men: ≥102 cm Women: ≥88 cm Consider adjusting for race
TGs (mmol/l)	≥ 1.7	≥ 2.0	≥ 1.7	≥ 1.7	> 1.7 or specific treatment for this abnormality	≥ 1.7 or treatment for elevated TGs (fibrates and nicotinic acid)
HDL-C (mmol/l)	Men: ≤ 0.9 Women: ≤ 1.0	< 1.0	Men: < 1.03 Women: < 1.3	Men: ≤ 1.03 Women: ≤ 1.3	Men: ≤ 1.03 Women: ≤ 1.3 or specific treatment for this abnormality	Men: < 1.03 Women: < 1.3 or treatment for low HDL-C (fibrates and nicotinic acid)
Blood pressure (mm Hg)	≥ 160/90	≥ 140/90 or treatment for hypertension	≥ 130/85	≥ 130/85	Systolic: ≥ 130 or diastolic: ≥ 85 or treatment of previously diagnosed hypertension	Systolic: ≥ 135 or diastolic: ≥ 85 or antihypertensive treatment in a patient with a history of hypertension
Fasting plasma glucose (mmol/l)	For patients with T2DM: Fasting: ≥ 7.0 or 2-h post: ≥ 11.1 For patients with impaired glucose tolerance: Fasting: < 7.0 and 2-h post: 7.8–11.1 For patients with impaired fasting glycemia: Fasting: 6.1–7.0 2-h post: < 7.8	Non-diabetics only and fasting plasma glucose ≥ 6.1	≥ 6.1	Impaired fasting glucose (6.1–6.9) ^a or ≥ 7.7 after 120 min post-glucose challenge (75 g)	≥ 5.6 or previously diagnosed T2DM If above 5.6, OGTT recommended but not required	≥ 5.6 or on drug treatment for elevated glucose
Insulin resistance	Glucose uptake below lowest quartile for background population under investigation (assessed by clamp study)	Required Fasting hyperinsulinemia	Not required	Patients must have risk factors for insulin resistance ^b	—	Not required
Urinary protein	Microalbuminuria: ≥ 20 μg/min Albumin/creatinine ratio ≥ 20 mg/g	—	—	—	—	—
No. of criteria required	One of glucose intolerance, impaired glucose tolerance, or diabetes mellitus and two of either: blood pressure, dyslipidemia (TGs or HDL-C), obesity, urinary protein	Insulin resistance and two of: hyperglycemia, hypertension, dyslipidemia (TGs or HDL-C), central obesity	3 of 5 above	At least 2 of 4 metabolic abnormalities of blood pressure, plasma glucose, TGs, and HDL-C in an individual with risk factors constituting the insulin resistance syndrome	Central obesity as assessed by waist circumference and two others above	Any 3 of 5 above

AACE, American Association of Clinical Endocrinologists; AHA/NHLBI, American Heart Association/National, Heart, Lung, and Blood Institute; ATPIII, National Cholesterol Education Program—Adult Treatment Panel III; BMI, body mass index; EGIR, European Group for Insulin Resistance; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; MetS, metabolic syndrome; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; TG, triglyceride; WHO, World Health Organization; WHR, waist-hip ratio. ^aThis was modified in 2004 and reduced to ≥ 5.6 mmol/l. ^bDiagnosis of cardiovascular disease, hypertension, polycystic ovarian syndrome, non-alcoholic fatty liver disease, acanthosis nigricans, family history of gestational diabetes or glucose intolerance, non-Caucasian ethnicity, sedentary lifestyle, BMI > 25.0 kg/m² (or waist circumference > 101.6 cm in men, > 88.9 cm in women); age > 40 years.

lifestyle and pharmacological treatments in reducing patients' overall risk. Although they alluded to the importance of abdominal obesity, this consortium failed to describe a unifying pathophysiological mechanism to explain these metabolic abnormalities.

In 2003, the American Association of Clinical Endocrinologists (AACE) reintroduced the concept of insulin resistance as the underlying means of linking the underlying metabolic abnormalities.¹¹ This group did not mandate that a specific number of factors were required to make the diagnosis of MetS. Rather, greater emphasis was placed on the discretion of the treating clinician. They stressed that MetS patients were at increased risk for developing not only T2DM or CV disease but also associated insulin-resistant states, including hypertension, fatty-liver disease, obstructive sleep apnea, and polycystic ovarian syndrome. In 2005, the International Diabetes Federation (IDF) modified the ATP III criteria, asserting that abdominal obesity was correlated with and easier to measure than insulin resistance.⁷ This organization also recognized the importance of geographic and ethnic variation by providing race-specific normal values for waist circumference (Table 2).

The American Heart Association (AHA) and National Heart, Lung and Blood Institute (NHLBI) recognized the clinical simplicity of the ATP III definition and accepted the limitations of the remaining research questions pertaining to underlying pathophysiological mechanisms.¹⁰ This organization reduced the threshold for impaired fasting glucose to 5.6 mmol/l (100 mg/dl), as outlined by the American Diabetes Association¹² and also recognized the ethnicity-dependent measurement of waist circumference. This definition and treatment guidelines for hypertension and dyslipidemia included patients with established CV disease or diabetes if they fulfilled the appropriate criteria. However, they reaffirmed the belief that obesity may be the root cause of MetS.

It is practically impossible to determine which is the best definition for MetS. Granted, the appropriateness of each definition is relative to the purposes and expectations of those using it. For instance, if simplicity is an expected feature to either implement the definition into clinical practice or use it in large epidemiologic studies, the AHA/NHLBI criteria might be the best. On the contrary, if a more accurate diagnosis of insulin resistance is expected, then the WHO definition might be the ideal one. Besides the practicality and the discriminatory power to differentiate a disease condition from other similar entities, another important attribute for the definition of a disease is its ability to predict risk for adverse events. In this regard, all definitions have similar associations of risk, although the ATP III criteria might have a higher relative risk (RR) for CV events than other definitions.¹³ However, the prognostic performance of a set of criteria is not limited to the magnitude of the risk estimate and should include estimates of the area under the receiver operating characteristic curves. Unfortunately, there are no head-to-head comparisons of areas under these curves

among two or more MetS definitions, and therefore it is still unclear which definition provides the best prognostic performance.

GLOBAL EPIDEMIOLOGY

Numerous studies have examined the epidemiology of overweight and obesity worldwide. This overview will focus on the rise in prevalence of MetS in the United States and in other countries for which data have been collected.^{14–34}

The National Health and Nutrition Examination Surveys (NHANES) have been instrumental in epidemiological analyses in the United States since their inception in 1960.³⁵ The sample data are representative of the non-institutionalized civilian population over the age of 2 years. According to NHANES, the prevalence of adult obesity has risen at an alarming rate over the past few decades and can be best appreciated in Figure 1.^{21,22} Accordingly, the prevalence of the ATP III-defined MetS has risen as well, from an overall age-adjusted prevalence of 23.7% in NHANES III to 34.5% in NHANES 1999–2002.^{23,24} According to the 2000 census, this translates to an approximate increase from 47 to 69 million Americans who fulfill the diagnosis of MetS. In a separate

Table 2 Ethnic-specific values for waist circumference—IDF 2005⁷

Ethnic group	Waist circumference (cm) (as a measure of central obesity)	
	Male	Female
Europids In the United States, the ATP III values ⁹ (102 cm in male and 88 cm in female subjects) are likely to continue to be used for clinical purposes) In future epidemiological studies of populations of Europid origin, prevalence should be given using both European and North American cut points to allow better comparisons	≥94	≥80
South Asian and Chinese	≥90	≥80
Japanese	≥85	≥90
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

ATP III, National Cholesterol Education Program—Adult Treatment Panel III; IDF, International Diabetes Federation. Reprinted with permission of Elsevier (*Lancet* 366, 1059–1061 (2005)).

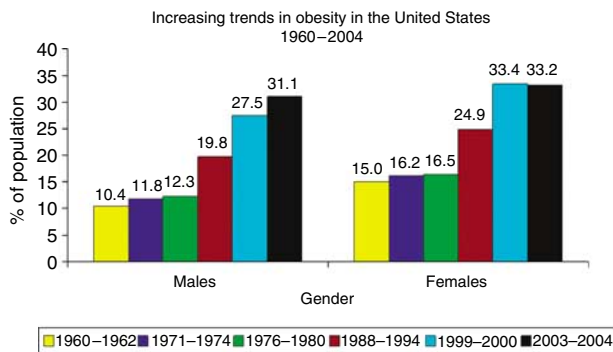


Figure 1 The changing sex-specific prevalence of obesity in %, defined as a BMI ≥ 30 kg/m², from the National Health Examination Survey and NHANES, from 1960 until 2003-2004.^{21,22} These numbers represent non-institutionalized patients over the age of 20 years, from all racial/ethnic groups.

analysis, Park *et al.*²⁵ examined NHANES III data and found that age, body mass index (BMI), and Mexican-American origin were associated with increased odds of developing MetS.

The high adult prevalence of MetS in the United States extends to the adolescent population as well, with 31.2% of overweight or obese classified as having MetS.²⁶ Two-thirds of patients of this study had at least one metabolic abnormality, and 10% of all study participants fulfilled at least three criteria for MetS. Another study demonstrated similar results and estimated that 910,000 adolescents in the United States would qualify for the diagnosis of MetS.²⁷

Unfortunately, the prevalence of obesity and MetS is also increasing worldwide. Exact comparisons of MetS prevalence are often difficult to elicit, but are nevertheless made, due to the variation in study-defined MetS, study design, and year of study. Although the prevalence of MetS in both the Northern European and Mediterranean populations is less than that observed in North America, their population reflects a generally less overweight and obese one, whose diet is beneficial (described below). MetS is a significant burden even in less developed nations.^{16,19,34,36,37} It is evident that the prevalence of MetS is high and growing and that it affects populations irrespective of their geographic location, sex, or age. Cameron *et al.*²⁸ thoroughly examined the existing literature demonstrating that MetS is highly prevalent around the globe, with significant country-to-country variability, and we outline some key studies from around the world in **Table 3**.

CARDIOVASCULAR RISK AND METABOLIC SYNDROME

There is general agreement in the literature that MetS imparts elevated CV risk.^{13,38-46} Using data from NHANES II, Malik *et al.*⁴⁰ examined the impact of ATPIII-defined MetS on coronary heart disease, CV disease, and all-cause mortality. They dichotomized MetS patients with a diagnosis of diabetes. MetS was associated with a hazard ratio (HR) of 2.02 for coronary heart disease. Patients with baseline CV disease had an even higher risk with an HR of 4.19. The HR

for overall mortality in MetS patients was 1.40; in those with pre-existing CV disease, it was 1.87. The HRs in MetS patients without diabetes, MetS with diabetes, MetS with CV disease but no diabetes, and MetS with both T2DM and CV disease, were 1.65, 2.87, 3.89, and 6.45, respectively. The risks of CV mortality paralleled these values and also supported previous studies demonstrating that the higher the number of MetS components, the higher the risks of coronary heart disease, CV mortality, and all-cause mortality.^{9,38,41,44,46-49} MetS as an entity increasingly predicts the risk for coronary heart disease, CV disease, and overall mortality compared to its individual components.⁴¹

Tong *et al.*⁴² examined the incremental risk of coronary heart disease in patients with MetS in NHANES III. The authors included patients in the age range of 35-74 years, as the younger age groups would have lower coronary heart disease incidence, and older patients would have an element of survival bias favoring female subjects. The prevalence of MetS in female subjects was 21 and 24% in the 35-54 and 55-74 years age groups, respectively. The prevalence in male subjects was 39 and 38%. The odds ratio (OR) of MetS for coronary heart disease was 1.05 and 1.95, respectively, in 35- to 54 and 55- to 74-year-old female subjects, and 2.22 and 1.96 in the similar age group in male subjects. These results suggest that in patients over the age of 55 years, there is at least a twofold greater risk of coronary heart disease in both genders. The authors concluded that the lower prevalence of MetS in the younger female population may be due to an estrogen protective effect in the premenopausal female. The above data also hold true in an elderly population. Using the Cardiovascular Health Study data,⁴³ McNeill and co-workers examined 3,585 community dwelling patients, 65 years and older, to determine whether MetS was predictive of CV disease. The HR for CV disease in MetS patients was 1.30 and 1.35 for female and male subjects, respectively.

In a low-risk coronary heart disease-free population from the San Antonio Heart Study,⁴⁵ the predictive nature of ATPIII for all-cause and CV mortality was 2.01, a value not significantly different from that using the WHO criteria. However, when including patients with coronary heart disease, the application of ATPIII or WHO criteria led to differences in HRs for all-cause mortality at 1.47 and 1.27, respectively. These results suggest that both definitions were predictive in the overall population but that the simpler ATPIII criteria were more predictive in lower risk subjects.

The RR of coronary heart disease, myocardial infarction, or stroke with WHO-defined MetS patients in a Scandinavian cohort⁴¹ was 2.96, 2.63, and 2.27, respectively (all $P < 0.001$). MetS was predictive of CV mortality with an RR of 1.81. However, this latter study included patients with T2DM in their cohort. These findings underscore the importance of a careful application of MetS definitions on specific patient cohorts.

Unfortunately, despite efforts that suggest MetS precedes T2DM, many analyses fail to exclude T2DM patients, making comparisons difficult.^{40,41,45,46,50-54} Applying modified

Table 3 Geographic variation of ATPIII-defined MetS prevalence

Country	Study population year	Total number of subjects	Population group	Prevalence (%)			Study
				Overall	Males	Females	
Brazil	1999–2000	1,439	Brazilian population	19	13.6	22.9	Barbosa <i>et al.</i> ¹⁵
Brazil	2005	240	Semi-arid rural population	24.8	18.6	38.4	de Oliveira <i>et al.</i> ¹⁶
Ecuador	2005	325	Postmenopausal	—	—	41.5	Chedraui <i>et al.</i> ¹⁸
Finland	1988–1993	1,005	Finnish males	—	13.7	—	Laaksonen <i>et al.</i> ²⁹
France	1994–1996	4,293	French subjects 30–64 years old	—	10	7	Balkau <i>et al.</i> ³⁰
Greece	2003	4,153	Native Greeks	23.6	24.2	22.8	Athyros <i>et al.</i> ⁵⁸
India	1995	475	Urban Asian Indian adults	41.4	46.5	36.4	Ramachandran <i>et al.</i> ³³
Iran	1999–2001	10,368	Iranians	33.7	24	42	Azizi <i>et al.</i> ³⁴
Ireland	1998	890	Irish ethnic origin aged 50–69 years	20.7	21.8	21.5	Villareal <i>et al.</i> ³⁷
Latin America	2005	3,965	Postmenopausal	—	—	35.1	Royer <i>et al.</i> ¹⁹
New Zealand	2002–2003	1,006	Maori	32	34	30	Gentles <i>et al.</i> ¹³⁴
		996	Pacific	39	41	37	
		2,020	Others	16	17	15	
Turkey	1997–2001	2,398	Turkish adults	—	32.2	45	Onat <i>et al.</i> ³⁶
USA	1992–1999	294	Filipina women living in San Diego	—	—	34.3	Araneta <i>et al.</i> ²⁰
		379	Caucasian	—	—	12.9	
USA	1988–1994	1,960	Overall	9.2	9.5	8.9	de Ferranti <i>et al.</i> ²⁶
		—	African American	2.5	—	—	
		—	Mexican American	12.9	—	—	
		—	Whites	10.9	—	—	
USA	1988–1994	8,814	Overall	23.7	24.0	23.4	Ford <i>et al.</i> ²⁴
		3,599	White	23.8	24.8	22.8	
		1,116	African American	21.6	16.4	25.7	
		2,449	Mexican American	31.9	28.3	35.6	
		354	Other	20.3	20.9	19.9	
USA	1999–2002	3,601	Overall	34.6	34.4	34.5	Ford ²³
		1,834	White	—	35.4	—	

Table 3 continued on the following page

Table 3 Continued

Country	Study population year	Total number of subjects	Population group	Prevalence (%)			Study
				Overall	Males	Females	
USA	1988–1994	631	African American	—	24.5	—	Park <i>et al.</i> ²⁵
		884	Mexican American	—	40.3	—	
		12,363	Overall	—	22.6	22.8	
		3,305	Black	—	13.9	20.9	
		3,477	Mexican Americans	—	20.8	27.2	
		5,581	White	—	24.3	22.9	
Venezuela	1999–2001	3,108	Overall	31.2	35.0	29.8	Florez <i>et al.</i> ¹⁴
		265	Amerindian	28.1	17.1	29.9	
		284	Black	29.4	27.2	30.9	
		385	White	30.9	33.3	30.9	
		2,174	Mixed	31.9	37.4	29.6	

ATPIII, National Cholesterol Education Program—Adult Treatment Program III; IDF, International Diabetes Federation; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; WC, waist circumference. —, studies that did not report results or were non-applicable to the given patient subgroup. Total number of patients represents the sum of both male and female participants, unless otherwise indicated. Total number of patients may not add up to the overall numbers due to primary authors of the above studies not reporting underrepresentative population groups.

ATPIII criteria, using BMI for waist circumference, to data from the West of Scotland Coronary Prevention Study,⁴⁶ and excluding patients with baseline T2DM, over a 4.9-year follow-up period, the HR in MetS patients for developing a CV event or diabetes was 1.76 and 3.50, respectively. MetS continued to predict CV disease in a multivariate model incorporating traditional CV risk factors (HR: 1.30). Their data also suggested that men with a high number of metabolic abnormalities will augment the risk for developing both diabetes and CV disease. In particular, over four metabolic abnormalities would lead to a 3.7 and 24.5 times risk of CV event and diabetes, respectively. Similar results were observed in 12,089 patients, free of T2DM and CV disease at baseline, in the Atherosclerosis in Risk Community Study,⁴⁴ where 23% of patients fulfilled ATPIII-defined MetS. The HR for coronary heart disease in MetS patients was 2.05 and 1.46 in women and men, respectively. Their results demonstrated that as the number of components of MetS increases, so does the risk of developing coronary heart disease, but more so in women than in men. Recently, in 3,234 participants with impaired glucose tolerance in the Diabetes Prevention Program,³⁸ a Cox proportional hazards model was used to assess the effect of AHA/NHLBI-defined MetS and components on diabetes developing over 3.2 years of follow-up. They found that adding MetS had prognostic value and that its presence increased the risk of diabetes. After excluding the effect of fasting glucose, waist circumference was the most important predictor of diabetes, and the presence of obesity and/or high triglycerides (TGs) identified patients with higher T2DM risk.

Two recent meta-analyses have examined CV disease risk and mortality in MetS patients.^{13,39} The first analysis³⁹ examined a total of 21 prospective cohort studies (11 conducted in the United States, 10 in Europe), with sample sizes varying from 318 to 19,223 patients. Overall, RRs of CV disease for 16 ATPIII studies and 5 WHO studies were 1.61 and 1.82, respectively. The combined RR was 1.61. The RRs for all-cause mortality and CV mortality were 1.35 and 1.74 (six studies each), respectively. A second analysis by Gami *et al.*¹³ examined 37 eligible studies and confirmed these results, demonstrating that the RR of CV events and death was 1.78 in MetS patients (Figure 2). We believe that the above data indeed prove that MetS, regardless of the definition used, certainly increases CV risk.

CONTROVERSIES SURROUNDING THE METABOLIC SYNDROME

Variability of metabolic syndrome’s definition

Much has been written as to the legitimacy of MetS as a real “syndrome” or whether it is the culmination of different factors needing individual treatment.⁵⁵ Yet credence to its existence stems from the International Classification of Disease 9 code that it has been assigned.⁵⁵ The goal of MetS concept is practitioner identification of patients at higher risk of developing CV disease or T2DM, as described by the AHA/NHLBI and ATPIII.¹⁰ Abdominal obesity is defined differently by the ATPIII and IDF. None of the definitions of MetS incorporate any of the traditional or non-traditional CV risk factors, including smoking, physical inactivity, family history, elevated low-density lipoprotein cholesterol (LDL-C), or prothrombotic and proinflammatory markers,

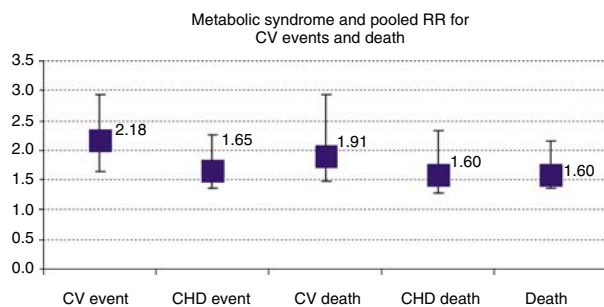


Figure 2 The pooled RR for CV events and death in patients with the metabolic syndrome. There were 11 studies examined for CV events, 18 studies for coronary heart disease (CHD) events, 10 studies for CV death, 7 studies for CHD death, and 12 studies for death. The squares on the graph represent the pooled RRs, and the bars represent the 95% confidence intervals. The data were adapted from Gami *et al.*¹³

or microalbuminuria (other than the WHO definition⁶), all of which are known to increase cardiac risk.⁵⁶ Furthermore, it is unclear whether patients with established diagnoses or those receiving treatments for these disorders should be included or not. Prevalence varies by study, much of which is dependent on the definition applied, the study design, time to follow-up, and whether or not patients with diabetes are included.

There is limited information comparing all of these definitions head-to-head to draw any meaningful conclusions regarding which definition is the most optimal to predict risk for CV disease or T2DM.^{45,50,57-60} In one study, an additional 9% of patients were classified as having MetS using the AHA/NHLBI criteria over the ATP III criteria.⁴³ Using the Dallas Health Study, NHANES III, and the Prospective Cardiovascular Munster Study, application of the ATP III and IDF definitions demonstrated that the prevalence of MetS in the US population was higher than in the European sample when the ATP III criteria were used, but the converse was true when the IDF definitions were applied to the same patient cohorts.⁵⁷ The predictive power for coronary events was less using the IDF criteria. The authors attributed these differences to the definition of abdominal obesity. Tong *et al.*⁵⁰ examined 4,350 diabetic patients and also found that IDF criteria failed to identify the subgroup of patients who had the highest risk of CV disease. The ATP III definition identified 786 additional subjects (18.1%) with MetS that did not fulfill the IDF criteria.

Balkau *et al.*³⁰ used the WHO and EGIR definitions in a cohort of 17,563 volunteers to determine the frequency of MetS. Using WHO-defined criteria, the prevalence varied from 7 to 36% in male subjects and from 5 to 22% in female subjects. Using the EGIR definitions, the prevalence was 1-22% in male subjects and 1-14% in female subjects. The authors concluded that there was great variability in the prevalence of its MetS syndrome due to inherent population and definition differences. To the contrary, studies in India did not find any differences in prevalence, using ATP III and EGIR definitions, at 12.8 and 11.2%, respectively.^{31,32}

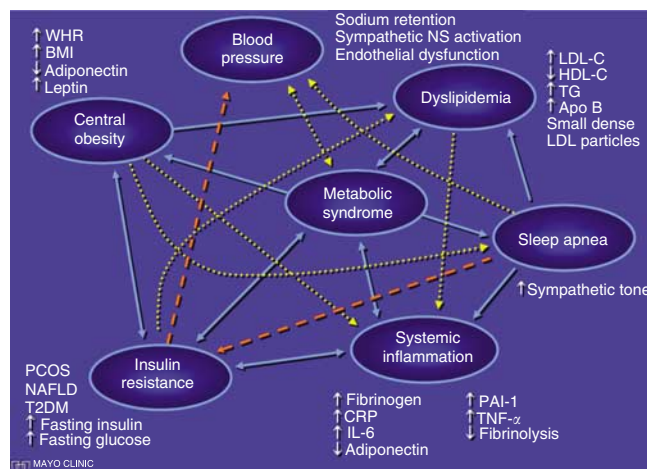


Figure 3 Six circles reflecting the differing pathophysiological mechanisms that are implicated in the metabolic syndrome. Metabolic syndrome is at the center of this diagram, which emphasizes that no one mechanism is responsible for explaining the syndrome and that each of these components is likely to have an impact on its prevalence and pathophysiology. Apo, apolipoprotein; BMI, body mass index; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; NAFLD, non-alcoholic fatty liver disease; NS, nervous system; PAI-1, plasminogen-activating inhibitor-1; PCOS, polycystic ovarian syndrome; T2DM, type 2 diabetes mellitus; TG, triglyceride; TNF, tumor necrosis factor; WHR, waist-hip ratio.

Numerous other comparisons exist that report concordance rates between ATP III and IDF criteria.⁵⁸⁻⁶⁰ Currently, we agree that despite the inconsistent definitions, patients assessed for MetS should be managed not only for traditional CV risk factors but also for factors that may be associated with MetS (Figure 3).

Thresholds and dichotomizing variables

Using thresholds to dichotomize a variable as normal/abnormal is widely applied in medicine to facilitate clinical decision making.⁶¹ Unfortunately, there is a tradeoff in the process of selecting thresholds to define normality. First, extremely abnormal values for any particular criterion receive the same weight as values that are barely abnormal, even though the risk for adverse events related to several components of MetS is either linear or exponential.^{9,35,62,63} Conversely, some patients may be misclassified as “normal” when indeed they have values that are close to the upper limit of normal. This is particularly relevant to waist circumference, given the significant interobserver variability of waist measurements,⁶⁴ and also because certain races or ethnic groups might be susceptible to metabolic dysregulation with waist circumference values that are not large enough to be called abnormal. Indeed, just by altering the cutoff for central obesity adjusted by race, the prevalence of MetS can be significantly different.^{29,33} Modifying waist circumference appropriate for the Indian population (90 cm for male subjects and 85 cm for female subjects), for instance, demonstrated that ATP III-defined prevalence was markedly higher at 41.1%.³³ Laaksonen *et al.*²⁹ modified waist circumference

measurements to 94 cm in the EGIR and ATP III definitions and found that the respective prevalence of MetS was 3.8% lower and 6.8% higher, respectively. Finally, the selection of cutoff points has been arbitrary, in the most part, and not guided by biological and epidemiological principles of normality. Indeed, all of MetS parameters are somehow related to CV risk in a linear manner. Moreover, the AHA/NHLBI definition¹⁰ considers patients under treatment for hypertension or dyslipidemia as qualifying for the blood pressure or dyslipidemia domains, regardless of the level of control they may have for those disease conditions. Further research would be required to systematically examine the thresholds of each MetS component on the incident and incremental risk (if any) of CV disease or to use categories for each variable instead of being present or absent. This may facilitate appropriate CV risk stratification.

Number of criteria required to fulfill the diagnosis

The number of criteria required to fulfill the diagnosis of MetS varies from method to method. The AHA/NHLBI definition,¹⁰ which is probably the most widely used definition of MetS, requires three or more criteria, even though the risk for CV events and mortality is directly proportional to the number of criteria present, from 0 to 5. The main problem with this approach is the assumption that each one of the criteria has a similar risk value. However, studies assessing the prognostic value of each of the five criteria have shown different levels of association, the highest to low high-density lipoprotein (HDL) levels and the lowest to elevations of TGs, based on β -coefficients from multivariate logistic regression analyses.^{9,38,41,44,46-49} The second limitation with this approach is that it assumes complete independence among all criteria, when in reality there is a significant and not uniform correlation among all criteria. Finally, the selection of a cutoff number of criteria to make the diagnosis clusters people with a very high risk for diabetes and CV disease (those with five criteria) with those who fulfill only three criteria. This also clusters patients who were very close in qualifying for the diagnosis, with two criteria, with those who are perfectly healthy, with no criteria.

Ideally, MetS should have been considered more as a risk score for either adverse events or the development of diseases, rather than as a yes or no parameter. Indeed, risk functions such as the Framingham⁶⁵ and the United Kingdom Prospective Diabetes Study (UKPDS)⁶⁶ use several parameters as categorical instead of binomial to classify patients according to the total risk score. This could explain why MetS definitions fall short in predicting risk for either coronary artery disease or T2DM when compared to the Framingham risk score.⁴⁸ Obviously, a multidimensional parameter system that takes into account correlative item-dependent risk values will have a higher level of complexity and probably a limited use in clinical practice.

Pathophysiological basis of metabolic syndrome

This is a point of contention among the different organizations. Although insulin resistance plays an important role in

fatty acid and glucose tolerance, it fails to explain the alterations observed in lipid metabolism, blood pressure, endothelial dysfunction, systemic inflammation, and hypercoagulability. In addition, in one study,⁶⁷ only 48% of patients with insulin resistance had ATP III-defined MetS, but 78% of patients with MetS had insulin resistance. Laboratory and clinical measurement of insulin resistance is difficult, and although studies have used fasting insulin levels as a surrogate, lack of assay standardization makes this approach impractical.⁶⁸ Other proponents have suggested that although abdominal obesity may be the root cause, yet insulin resistance will occur in up to 15% of non-obese patients.⁶⁹ Elevated free fatty acids can impair insulin sensitivity, promote hypercholesterolemia, and impact endothelial dysfunction, thereby promoting hypertension.⁷⁰ Adipose tissue has been shown to be an active endocrine organ releasing adipokines, impacting insulin resistance, affecting inflammatory cytokines, and influencing CV risk by playing a role in dyslipidemia, hypertension, and impaired glucose tolerance, further strengthening the association between obesity and inflammation.⁷⁰ There are likely other unmeasurable factors or entities, which are yet to be characterized, that may provide the link necessary to truly understand the pathophysiology of this syndrome.

The American Diabetes Association often questions not only the utility of the syndrome, as it is poorly defined, but also whether the components of MetS are associated with insulin resistance.⁵⁵ They argue that CV risk using individual components, as measured by the Framingham risk score, would be equal rather than additive. However, Malik *et al.*⁴⁰ described the predictive value of each additional criterion for MetS and found that as the numbers increase, so does the risk for CV disease. Unfortunately, even universally adopted cardiac risk scores, such as the Framingham, omit obesity, BMI, or measures of glucose intolerance as part of the equation, and hence may actually underestimate the risk.⁷¹ A recently published statement by the American Heart Association and American Diabetes Association⁷² demonstrated commitment to the long-term reduction of CV disease and diabetes, acknowledging the unresolved scientific issues in the literature. They believe that aggressive lifestyle modifications and weight loss in the early stages of each individual disease condition are warranted.

Should we treat the syndrome or each of the individual factors? MetS represents a clinical spectrum whereby there exists a lag time between disease onset and clinical manifestations of diabetes, hypertension, and dyslipidemia. By delaying the identification of high-risk patients, clinicians may lose the window period to intervene in borderline or subthreshold abnormality patients until they develop a disease. Although this has not been demonstrated in a randomized way, it is possible that patients will be more likely to make lifestyle changes if they are diagnosed with conditions that are associated with a high risk of developing CV disease and diabetes.

TREATMENT OF METABOLIC SYNDROME

The treatment of MetS requires targeting the most prevalent cause of it, namely a sedentary lifestyle along with inappropriate diet. The treatment also requires medical management of dyslipidemia, hypertension, and obesity when conservative management has failed or when numbers exceed thresholds already defined by medical organizations. Thus, treatment regimens include lifestyle modification, including exercise and dietary modifications in efforts to lose weight, pharmacological and surgical interventions, and managing risk factors in attempts to reduce the risk of developing T2DM or CV disease (Table 4). We aim to highlight key trials regarding these entities.

Lifestyle modifications

Exercise. Physical activity has clearly been shown to improve glucose tolerance, improve insulin sensitivity, and reduce the risk of CV disease.⁷³ Reductions in adipose tissue, particularly visceral fat, may mediate insulin sensitivity following weight loss. The Diabetes Prevention Trial randomized patients to an intervention group vs a placebo group, with a mean follow-up of 3.2 years, to assess whether the onset of diabetes could be prevented.⁷⁴ The cumulative incidence of diabetes was lower in the intervention group in contrast to the control group (11 vs 23%), with a 58% reduction in the risk of diabetes. Ekelund *et al.*,⁷⁵ using physical activity energy expenditure methods, determined that over a period of 5.6 years, patients with higher expenditures had a lower rate of progression to MetS, as defined by the WHO.

Regular exercise is known to improve other metabolic variables such as insulin and leptin levels in patients who may be overweight or obese.⁷⁶ Cox *et al.*⁷⁷ have shown the additive effects of caloric restriction and vigorous energy expenditure on fasting glucose and insulin levels. Both exercise-induced weight loss and exercise without weight loss have been proven to reduce abdominal fat, itself a predictor of insulin resistance and dyslipidemia. Both aerobic and resistance activity coupled with dietary restrictions are known to improve fasting insulin and oral glucose tolerance test insulin levels, which are greater than those seen in diet alone.⁷⁸ Torjesen *et al.*⁷⁹ reported that insulin resistance was inversely related to a diet and exercise intervention but was positively correlated with BMI.

Katzmarzyk *et al.*⁸⁰ examined the impact of cardiorespiratory fitness on the development of MetS and its effect on CV disease and all-cause mortality using 19,223 men from the Aerobics Center Longitudinal Study. The RR of all-cause mortality and CV disease was not surprisingly higher in MetS patients, but after including cardiorespiratory fitness in their model, these associations were no longer significant, suggesting that increased mortality risk was attributed to this entity. These results were further corroborated in a subsequent study by the same group.⁸¹ The OR of having MetS in obese patients compared to normal weight patients was 30.6. In patients with MetS, obese patients had higher

Table 4 Therapeutic recommendations for MetS patients

Metabolic risk factor	Therapeutic recommendation
Central/abdominal obesity	Lifestyle modifications encouraging patients to lose weight through a balanced diet, physical activity program, and behavioral modifications. Pharmacotherapy using sibutramine, orlistat, and rimonabant may be useful. Bariatric surgery can be recommended in patients who fulfill prespecified criteria
Physical inactivity	Encourage at least 30 min of aerobic exercise a minimum of 5 days/week, preferably daily. Provide patients with an exercise prescription that includes details about the type, amount, duration, and intensity of the recommended exercise. Set a target heart rate and perceived effort as a measure of intensity. Encourage incorporating non-exercise physical activity in daily life
Dietary indiscretion	Limit caloric intake and use of added sugar. Consider using the glycemic index as a guide to identify highly refined carbohydrates. Decrease the intake of saturated fats and allow modest amounts of mono- or polyunsaturated fats. Use the Dietary Approaches to Stop Hypertension diet for patients with hypertension or prehypertension. Consider referral to a dietitian
Dyslipidemia	Initially aim to reduce LDL-C according to the goals of the ATPIII ⁹ criteria. Once achieved, aim to target non-HDL cholesterol followed by reducing HDL-C
Blood pressure	Aim to reduce blood pressure according to the goals of the JNC VII criteria ⁶²
Impaired fasting glucose	Aim to implement lifestyle modifications to prevent development of T2DM
Diabetes mellitus	Reduce HbA1c to below 6.5%; ensure patients receive regular physical examinations, ophthalmological visits, and aggressive blood pressure and lipid evaluations. Encourage use of aspirin for cardiovascular disease prevention

ATPIII, National Cholesterol Education Program—Adult Treatment Panel III; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; JNC, Joint National Committee; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus.

OR for all-cause mortality (1.55 vs 1.09) and CV disease (2.83 vs 2.06) compared to normal weight patients. As in their previous study, these associations, however, became insignificant following the inclusion of cardiorespiratory fitness in their model.

Lifestyle interventions are a key to any program of weight loss, and the current literature proves its impact not only on the traditional CV risk factors but also on glucose tolerance and insulin sensitivity.^{78,79,82} However, these authors must caution readers that the vast majority of studies are cross-

sectional and are subjected to numerous biases. Further prospective studies are needed to better clarify the risk of developing MetS in patients undergoing an exercise program. Physical activity and diet are likely inversely related to the development of MetS.

Diet. Caloric restriction in MetS patients who are obese or overweight should be a cardinal focus of dietary therapy. Dietary modification is a key component to any weight loss program. The influence of diet on CV function has been well delineated,⁸³ but increasing evidence has surfaced about the composition of particular macronutrients that may favorably affect the patient's metabolic profile. For this, preliminary data demonstrated that the Mediterranean diet may be superior to the standard low-fat or very low-fat diets.^{84,85} The Mediterranean diet comprises a spectrum of dietary regimens observed among countries such as Spain, Italy, Greece, and France. Characteristics of the diet include the consumption of a large amount of olive oil, wheat, grapes, and their derivatives. The ratio of monounsaturated to saturated fats is higher than in diets consumed in the United States or northern Europe. Furthermore, the consumption of cheese, wine, fish, and omega-3 fatty oils is relatively high. Much interest has surfaced in the impact of this diet, as it has been associated epidemiologically with improvements in CV risk factors,⁸⁶ prolonged survival, and has been cited in an AHA statement as improving CV morbidity.⁸⁴ A recent study by Esposito *et al.*⁸⁵ found that Mediterranean diet-treated patients compared to those with standard dietary intake had lost 2.8 kg more in a 2-year period and had improved serum concentrations of inflammatory markers, including high-sensitivity C-reactive protein, decreased insulin resistance, and interleukin-6, with improved endothelial function. Patients treated with the Mediterranean diet, compared to the control diet, had a 43 vs 17% reduction in MetS prevalence.

Dansinger *et al.*⁸² evaluated, in a single-center randomized trial of overweight or obese adults with hypertension, dyslipidemia, or impaired fasting glucose, the degree of weight loss and changes in lipid, insulin, and C-reactive protein levels between patients following the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss. These diets are meant to restrict carbohydrates, fat, macronutrients and glycemic loads, and portions and calories, respectively. Regardless of the diet employed, total and high-density lipoprotein cholesterol (HDL-C), C-reactive protein, and improvements in insulin levels were associated with weight loss, but there were no effects on glucose or blood pressure. A limitation of this study included the high number of non-compliers to these diets (35–50%). The Atkins diet (low-carbohydrate) may be a particularly useful diet in MetS patients. In a study examining 132 obese adults with a BMI > 35 kg/m², 83% having diabetes or MetS, weight change was not different comparing conventional vs low-carbohydrate diet, but there were improvements in the latter group in HDL-C, serum TG, and hemoglobin A1c (HbA1c) levels.⁸⁷

One recent randomized crossover study determined the use of soy in MetS.⁸⁸ In the 42 postmenopausal female subjects with MetS, a diet fortified with either soy-protein or soy-nut found improvements in fasting glucose, LDL-C, and reductions in C-peptide concentrations. This study did not determine the change in prevalence of MetS following therapy.

Pharmacological management

Insulin sensitizers and biguanides. The uses of insulin sensitizers and biguanides such as metformin and thiazolidinediones have been studied extensively in patients with polycystic ovarian syndrome, a patient population that is believed to have an element of insulin resistance. Literature exists regarding their use in T2DM, which is outside the scope of this review. Orchard *et al.*⁸⁹ randomly assessed the impact of metformin 850 mg twice daily, intensive lifestyle intervention, and placebo (standard lifestyle intervention) on 3,234 patients from the Diabetes Prevention Program. They defined intensive lifestyle intervention as a weight reduction of at least 7% of body weight with a low-calorie, low-fat diet with moderate-intensity physical activity of 150 min/week. In patients without ATPIII-defined MetS at baseline, 53% had acquired MetS in the placebo arm compared to 38% in the lifestyle group and 47% in the metformin group at 3 years. Using proportional hazard modeling, there was a reduction of 41 and 17% in the incidence of MetS compared to placebo in the lifestyle and metformin groups, respectively. In these patients, lifestyle interventions reduced all ATPIII-defined MetS components with the exception of HDL, whereas metformin reduced waist circumference and fasting glucose values. In patients who had MetS at baseline, prevalence decreased by 18% in placebo, 23% in the metformin group, and 38% in the lifestyle group. Despite the implicit selection bias for impaired glucose tolerance, these data suggest improved incidence of MetS and possibly further reductions in CV disease. However, the Diabetes Prevention Program Research group has prospectively demonstrated that in non-diabetic patients with elevated fasting glucose, lifestyle interventions with metformin use were associated with reduced incidence of diabetes.⁹⁰ Details on CV outcomes from this study are still pending.

Derosa's group in Italy has examined the impact of insulin sensitizers in MetS patients. They randomized a cohort with T2DM and MetS to glimepiride/metformin or rosiglitazone/metformin and found improved insulin resistance parameters in the latter group.⁹¹ The same group examined the impact of coadministration of metformin and thiazolidinediones in ATPIII-defined MetS patients on coagulation and fibrinolysis parameters and demonstrated that patients administered pioglitazone had reduced HbA1c, fasting glucose, and improved insulin resistance indices and decreased plasminogen-activating inhibitor-1 levels.⁹² Similar results were observed in the rosiglitazone-treated group as well. However, there was no placebo group to enable any appropriate conclusions to be made about the use of this class of medications in MetS.

A recent meta-analysis has demonstrated the risks of rosiglitazone on the development of CV outcomes and death.⁹³ After evaluating 42 trials in which the mean age of patients was 56 years, the OR for myocardial infarction was 1.43, whereas the OR for CV death was 1.64 compared to placebo or other diabetic medications (metformin or sulfonyleureas). These results have particular implications for the diabetic population, as CV disease accounts for 65% of their deaths.⁹⁴ A follow-up interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes trial⁹⁵ demonstrated no difference in CV disease and mortality risk after 3 years in 4,447 T2DM patients treated with rosiglitazone. This study, however, was underpowered. Presently, the American Diabetes Association and AHA recommend exercising caution when initiating or continuing insulin sensitizer drugs.

Orlistat. As an intestinal lipase inhibitor that is minimally absorbed systemically, orlistat can reduce dietary TGs and fat absorption. One study demonstrated that at 1 year, orlistat-treated patients lost 8.76 kg compared to 5.81 kg in the placebo group.⁹⁶ Patients receiving a higher dose of orlistat during year 2 of the study had less regain (3.2 kg) compared to those receiving the lower dose of 60 mg (4.26 kg) or placebo (5.63 kg). This medication also proved to significantly improve total cholesterol, LDL-C, HDL-C, TG, and fasting insulin levels. These results supported the European study led by Sjostrom *et al.*,⁹⁷ which demonstrated similar results.

A limited number of studies focus solely on patients with MetS.^{98–102} In the Xenical in the Prevention of Diabetes in Obese Subjects study,¹⁰¹ 3,304 patients, 40% of whom had MetS, were treated with orlistat vs placebo. The orlistat group lost 6.4 vs 2.9 kg in the placebo group and had favorable reductions in waist circumference, TGs, blood pressure, and improvements in HDL, with fewer patients progressing to T2DM than patients on diet alone (9.8 vs 13.7%). In the FenOrli study,¹⁰² after 3 months of treatment, 43.5% of patients no longer met ATPIII-defined MetS criteria, the results of which were corroborated in the ARCOS study.¹⁰⁰ Another study⁹⁹ investigated 94 patients with ATPIII-defined MetS but free of CV disease and demonstrated improvements in body weight, dyslipidemia, and insulin resistance after a 6-month trial of orlistat. There was a 35% reduction in the number of patients fulfilling the criteria for MetS. Triglyceridemia was reduced in obese, non-diabetic patients with ATPIII MetS in another study following treatment with orlistat.⁹⁸ Gastrointestinal side effects limit its tolerability and use, and hence clinicians must weigh the risks/benefits of recommending this medication for the purposes of treating MetS.

Sibutramine. Sibutramine was initially developed as a weight-loss-inducing antidepressant that acts by inhibiting norepinephrine and serotonin reuptake in the central nervous system, leading to a sense of satiety and fullness.

The European Sibutramine trial of Obesity Reduction and Maintenance study examined the impact of sibutramine following a 6-month hypocaloric diet-induced weight loss (net deficit of 600 kcal/day).¹⁰³ In the 467 randomized patients who completed the trial, 43% maintained 80% of their original weight loss compared to 16% in the placebo arm. At the study completion, 69% maintained a 5% weight loss, 46% maintained a 10% weight loss, and 27% maintained full initial weight loss. Secondary outcomes examined individual components of MetS (as opposed to a diagnosis as a whole), including biochemical lipid markers, insulin, and C-peptide levels, all of which improved and were sustained. This study was unfortunately plagued by a high attrition rate of 42% in the treatment arm and 50% in the placebo arm.

In another study, Wadden *et al.*¹⁰⁴ randomized 224 obese patients to a hypocaloric diet of 1,200–1,500 kcal/day with an exercise regimen for 1 year to one of four arms—sibutramine-only, lifestyle modification counseling delivered in a group session alone, sibutramine with group counseling sessions, or sibutramine with lifestyle modification counseling delivered by a primary care provider. At 1 year, there was a loss of 5.0, 6.7, 7.5, and 12.1 kg, respectively, in each of these groups. At 1 year, of subjects losing at least 5% of their initial weight, 73, 42, 53, and 56% of patients, respectively, in each of these groups fulfilled these criteria. Furthermore, 52% of patients in the combined medication and group counseling approach lost at least 10% of their weight compared to those in the other arms. Their secondary outcomes examined the impact of these study arms on CV risk factor change, in particular components of MetS, but the authors did not observe any significant differences. However, overall significance combining the four groups suggested that there were improvements in TGs, glucose, insulin resistance, total cholesterol, and HDL-C. Sibutramine should be used adjunctively in lieu of an alternative to lifestyle modifications for weight loss. The data presented above suggest that the degree of weight loss is modest at best. Unfortunately, no studies examine its use exclusively in MetS patients, although improvements in its individual components are undoubtedly convincing. Further studies using this medication in MetS would be warranted.

Phentermine. This agent has been available for many years and its use as a weight loss therapy has been somewhat precluded by the adrenergic response in increasing blood pressure and heart rate, which may be harmful in patients at higher risk for CV disease. Haddock *et al.*¹⁰⁵ examined six studies ranging from 2 to 24 weeks of treatment with phentermine plus lifestyle modification and found that there was a mean loss of 6.3 kg compared to 2.8 kg lost with placebo. With safer and more promising medications on the horizon, this medication has fallen out of favor in our practice.

Rimonabant. This is a new, exciting, and promising agent for the treatment of obesity that works as an endocannabi-

noid-1 receptor blocker. This receptor is located in the central and peripheral nervous system, adipose tissue, the gastrointestinal tract, liver, and muscle. It prevents weight gain by abating the overactivation of the endocannabinoid system both centrally and peripherally, regulating energy balance and body composition. Adipose tissue stimulation of these receptors inhibits adiponectin production and promotes lipogenesis, all of which have significant implications on endothelial, atherosclerotic, and insulin sensitivity function.^{106,107} In addition, the use of this medication does not cause an increase in heart rate or blood pressure, as do some of the other appetite suppressants. The Rimonabant in Obesity (RIO)-North America trial,¹⁰⁸ which compared the efficacy and safety of this medication with placebo, combined with dietary and exercise modifications, was a large randomized, double-blinded, placebo-controlled trial of both obese and overweight patients, aimed at determining body weight change and maintenance of weight loss, with secondary outcomes on cardiometabolic factors. Although the dropout rate of the study was high (49%), preliminary data illustrated sustained weight loss at 2 years. There was also a significant reduction in ATPIII-defined MetS from 34.8 to 21.2% using rimonabant compared to 31.7 to 29.2% using placebo. Other RIO trials have demonstrated similar results on weight and lipid parameters, including the RIO diabetes trials,^{109,110} which showed a reduction in the prevalence of MetS from 79 to 64%.¹¹⁰ The RIO-Lipids trial evaluated the use of 20 mg of rimonabant on untreated dyslipidemia by randomizing 1,036 patients with a BMI between 27 and 40 kg/m² to a hypocaloric diet with either rimonabant or placebo.¹¹¹ This study demonstrated significant improvements in weight (-6.7 kg), HDL-C (+10.0 mg/dl (0.26 mmol/l)), TGs (-13.0 mg/dl (0.15 mmol/l)), and adiponectin levels (+57.7%) at 12 months, corresponding to a 23.4% increase in HDL-C levels and 15.8% decrease in HDL levels but no change in LDL-C levels. Plasma adiponectin levels also increased. These trials suggest that endocannabinoid receptor blockers are indeed a promising approach in promoting weight loss and improving lipid parameters, both of which are cardinal features of MetS. Although rimonabant is commercially available in Europe and Argentina, it has yet to be approved by the Food and Drug Administration in the United States.

Surgical management: bariatric surgery

Bariatric surgery is an effective weight loss treatment for patients with class II or III obesity who fulfill prespecified criteria. The Roux-en-Y gastric bypass is the most commonly performed procedure in the United States and is associated with the fewest complications and lowest potential for long-term weight regain compared with other procedures.^{112,113} Its safety has been demonstrated in patients with pre-existing coronary artery disease.¹¹⁴ The impact of bariatric surgery on CV risk factors has been well established.¹¹⁵ CV risk modeling using the NHANES I and NHANES I Epidemiological Follow-up Studies data sets demonstrated significant

reductions in all-cause mortality, CV mortality, and CV events in an operatively treated group compared to a non-operatively managed group.¹¹⁶ Two other recently published studies have confirmed these data using the Framingham risk score,^{117,118} although this score⁶⁵ does not factor BMI or weight into its equation, thereby likely underestimating the additive impact of obesity on CV risk. Long-term CV disease outcomes are limited, but all have demonstrated reductions in CV events.^{119,120} The study by MacDonald *et al.*¹¹⁹ demonstrated that in T2DM patients, mortality was lower in the surgical group, predominantly because of a reduction in CV deaths. Sampalis *et al.*¹²⁰ used administrative data to show that RRs at 5 years of myocardial infarction, angina pectoris, and pulmonary edema were 0.71, 0.53, and 0.42, respectively, and all were significant.

Many patients who qualify for bariatric surgery often have MetS. Few studies have specifically examined its impact on MetS, and most were in European cohorts.¹²¹⁻¹²⁶ Gazzaruso *et al.*¹²¹ examined 51 premenopausal patients following the Swedish Adjustable Gastric Banding procedure and found a reduction in the prevalence of MetS from 58.8 to 21.6% using EGIR criteria. Mattar *et al.*¹²² found a reduction in ATPIII-defined MetS from 70 to 14% in a series of 70 patients undergoing laparoscopic Roux-en-Y gastric bypass, and Coppini *et al.*¹²³ demonstrated complete resolution at 1 year. Madan *et al.*¹²⁴ used similar criteria in 53 patients and determined a prevalence reduction at 1 year following laparoscopic Roux-en-Y from 78 to 2%. Finally, in two other studies, the prevalence of MetS was significantly reduced following gastric banding¹²⁵ and biliopancreatic diversion.¹²⁶ Lee *et al.*'s¹²⁷ prospective study results afford more credence, as bariatric surgery promoted a 95.6% resolution in 645 patients with ATPIII-defined MetS at 1 year following surgical intervention. Regardless of the definition or procedure used, bariatric surgery appears to reduce the prevalence of MetS.

Other promising interventions

With an increased understanding of the metabolically active role of adipose tissue in obese patients, promising new therapies will likely be available in targeting this disorder at the cellular and molecular level.

Exanetide is a newer class of medication termed incretin mimetics that affect glucagon-like peptide-1 receptors, which enhances insulin secretion not only by impairing gastric emptying and reducing food intake but also by inhibiting glucagon secretion. All studies thus far have been performed in patients with diabetes and no studies have specifically examined its impact on MetS. In combination with thiazolidinediones, with or without metformin, there is approximately a 1% reduction in HbA1c and a loss of 1.5 kg body weight compared to placebo, with concomitant improvements in lipid and blood pressure parameters.^{128,129} This medication is promising, but further investigation is required to recommend its use solely in MetS patients without diabetes.

Pramlintide is an amylin analog that has been studied exclusively in diabetic patients,^{130,131} demonstrating improvements in HbA1c and body weight. Amylin is believed to regulate the appearance of glucose into the circulation and may act centrally to regulate food intake and body weight. In one study, HbA1c was reduced by 0.41% and patients lost 1.8 kg from baseline, with patients randomized to 120 μ g of pramlintide twice daily.¹³¹ Thompson's results included measurements of fasting lipids and found significant reductions in total cholesterol.¹³⁰

Peroxisome proliferator-activated receptors that are available include fenofibrate and gemfibrozil, both lipid modulators. Dual-receptor agonists (α and γ) have been tested. Muraglitazar monotherapy is effective at reducing HbA1c by 1.23% compared to placebo, achieving a fasting plasma glucose goal, improving TGs and HDL-C by 27 and 16%.¹³² However, a safety study evaluating muraglitazar in T2DM compared to either pioglitazone or placebo demonstrated a RR of 2.23 for death, myocardial infarction, or stroke in the muraglitazar-treated patient group.¹³³ The safety of this medication has precluded its clinical use.

CONCLUSION

On a global scale, obesity prevalence continues to worsen both in developed and developing countries. This epidemic is now followed by a worldwide epidemic of MetS. Younger children and adults are being faced with the dangers of dietary indiscretion and physical inactivity. Clearly standardized methods for defining MetS are needed not only to account for geographical and ethnic variation but also for proper data analysis in epidemiological studies. Future work should focus on delineating the underlying physiological disturbances in MetS patients. Although there are multiple categorizations of MetS, it is unclear if any one is superior to another, as all have their strengths and limitations. Irrespective of the definition used, MetS predicts increasing CV and T2DM risk, and nevertheless needs to be considered an entity in itself. We propose that clinicians identify patients who meet criteria or whose values approach the upper limit of normal, so they can be motivated to initiate or increase their physical activity level, lose weight, improve their diet, and if necessary, initiate pharmacologic or surgical treatment for optimal control of MetS and its components.

ACKNOWLEDGMENTS

This work was not supported by any fund.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

© 2007 American Society for Clinical Pharmacology and Therapeutics

1. Kylin, E. Studien uber das Hypertonie-Hyperglykämie-Hyperurikämiesyndrom. *Zentrabl. finnere. Med. Leipz.* **81**, 105–127 (1923).
2. Vague, J. Sexual differentiation, a factor affecting the forms of obesity. *Presse Med.* **30**, 339–340 (1947).
3. Albrink, M.J. & Meigs, J.W. The relationship between serum triglycerides and skinfold thickness in obese subjects. *Ann. NY Acad. Sci.* **131**, 673–683 (1965).

4. Avogaro, P., Battaglia, G., Pujatti, G., Chioin, R. & Locatelli, C. On an unusual syndrome of supraaortic stenosis, mental retardation and hypercalcemic facies. *Mal. Cardiovasc.* **8**, 631–647 (1967).
5. Reaven, G.M. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* **37**, 1595–1607 (1988).
6. Alberti, K.G. & Zimmet, P.Z. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet. Med.* **15**, 539–553 (1998).
7. Alberti, K.G., Zimmet, P. & Shaw, J. The metabolic syndrome—a new worldwide definition. *Lancet* **366**, 1059–1062 (2005).
8. Balkau, B. & Charles, M.A. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabet. Med.* **16**, 442–443 (1999).
9. Grundy, S.M. *et al.* Executive summary of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* **285**, 2486–2497 (2001).
10. Grundy, S.M. *et al.* Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* **112**, 2735–2752 (2005).
11. Einhorn, D. *et al.* American college of endocrinology position statement on the insulin resistance syndrome. *Endocr. Pract.* **9**, 237–252 (2003).
12. Genuth, S. *et al.* Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* **26**, 3160–3167 (2003).
13. Gami, A.S. *et al.* Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J. Am. Coll. Cardiol.* **49**, 403–414 (2007).
14. Florez, H. *et al.* Prevalence and risk factors associated with the metabolic syndrome and dyslipidemia in White, Black, Amerindian and Mixed Hispanics in Zulia State, Venezuela. *Diabetes Res. Clin. Pract.* **69**, 63–77 (2005).
15. Barbosa, P.J., Lessa, I., de Almeida Filho, N., Magalhaes, L.B. & Araujo, J. Criteria for central obesity in a Brazilian population: impact on metabolic syndrome. *Arq. Bras. Cardiol.* **87**, 407–414 (2006).
16. de Oliveira, E.P., de Souza, M.L. & de Lima, M.D. Prevalence of metabolic syndrome in a semi-arid rural area in Bahia. *Arq. Bras. Endocrinol. Metabol.* **50**, 456–465 (2006).
17. Ramirez-Vargas, E., Arnaud-Vinas, M.D. & Delisle, H. Prevalence of the metabolic syndrome and associated lifestyles in adult males from Oaxaca, Mexico. *Salud Publica Mex.* **49**, 94–102 (2007).
18. Chedraui, P. *et al.* Quality of life among postmenopausal Ecuadorian women participating in a metabolic syndrome screening program. *Maturitas* **56**, 45–53 (2007).
19. Royer, M. *et al.* The US National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III): prevalence of the metabolic syndrome in postmenopausal Latin American women. *Climacteric* **10**, 164–170 (2007).
20. Araneta, M.R., Wingard, D.L. & Barrett-Connor, E. Type 2 diabetes and metabolic syndrome in Filipina-American women: a high-risk nonobese population. *Diabetes Care* **25**, 494–499 (2002).
21. Flegal, K.M., Carroll, M.D., Kuczmarski, R.J. & Johnson, C.L. Overweight and obesity in the United States: prevalence and trends, 1960–1994. *Int. J. Obes. Relat. Metab. Disord.* **22**, 39–47 (1998).
22. Ogden, C.L. *et al.* Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* **295**, 1549–1555 (2006).
23. Ford, E.S. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the US. *Diabetes Care* **28**, 2745–2749 (2005).
24. Ford, E.S., Giles, W.H. & Dietz, W.H. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* **287**, 356–359 (2002).
25. Park, Y.W. *et al.* The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. *Arch. Intern. Med.* **163**, 427–436 (2003).
26. de Ferranti, S.D. *et al.* Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. *Circulation* **110**, 2494–2497 (2004).
27. Cook, S., Weitzman, M., Auinger, P., Nguyen, M. & Dietz, W.H. Prevalence of a metabolic syndrome phenotype in adolescents:

findings from the third National Health and Nutrition Examination Survey, 1988–1994. *Arch. Pediatr. Adolesc. Med.* **157**, 821–827 (2003).

28. Cameron, A.J., Shaw, J.E. & Zimmet, P.Z. The metabolic syndrome: prevalence in worldwide populations. *Endocrinol. Metab. Clin. North Am.* **33**, 351–375; table of contents (2004).

29. Laaksonen, D.E. *et al.* Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. *Am. J. Epidemiol.* **156**, 1070–1077 (2002).

30. Balkau, B. *et al.* Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. *Diabetes Metab.* **28**, 364–376 (2002).

31. Gupta, A. *et al.* Prevalence of diabetes, impaired fasting glucose and insulin resistance syndrome in an urban Indian population. *Diabetes Res. Clin. Pract.* **61**, 69–76 (2003).

32. Deepa, R., Shanthirani, C.S., Premalatha, G., Sastry, N.G. & Mohan, V. Prevalence of insulin resistance syndrome in a selected south Indian population—the Chennai urban population study-7 [CUPS-7]. *Indian J. Med. Res.* **115**, 118–127 (2002).

33. Ramachandran, A., Snehalatha, C., Satyavani, K., Sivasankari, S. & Vijay, V. Metabolic syndrome in urban Asian Indian adults—a population study using modified ATP III criteria. *Diabetes Res. Clin. Pract.* **60**, 199–204 (2003).

34. Azizi, F., Salehi, P., Etemadi, A. & Zahedi-Asl, S. Prevalence of metabolic syndrome in an urban population: Tehran Lipid and Glucose Study. *Diabetes Res. Clin. Pract.* **61**, 29–37 (2003).

35. Centers for Disease Control. The National Health and Nutrition Examination Surveys <<http://www.cdc.gov/nchs/nhanes.htm>>. Accessed 10 July 2007.

36. Onat, A. *et al.* Metabolic syndrome: major impact on coronary risk in a population with low cholesterol levels—a prospective and cross-sectional evaluation. *Atherosclerosis* **165**, 285–292 (2002).

37. Villareal, D.T. *et al.* Effect of lifestyle intervention on metabolic coronary heart disease risk factors in obese older adults. *Am. J. Clin. Nutr.* **84**, 1317–1323 (2006).

38. Florez, H. *et al.* Metabolic syndrome Increases diabetes risk in IGT subjects: effects across diabetes prevention program interventions. Abstract 1299-P. *American Diabetes Association 67th Scientific Session* (Chicago, IL, 2007); *Diabetes* **56**(6): Supplement June 2007.

39. Galassi, A., Reynolds, K. & He, J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am. J. Med.* **119**, 812–819 (2006).

40. Malik, S. *et al.* Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* **110**, 1245–1250 (2004).

41. Isomaa, B. *et al.* Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* **24**, 683–689 (2001).

42. Tong, W. *et al.* Age, gender and metabolic syndrome-related coronary heart disease in US adults. *Int. J. Cardiol.* **104**, 288–291 (2005).

43. McNeill, A.M. *et al.* Metabolic syndrome and cardiovascular disease in older people: The Cardiovascular Health Study. *J. Am. Geriatr. Soc.* **54**, 1317–1324 (2006).

44. McNeill, A.M. *et al.* The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. *Diabetes Care* **28**, 385–390 (2005).

45. Hunt, K.J., Resendez, R.G., Williams, K., Haffner, S.M. & Stern, M.P. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. *Circulation* **110**, 1251–1257 (2004).

46. Sattar, N. *et al.* Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* **108**, 414–419 (2003).

47. Lorenzo, C., Williams, K., Gonzalez-Villalpando, C. & Haffner, S.M. The prevalence of the metabolic syndrome did not increase in Mexico City between 1990–1992 and 1997–1999 despite more central obesity. *Diabetes Care* **28**, 2480–2485 (2005).

48. Wannamethee, S.G., Shaper, A.G., Lennon, L. & Morris, R.W. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch. Intern. Med.* **165**, 2644–2650 (2005).

49. Wilson, P.W., D’Agostino, R.B., Parise, H., Sullivan, L. & Meigs, J.B. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* **112**, 3066–3072 (2005).

50. Tong, P.C. *et al.* The usefulness of the International Diabetes Federation and the National Cholesterol Education Program’s Adult Treatment Panel III definitions of the metabolic syndrome in predicting coronary heart disease in subjects with type 2 diabetes. *Diabetes Care* **30**, 1206–1211 (2007).

51. Carle, F. *et al.* Diabetes incidence in 0- to 14-year age-group in Italy: a 10-year prospective study. *Diabetes Care* **27**, 2790–2796 (2004).

52. Bruno, G. *et al.* Metabolic syndrome as a predictor of all-cause and cardiovascular mortality in type 2 diabetes: the Casale Monferrato Study. *Diabetes Care* **27**, 2689–2694 (2004).

53. Cerutti, F. *et al.* Younger age at onset and sex predict celiac disease in children and adolescents with type 1 diabetes: an Italian multicenter study. *Diabetes Care* **27**, 1294–1298 (2004).

54. Yano, Y. *et al.* Tumor necrosis factor-alpha is associated with increased protein C activation in nonobese type 2 diabetic patients. *Diabetes Care* **27**, 844–845 (2004).

55. Kahn, R., Buse, J., Ferrannini, E. & Stern, M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* **28**, 2289–2304 (2005).

56. Grundy, S.M., Pasternak, R., Greenland, P., Smith, S. Jr. & Fuster, V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* **100**, 1481–1492 (1999).

57. Assmann, G. *et al.* Harmonizing the definition of the metabolic syndrome: comparison of the criteria of the Adult Treatment Panel III and the International Diabetes Federation in United States American and European populations. *Am. J. Cardiol.* **99**, 541–548 (2007).

58. Athyros, V.G. *et al.* Awareness, treatment and control of the metabolic syndrome and its components: a multicentre Greek study. *Hellenic J. Cardiol.* **46**, 380–386 (2005).

59. Guerrero-Romero, F. & Rodriguez-Moran, M. Concordance between the 2005 International Diabetes Federation definition for diagnosing metabolic syndrome with the National Cholesterol Education Program Adult Treatment Panel III and the World Health Organization definitions. *Diabetes Care* **28**, 2588–2589 (2005).

60. Adams, R.J. *et al.* Population comparison of two clinical approaches to the metabolic syndrome: implications of the new International Diabetes Federation consensus definition. *Diabetes Care* **28**, 2777–2779 (2005).

61. Pauker, S.G. & Kassirer, J.P. The threshold approach to clinical decision making. *N. Engl. J. Med.* **302**, 1109–1117 (1980).

62. Chobanian, A.V. *et al.* The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* **289**, 2560–2572 (2003).

63. Stamler, J., Vaccaro, O., Neaton, J.D. & Wentworth, D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* **16**, 434–444 (1993).

64. Rowland, M.L. Self-reported weight and height. *Am. J. Clin. Nutr.* **52**, 1125–1133 (1990).

65. Wilson, P.W. *et al.* Prediction of coronary heart disease using risk factor categories. *Circulation* **97**, 1837–1847 (1998).

66. Stevens, R.J., Kothari, V., Adler, A.I. & Stratton, I.M. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). *Clin. Sci. (Lond)* **101**, 671–679 (2001).

67. McLaughlin, T. *et al.* Use of metabolic markers to identify overweight individuals who are insulin resistant. *Ann. Intern. Med.* **139**, 802–809 (2003).

68. Ferrannini, E. & Balkau, B. Insulin: in search of a syndrome. *Diabet. Med.* **19**, 724–729 (2002).

69. Reaven, G.M. The metabolic syndrome: requiescat in pace. *Clin. Chem.* **51**, 931–938 (2005).

70. Fonseca, V.A. The metabolic syndrome, hyperlipidemia, and insulin resistance. *Clin. Cornerstone* **7**, 61–72 (2005).

71. D’Agostino, R.B. Sr., Grundy, S., Sullivan, L.M. & Wilson, P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* **286**, 180–187 (2001).

72. Eckel, R.H., Kahn, R., Robertson, R.M. & Rizza, R.A. Preventing cardiovascular disease and diabetes: a call to action from the American Diabetes Association and the American Heart Association. *Circulation* **113**, 2943–2946 (2006).

73. Wannamethee, S.G. & Shaper, A.G. Physical activity in the prevention of cardiovascular disease: an epidemiological perspective. *Sports Med.* **31**, 101–114 (2001).
74. Tuomilehto, J. *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* **344**, 1343–1350 (2001).
75. Ekelund, U. *et al.* Physical activity energy expenditure predicts progression toward the metabolic syndrome independently of aerobic fitness in middle-aged healthy Caucasians: the Medical Research Council Ely Study. *Diabetes Care* **28**, 1195–1200 (2005).
76. Frank, L.L. *et al.* Effects of exercise on metabolic risk variables in overweight postmenopausal women: a randomized clinical trial. *Obes. Res.* **13**, 615–625 (2005).
77. Cox, K.L., Burke, V., Morton, A.R., Beilin, L.J. & Puddey, I.B. Independent and additive effects of energy restriction and exercise on glucose and insulin concentrations in sedentary overweight men. *Am. J. Clin. Nutr.* **80**, 308–316 (2004).
78. Rice, B., Janssen, I., Hudson, R. & Ross, R. Effects of aerobic or resistance exercise and/or diet on glucose tolerance and plasma insulin levels in obese men. *Diabetes Care* **22**, 684–691 (1999).
79. Torjesen, P.A. *et al.* Lifestyle changes may reverse development of the insulin resistance syndrome. The Oslo Diet and Exercise Study: a randomized trial. *Diabetes Care* **20**, 26–31 (1997).
80. Katzmarzyk, P.T., Church, T.S. & Blair, S.N. Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. *Arch. Intern. Med.* **164**, 1092–1097 (2004).
81. Katzmarzyk, P.T., Church, T.S., Janssen, I., Ross, R. & Blair, S.N. Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. *Diabetes Care* **28**, 391–397 (2005).
82. Dansinger, M.L., Gleason, J.A., Griffith, J.L., Selker, H.P. & Schaefer, E.J. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA* **293**, 43–53 (2005).
83. Lichtenstein, A.H. *et al.* Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation* **114**, 82–96 (2006).
84. Kris-Etherton, P., Eckel, R.H., Howard, B.V., St Jeor, S. & Bazzarre, T.L. AHA Science Advisory: Lyon Diet Heart Study. Benefits of a Mediterranean-style, National Cholesterol Education Program/American Heart Association Step I Dietary Pattern on Cardiovascular Disease. *Circulation* **103**, 1823–1825 (2001).
85. Esposito, K. *et al.* Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* **292**, 1440–1446 (2004).
86. Estruch, R. *et al.* Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann. Intern. Med.* **145**, 1–11 (2006).
87. Stern, L. *et al.* The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann. Intern. Med.* **140**, 778–785 (2004).
88. Azadbakht, L. *et al.* Soy inclusion in the diet improves features of the metabolic syndrome: a randomized crossover study in postmenopausal women. *Am. J. Clin. Nutr.* **85**, 735–741 (2007).
89. Orchard, T.J. *et al.* The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann. Intern. Med.* **142**, 611–619 (2005).
90. Knowler, W.C. *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* **346**, 393–403 (2002).
91. Derosa, G. *et al.* Metabolic effects of pioglitazone and rosiglitazone in patients with diabetes and metabolic syndrome treated with metformin. *Intern. Med. J.* **37**, 79–86 (2007).
92. Derosa, G. *et al.* Long-term effect of glimepiride and rosiglitazone on non-conventional cardiovascular risk factors in metformin-treated patients affected by metabolic syndrome: a randomized, double-blind clinical trial. *J. Int. Med. Res.* **33**, 284–294 (2005).
93. Nissen, S.E. & Wolski, K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N. Engl. J. Med.* **356**, 2457–2471 (2007).
94. American Diabetes Association: Complications of Diabetes in the United States <<http://www.diabetes.org/diabetes-statistics/complications.jsp>>. Accessed 12 July 2007.
95. Home, P.D. *et al.* Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N. Engl. J. Med.* **357**, 28–38 (2007).
96. Davidson, M.H. *et al.* Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* **281**, 235–242 (1999).
97. Sjostrom, L. *et al.* Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet* **352**, 167–172 (1998).
98. Tzotzas, T., Samara, M., Constantinidis, T., Tziomalos, K. & Krassas, G. Short-term administration of orlistat reduced daytime triglyceridemia in obese women with the metabolic syndrome. *Angiology* **58**, 26–33 (2007).
99. Didangelos, T.P. *et al.* The ORLlistat and Cardiovascular risk profile in patients with metabolic syndrome and type 2 DIAbetes (ORLICARDIA) Study. *Curr. Med. Res. Opin.* **20**, 1393–1401 (2004).
100. Zanella, M.T. *et al.* Orlistat and cardiovascular risk profile in hypertensive patients with metabolic syndrome: the ARCOS study. *Arq. Bras. Endocrinol. Metabol.* **50**, 368–376 (2006).
101. Torgerson, J., Hauptman, J. & Boldrin, M. Efficacy of orlistat plus lifestyle changes in risk reduction of type 2 diabetes in obese patients with metabolic syndrome: a comparative analysis using National cholesterol Education Program Adult Treatment Panel III vs European Group for the Study of Insulin Resistance criteria. *Diabetologia* **47**, A249 (2004).
102. Filippatos, T.D. *et al.* Effect of orlistat, micronised fenofibrate and their combination on metabolic parameters in overweight and obese patients with the metabolic syndrome: the FenOrli study. *Curr. Med. Res. Opin.* **21**, 1997–2006 (2005).
103. James, W.P. *et al.* Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet* **356**, 2119–2125 (2000).
104. Wadden, T.A. *et al.* Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N. Engl. J. Med.* **353**, 2111–2120 (2005).
105. Haddock, C.K., Poston, W.S., Dill, P.L., Foreyt, J.P. & Ericsson, M. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. *Int. J. Obes. Relat. Metab. Disord.* **26**, 262–273 (2002).
106. Pagotto, U. & Pasquali, R. Fighting obesity and associated risk factors by antagonising cannabinoid type 1 receptors. *Lancet* **365**, 1363–1364 (2005).
107. Cota, D. *et al.* The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J. Clin. Invest.* **112**, 423–431 (2003).
108. Pi-Sunyer, F.X., Aronne, L.J., Heshmati, H.M., Devin, J. & Rosenstock, J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* **295**, 761–775 (2006).
109. Hollander, P. Endocannabinoid blockade for improving glycemic control and lipids in patients with type 2 diabetes mellitus. *Am. J. Med.* **120**, S18–S28; discussion S29–S32 (2007).
110. Scheen, A.J., Finer, N., Hollander, P., Jensen, M.D. & Van Gaal, L.F. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. *Lancet* **368**, 1660–1672 (2006).
111. Despres, J.P., Golay, A. & Sjostrom, L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N. Engl. J. Med.* **353**, 2121–2134 (2005).
112. Pope, G.D., Birkmeyer, J.D. & Finlayson, S.R. National trends in utilization and in-hospital outcomes of bariatric surgery. *J. Gastrointest. Surg.* **6**, 855–860; discussion 861 (2002).
113. Sjostrom, L. *et al.* Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N. Engl. J. Med.* **351**, 2683–2693 (2004).
114. Lopez-Jimenez, F., Bhatia, S., Collazo-Clavell, M.L., Sarr, M.G. & Somers, V.K. Safety and efficacy of bariatric surgery in patients with coronary artery disease. *Mayo Clin. Proc.* **80**, 1157–1162 (2005).
115. Buchwald, H. *et al.* Bariatric surgery: a systematic review and meta-analysis. *JAMA* **292**, 1724–1737 (2004).
116. Batsis, J.A. *et al.* Effect of weight loss on predicted cardiovascular risk: change in cardiac risk after bariatric surgery. *Obesity (Silver Spring)* **15**, 772–784 (2007).
117. Torquati, A., Wright, K., Melvin, W. & Richards, W. Effect of gastric bypass operation on Framingham and actual risk of cardiovascular events in class II–III obesity. *J. Am. Coll. Surg.* **204**, 776–782 (2007).

118. Vogel, J.A. *et al.* Reduction in predicted coronary heart disease risk after substantial weight reduction after bariatric surgery. *Am. J. Cardiol.* **99**, 222–226 (2007).
119. MacDonald, K.G. Jr. *et al.* The gastric bypass operation reduces the progression and mortality of non-insulin-dependent diabetes mellitus. *J. Gastrointest. Surg.* **1**, 213–220; discussion 220 (1997).
120. Sampalis, J.S., Sampalis, F. & Christou, N. Impact of bariatric surgery on cardiovascular and musculoskeletal morbidity. *Surg. Obes. Relat. Dis.* **2**, 587–591 (2006).
121. Gazzaruso, C. *et al.* Weight loss after Swedish adjustable gastric banding: relationships to insulin resistance and metabolic syndrome. *Obes. Surg.* **12**, 841–845 (2002).
122. Mattar, S.G. *et al.* Surgically-induced weight loss significantly improves nonalcoholic fatty liver disease and the metabolic syndrome. *Ann. Surg.* **242**, 610–617; discussion 618–620 (2005).
123. Coppini, L.Z., Bertevello, P.L., Gama-Rodrigues, J. & Waitzberg, D.L. Changes in insulin sensitivity in morbidly obese patients with or without metabolic syndrome after gastric bypass. *Obes. Surg.* **16**, 1520–1525 (2006).
124. Madan, A.K., Orth, W., Ternovits, C.A. & Tichansky, D.S. Metabolic syndrome: yet another co-morbidity gastric bypass helps cure. *Surg. Obes. Relat. Dis.* **2**, 48–51; discussion 51 (2006).
125. Giusti, V., Suter, M., Heraief, E., Gaillard, R.C. & Burckhardt, P. Effects of laparoscopic gastric banding on body composition, metabolic profile and nutritional status of obese women: 12-months follow-up. *Obes. Surg.* **14**, 239–245 (2004).
126. Larrad Jimenez, A. *et al.* Course of metabolic syndrome following the biliopancreatic diversion of Larrad. *Obes. Surg.* **14**, 1176–1181 (2004).
127. Lee, W.J. *et al.* Effects of obesity surgery on the metabolic syndrome. *Arch. Surg.* **139**, 1088–1092 (2004).
128. Blonde, L. *et al.* Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes. Metab.* **8**, 436–447 (2006).
129. Zinman, B. *et al.* The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. *Ann. Intern. Med.* **146**, 477–485 (2007).
130. Thompson, R.G., Pearson, L., Schoenfeld, S.L. & Kolterman, O.G. Pramlintide, a synthetic analog of human amylin, improves the metabolic profile of patients with type 2 diabetes using insulin. The Pramlintide in Type 2 Diabetes Group. *Diabetes Care* **21**, 987–993 (1998).
131. Hollander, P.A. *et al.* Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* **26**, 784–790 (2003).
132. Buse, J.B. *et al.* Muraglitazar, a dual (alpha/gamma) PPAR activator: a randomized, double-blind, placebo-controlled, 24-week monotherapy trial in adult patients with type 2 diabetes. *Clin. Ther.* **27**, 1181–1195 (2005).
133. Nissen, S.E., Wolski, K. & Topol, E.J. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* **294**, 2581–2586 (2005).
134. Gentles, D. *et al.* Metabolic syndrome prevalence in a multicultural population in Auckland, New Zealand. *N. Z. Med. J.* **120**, U2399 (2007).