The Metabolic Syndrome

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The "metabolic syndrome" (MetS) is a clustering of components that reflect overnutrition, sedentary lifestyles, and resultant excess adiposity. The MetS includes the clustering of abdominal obesity, insulin resistance, dyslipidemia, and elevated blood pressure and is associated with other comorbidities including the prothrombotic state, proinflammatory state, nonalcoholic fatty liver disease, and reproductive disorders. Because the MetS is a cluster of different conditions, and not a single disease, the development of multiple concurrent definitions has resulted. The prevalence of the MetS is increasing to epidemic proportions not only in the United States and the remainder of the urbanized world but also in developing nations. Most studies show that the MetS is associated with an approximate doubling of cardiovascular disease risk and a 5-fold increased risk for incident type 2 diabetes mellitus. Although it is unclear whether there is a unifying pathophysiological mechanism resulting in the MetS, abdominal adiposity and insulin resistance appear to be central to the MetS and its individual components. Lifestyle modification and weight loss should, therefore, be at the core of treating or preventing the MetS and its components. In addition, there is a general consensus that other cardiac risk factors should be aggressively managed in individuals with the MetS. Finally, in 2008 the MetS is an evolving concept that continues to be data driven and evidence based with revisions forthcoming. (*Endocrine Reviews* 29: 777–822, 2008)

I. Introduction

THE "METABOLIC SYNDROME" (MetS) is defined as a clustering of components that reflects the expanding waist lines of the world. Although steeped with controversy, the MetS has more than made its place in the medical literature of today with more than 24,000 citations now recorded in PubMed. Granted, many of the publications that occurred be-

fore May 2001, when the National Cholesterol Education Program's Adult Treatment Panel III (NCEP:ATPIII) definition of the MetS was put forth, did not address the MetS as we know it today; yet, since May 2001 more than 15,000 articles have surfaced, averaging over 40 per week. In comparison with another endocrine syndrome we know so well, the world's literature on Cushing's syndrome is approximately 11,500 articles. Of course the number of publications or related citations on a topic fails to provide the final word on scientific merit; nevertheless no one can argue with the claim that this volume of literature over the past 7 yr documents an escalating level of interest and potential scientific and clinical importance of the MetS.

So why is there so much controversy, bickering, and confusion about the MetS? We believe it centers predominantly around two issues: 1) the definition; and 2) the ability or inability of the MetS as currently defined to predict coronary heart disease (CHD) or other forms of cardiovascular disease (CVD) or type 2 diabetes (T2D) in a way superlative to the risk factors we know so well. For CHD, these would include low-density lipoprotein (LDL) cholesterol (LDL-C), tobacco, family history, and others that are included in the definition of the syndrome, *i.e.*, hypertension, low levels of high-density lipoprotein (HDL) cholesterol (HDL-C), and diabetes (if included as a component of the MetS). For T2D risk, this would simply be the fasting glucose concentration.

According to the NCEP:ATPIII panel, the primary purpose for identifying the MetS was to identify individuals at higher risk of CVD that extended beyond LDL-C and was obesity-related (1). The purpose of identifying these patients was to emphasize further the importance of a healthy lifestyle in reducing risk. Yet a syndrome is not a disease and cannot be viewed microscopically using hematoxylin and eosin. If one considers Cushing's syndrome as an example, facial rounding, plethora, supraclavicular fullness, proximal myopathy, cutaneous wasting, central obesity, nephrolithiasis, hypertension, glucose intolerance, hyperandrogenism, oligomenorrhea, hypogonadism, osteoporosis, and neuropsychiatric disorders could all be part of the clinical presentation. Yet because only a clustering of these components is typically present, we teach our students, house staff, and fellows to consider Cushing's syndrome when their patients demonstrate the presence of some but not all these components.

The purpose of this review is not to dwell on the controversy, but to acknowledge it. We then dissect the vast literature on the MetS highlighting the most important aspects of the epidemiology, pathophysiology, experimental models, and related clinical and population data. To conclude, some discussion of the conditions associated with the MetS and therapeutics follows. We are hopeful that this comprehensive review will not only inform the reader, but also challenge him/her to put the MetS into appropriate scientific and clinical perspective.

II. Definitions

A. Brief history: nomenclature of the metabolic syndrome

Although the term MetS has become widely used since its inception in 2001 by the NCEP:ATPIII (1), the concept of "clustering" metabolic disorders and CVD risk factors has been discussed in the scientific literature for many decades.

In fact, recent reviews have noted that independent scientists published reports of the association between diabetes mellitus and hypertension as early as the 1920s (2), when Kylin (3) documented a connection between hypertension, hyperglycemia, and gout. While the primer for understanding visceral adiposity did not occur until nearly 30 yr later (4), by the early 1990s visceral obesity was fully appreciated as a component of the insulin resistance syndrome (5). In 1980, the seminal work of Margaret Albrink (6) focused on the relationship between obesity, hypertriglyceridemia, and hypertension (7). It was not until 1988 when Reaven (8), in his landmark Banting Lecture, coined the term "Syndrome X" to describe the proposed interrelationships between resistance to insulin-stimulated glucose uptake, hypertension, T2D, and CVD. During the ensuing 10 yr, Syndrome X and other terms were used to describe the clustering of cardiovascular and metabolic risk factors, including "deadly quartet" (9) and the "insulin resistance syndrome" (10–12).

B. Diverging definitions: a syndrome rooted in controversy

The clinical utility of identifying people with the MetS has raised concerns from many scientific groups. In particular, the use of the term "syndrome" was examined and discussed by the International Diabetes Federation (IDF) (13). The IDF described a syndrome as "a recognizable complex of symptoms and physical or biochemical findings for which a direct cause is not understood…the components coexist more frequently than would be expected by chance alone. When causal mechanisms are identified, the syndrome becomes a disease." Although insulin resistance is present in a majority of people with the MetS, the IDF found insufficient evidence for a causal link between the two, a statement that agreed with the American Diabetes Association (ADA), which published its concerns about the lack of certainty regarding the causative pathogenesis of insulin resistance and its utility as a marker for CVD (14). In particular, the ADA emphasized the lack of clarity in the MetS definition and cautioned clinicians not to assume that the MetS is well characterized (14). Thus, the term syndrome in itself has sparked considerable controversy.

Overall, a combination of factors, such as improved methodologies and increased awareness of the comorbidity of cardiovascular and metabolic diseases, led to the notion that identifying such a syndrome could be predictive of CVD. Although there are divergent criteria for the identification of the MetS, they all tend to agree that the MetS core components include obesity [waist circumference (WC)], insulin resistance, dyslipidemia, and hypertension (13). The first formal definition of the MetS was put forth in 1998 by the World Health Organization (WHO) (15). This definition focused primarily on the presence of insulin resistance, identified by hyperinsulinemia, impaired glucose tolerance (IGT), or the diagnosis of T2D, which had to be present to make the diagnosis. In addition, two of the following also had to be present: dyslipidemia (reduced HDL-C and increased triglycerides), hypertension, and microalbuminuria (Table 1). Of interest, the earliest definition of hypertension was a blood pressure of at least 160/90 mm Hg, later revised to at least 140/90 mm Hg. According to the WHO, the pri-

TABLE 1. Criteria for the MetS definitions

WHO, 1998 (15)	EGIR, 1999 (12)	NCEP:ATPIII, 2001 (1)	AACE, 2003 (18)	IDF, 2006 (13)
High insulin levels, IFG or IGT, and two of the following:	Top 25% of the fasting insulin values among nondiabetic individuals and two of the following:	Three or more of the following:	IGT and two or more of the following:	Central obesity as defined by ethnic/racial, specific WC, and two of the following:
Abdominal obesity: WHR >0.9, BMI ≥30 kg/m^2, WC > 37 inches	WC: ≥94 cm for men, ≥80 cm for women	WC: >40 inches for men, >35 inches for women	Triglycerides ≥150 mg/dl	Triglycerides ≥150 mg/dl
Lipid panel with triglycerides > 150 mg/dl, HDL-C <35 mg/dl	Triglycerides ≥2.0 mmol/liter and HDL-C <1.0 mg/dl	Triglycerides ≥150 mg/dl	HDL-C: <40 mg/dl for men, <50 mg/dl for women	HDL-C: <40 mg/dl for men, <50 mg/dl for women
BP >140/90 mm Hg	BP ≥140/90 mm Hg or antihypertensive medication	HDL-C: <40 mg/dl for men, <50 mg/dl for women	BP ≥130/85 mm Hg	BP ≥130/85 mm Hg
	Fasting glucose ≥6.1 mmol/liter	BP ≥130/85 mm Hg		FPG ≥100 mg/dl
		FPG ≥110 mg/dl[a]		

Reference numbers are shown in *parentheses*. WHR, Waist-to-hip ratio; BP, blood pressure; FPG, fasting plasma glucose.
[a] In 2003, the ADA changed the criteria for IFG tolerance from >110 mg/dl to <100 mg/dl (16, 17).

mary purpose of identifying individuals with the MetS was to identify patients at high risk for developing CVD as well as nondiabetics at high risk for developing diabetes. The European Group for the Study of Insulin Resistance (EGIR) published a separate set of criteria shortly thereafter (12). The basic premise of the EGIR definition was that the MetS "is a syndrome of mild anomalies which, in combination, increase cardiovascular risk." This definition, although similar to the WHO definition, did not include microalbuminuria (Table 1). The EGIR emphasized that the presence of microalbuminuria was not a requirement for one to have the MetS. In 2001, the NCEP:ATPIII published a new set of criteria based on common clinical measurements: WC, blood lipids, blood pressure, and fasting glucose (1, 16, 17). The NCEP:ATPIII definition differed from both the WHO and EGIR definitions in that the presence of "insulin resistance," *per se*, was not a necessary criterion to make the diagnosis (Table 1). Again, the primary purpose of the NCEP:ATPIII definition of the MetS was to identify individuals at high risk for CVD that extended beyond the traditional cardiac risk factors.

Since these initial attempts to define the MetS, other groups, including the American Association of Clinical Endocrinologists (AACE) (18), have proposed working definitions to describe the interdependence of cardiovascular and metabolic diseases (Table 1). The AACE definition placed a greater focus on insulin resistance and excluded individuals with T2D. In their 2004 workshop, the IDF recognized the difficulties in identifying criteria for the MetS that were applicable across ethnic populations (13). Specifically, they argued that multiple definitions of the MetS led to difficulties in comparing data between studies and did not provide unified diagnostic criteria to identify the presence of the syndrome. The IDF definition emphasized central obesity as a necessary condition to make the diagnosis of the MetS (Table 1). The IDF also proposed a new set of criteria with ethnic/racial specific cutoffs. For example, WC ranges were specified for those from Europe, South Asia, China, Japan, ethnic South and Central America, sub-Saharan Africa, and

the Eastern Mediterranean/Middle East. Moreover, a guide for measuring WC was suggested, and there was discussion to the effect that in Australia, when the body mass index (BMI) is greater than 30 kg/m^2, a WC measurement is unnecessary. It is also notable that the most recent IDF criteria do not emphasize insulin resistance, but instead focus on fasting plasma glucose concentrations.

In general, until more evidence accumulates that elucidates the cause of the MetS and its impact on CVD and T2D incidence and outcomes, these controversies are unlikely to be resolved. However, identification of multiple components of the syndrome is undeniably an opportunity to encourage patients to make lifestyle changes that will attenuate their chances for CVD and metabolic disease later in life.

III. Epidemiology

The prevalence of the MetS is increasing throughout the world (19). Prevalence estimates of the MetS in the United States and around the world, however, are dependent on the definition that is used to determine inclusion as well as the composition (*e.g.*, sex, age, race, and ethnicity) of the population being studied. Moreover, lifestyle habits and socioeconomic status (SES) appear to influence prevalence across sex, age, and race/ethnicity cohorts.

A. Prevalence estimates according to definition

Estimates of the prevalence of the MetS differ depending on the definition (NCEP:ATPIII, WHO, IDF, EGIR) being used to categorize individuals. The WHO and NCEP:ATPIII definitions are similar with respect to criteria for obesity, hypertension, and dyslipidemia. However, insulin resistance, IGT, and/or T2D as prerequisites of the WHO definition make this definition relatively more restrictive. The exclusion of people with T2D from the EGIR definition also makes its definition less inclusive. On the other hand, the IDF definition, which has central obesity as its prerequisite, may

TABLE 2. Age-adjusted prevalence according to MetS definition within NHANES (unadjusted for sex or race/ethnicity and including those with T2D)

	n	ATPIII 2001	ATPIII revised	WHO	IDF
NHANES 1988–1994 (21)	8814	23.7%			
NHANES 1988–1994 (22)	8608	23.9%		25.1%	
NHANES 1988–1994 (23, 63)	6436	24.1%	29.2%		
NHANES 1999–2002 (23, 63)	1677	27.0%	32.3%		
NHANES 1999–2002 (24, 54)	3601		34.6%		39.1%

be relatively less restrictive than the NCEP:ATPIII definition. Prevalence estimates based on the original NCEP:ATPIII definition became more inclusive when the original criteria were revised to include the newer 2003 ADA-recommended cutoff for impaired fasting glucose (IFG) (*i.e.*, ≤100 *vs.* 110 mg/dl). Clearly, whether or not epidemiological studies using the NCEP:ATPIII or WHO criteria include or exclude individuals with T2D impacts their prevalence estimates because the vast majority of T2D patients meet the minimum criteria for the MetS (20). Differences in the age-adjusted prevalence estimates using the various definitions of MetS within two National Health and Examination Survey (NHANES) cohorts (NHANES 1988–1994 and NHANES 1999–2002) are illustrated in Table 2 (21–24). Prevalence estimates generally were: 1) higher when the NCEP:ATPIII definition was revised; 2) similar between WHO and NCEP:ATPIII; and 3) higher using IDF rather than NCEP:ATPIII criteria. Prevalence estimates also increased over time (across the two NHANES cohorts) from approximately 29% (1988–1994 cohort) to 35% (1999–2002 cohort). The cause of this apparent increase over such a short period of time is not known but was likely due to differences in WC and in the composition of the cohorts.

MetS prevalence estimates were compared, using the WHO, NCEP:ATPIII, and IDF definitions, in middle-aged adults from the San Antonio Heart Study stratified by sex and race/ethnicity (Table 3) (25). The San Antonio data demonstrated lower prevalence estimates using the WHO criteria and higher prevalence estimates using the IDF criteria, relative to NCEP:ATPIII. These data further demonstrated an interaction between sex and race/ethnicity on MetS prevalence in middle-aged adults, such that MetS prevalence appeared to be higher in white, non-Hispanic men compared with women, whereas MetS prevalence was similar in Mexican-American men and women.

As is the case for studies conducted in the United States, studies from other countries have reported varying MetS prevalence rates depending on the definition used (Table 4). Estimates of prevalence using the IDF criteria are often slightly higher than when the NCEP:ATPIII definition of MetS is used within the same population (26–31). However, both China and Iran seem to have lower prevalence rates when the IDF definition is used (32, 33). Other studies have found less consistent differences in MetS prevalence using the different definitions (34–38). Thus, definition-related differences in prevalence are not consistent among countries and may be attributed, in part, to the race-specific WC guidelines included in the IDF definition. Many global studies assessing MetS prevalence have included diabetic subjects in their sample population, which clearly impacts the number of people estimated to have MetS (27–29, 31, 35,

36, 39–52). Not surprisingly, the overall prevalence of the MetS often increases in parallel with increases in obesity (24, 41, 53).

B. Prevalence estimates by sex

In the United States, the age-adjusted prevalence of the MetS is somewhat different between women and men, but the directionality of that difference has been inconsistent across cohorts. In the NHANES 1988–1994 cohort, the prevalence of the MetS was lower in women than men (23.9 *vs.* 27.8%; n = 5775), whereas the prevalence was higher in women than men in the later 1999–2002 cohort (30.3 *vs.* 28.0%; n = 1514) (54). The age-adjusted prevalence increased dramatically in women over this timeframe but did not change in men. The reason for the increase in women is not clear, but it is likely that this was due, in part, to changes in the racial and ethnic composition of the female cohort. The relative impact of racial/ethnic composition on sex-related differences in MetS is illustrated in Table 5.

Although in many countries there is very little difference between rates of MetS among women and men, there are some countries that have noticeably greater numbers of women than men that meet the MetS criteria (30, 31, 33, 36, 39, 40, 43, 52, 55–58), whereas others report greater prevalence in men (26, 35, 59). Because sex-related differences in MetS prevalence are not universal, differences between women and men within specific countries may be due, for example, to differing SES, work-related activities, and cultural views on body fat. Importantly, the development of the inclusion criteria for each of the definitions was based upon epidemiological data primarily from westernized countries. Although the definitions may still be used to estimate prevalence in any population, it remains unclear how each of the individual criteria may impact sex-specific prevalence rates within certain countries. For example, a WC of more than 88 cm in women from the United States may be a reasonable threshold indicative of higher than normal central adiposity and therefore increased risk of CVD and T2D, but that same waist threshold in an Arab or Asian nation might be too high.

TABLE 3. Prevalence according to MetS definition (stratified by sex and race/ethnicity and including those with T2D) in the San Antonio Heart Study (25, 412)

	n	WHO	ATPIII	IDF
Women				
White, non-Hispanic	506	12.1%	16.8%	24.7%
Mexican-American	1171	27.3%	30.9%	38.5%
Men				
White, non-Hispanic	422	18.8%	24.0%	28.4%
Mexican-American	842	28.3%	29.6%	40.4%

TABLE 4. Prevalence of the MetS among various countries (by definition and by sex where data were provided)

	Ref.	n	Age (yr)	ATPIII 2001	WHO	IDF	EGIR
Australia	26	11,247 (8438 no DM)	≥25	24.4% m, 19.9% w	25.4% m, 18.2% w	34.4% m, 27.2% w	15.6% m, 11.3% w
Brazil	56	1,242	40–74	25.9% m, 40.9% w			
Cameroon	99	1,573	24–74[b]	0% m, 0% w	4.9% m, 2% w	0% m, 0% w	
Canada (non-Aboriginal)	39	2,058[a]	18+	30.6% m, 29.2% w			
Canada (Inuits)	39	238[a]	18+	6.7% m, 18.8% w			
China	32	6,610	~52	18.5% m, 15.7% w	18.1% m, 22.4% w	16.2% m, 19.0% w	11.8% m, 12.2% w
China	40	15,540[a]	35–74	9.8% m, 17.8% w			
Denmark	29	2,493[a]	41–72	18.6% m, 14.3% w		23.8% m, 17.5% w	
Finland	34	2,182	24–39	13.0% m/w		14.9% m/w	9.8% m/w
Finland	35	2,049[a]	45–64		38.8% m, 22% w		
France	41	3,770[a]	30–64	11.0% m, 8.0% w			
Greece	59	2,282	>18	25.2% m, 14.6% w			
Greenland	36	917[a]	≥35	13% m, 22% w	20% m, 22% w		
Hungary	27	13,383[a]	30–60	6.7% m, 9.8% w		14.9% m, 8.6% w	
Southern India (Urban)	28	2,350[a]	20+[b]	17.1% m, 19.4% w	27.3% m, 19.7% w	23.1% m, 28.2% w	
Northern India (Urban)	57	300	20+	18.4% m, 30.9% w			
Iran	33	10,368	20+	24.0% m, 40.5% w	17.0% m, 20.0% w	21.0% m, 41.0% w	
Ireland	42	890[a]	50–69	21.8% m, 21.5% w	24.6% m, 17.8% w		
Italy	56	1,198	40–74	26.8% m, 23.7% w			
Northern Jordan	43	1,121[a]	25–85	28.7% m, 0.9% w			
Mexico	44	2,158[a]	20–69	28.5% m, 25.2% w	13.4% m, 13.8% w		
Oman	45	1,419[a]	20–99	19.5% m, 23.0% w			
Palestine	46	992[a]	30–65		17.0% m/w		
Peru	47	1,878[a]	20–80	18.1% m/w			
Philippines	48	4,541[a]	>20	14.3% m, 14.1% w			
Russia	49	146[a]	25–89	66.9% m/w			
Slovakia	50	657[a]	≥30		20.0% m/w		
South Korea	51	40,698[a]	20–82	5.2% m, 9.0% w			
Spain	30	2,540	35–64	22.0% m, 28.8% w		27.3% m, 31.7% w	
Sweden	37	5,047	46–68	20.6% m/w		21.9% m/w	18.8% m/w
Sweden	24	1,007	45–69	14.8% m, 15.3% w			
Sweden	38	508	70	26.3% m, 19.2% w			
Tunisia	31	863[a]	40+	14.6% m, 30.8% w	25.7% m, 30.8% w	30.0% m, 55.8% w	
Turkey	52	4,259[a]	20–90	28.0% m, 39.6% w			
Turkey	58	2,296	28+	32.2% m, 45.0% w			
Taiwan	55	5,936	20–80	18.3% m, 13.6% w		16.1% m, 13.3% w	

DM, Diabetes mellitus; m, men; w, women.
[a] T2D included.
[b] Not age-adjusted.

Indeed, the addition of the ethnicity-specific WC criteria to the IDF 2005 definition attempted to take this possibility into account, lowering the WC threshold from at least 88 cm to at least 80 cm for women of certain African, Arab, and Asian populations. However, apart from slightly shifting prevalence rates up or down in women and men, it is unclear whether making the WC criteria more inclusive in these populations more effectively captures those who are at greatest risk of CVD and T2D.

C. Prevalence estimates by race/ethnicity

Within the United States, sex-related differences in MetS prevalence are influenced by race and ethnicity-related differences (Table 5). For example, age-adjusted prevalence of MetS in the NHANES studies was lower in white, non-

Hispanic women than men, whereas prevalence was higher in African-American women than men. Mexican-American women had a higher prevalence of MetS compared with men in the earlier NHANES 1988–1994 cohort, but the prevalence almost doubled in Mexican-American men in the later NHANES 1999–2002 cohort such that age-adjusted prevalence was lower in Mexican-American women than men. On the other hand, MetS prevalence was not different between Mexican-American men and women in the San Antonio Heart Study. Thus, sex-related differences in MetS prevalence appear to be largely dependent on the racial and ethnic composition of the cohort being studied. Comparison of MetS prevalence among cohorts from other countries further highlights the relative impact of racial/ethnic composition on sex-related differences in MetS (Table 4).

TABLE 5. Age-adjusted prevalence of MetS by race/ethnicity and sex (using NCEP:ATPIII criteria, including those with T2D)

	White, non-Hispanic		African-American		Mexican-American	
	Male	Female	Male	Female	Male	Female
NHANES 1988–1994 (22)	25.1%	22.7%	16.5%	26.1%	28.0%	36.3%
NHANES 1999–2002 (54)	35.4%	31.5%	24.5%	36.4%	50.6%	46.2%
San Antonio Heart Study (25)	24.0%	16.8%			29.6%	30.9%

D. Prevalence estimates by age

1. MetS in older populations. Not surprisingly, the MetS becomes more prevalent with each decade of life, increasing in parallel with age-related increases in obesity and, in particular, central adiposity (23, 60, 61). In the NHANES cohorts, MetS prevalence continued to increase with age into the sixth decade, with prevalence in women catching up to and then exceeding that in men after the age of 60 yr (62, 63) (Fig. 1). These trends suggest an interaction between age and sex on the prevalence of the MetS. The definition used to estimate prevalence, however, may influence this interaction. The Cardiovascular Health Study, which studied men and women over the age of 65 yr, observed higher MetS prevalence in women than men (37.4 *vs.* 32.1%) using the NCEP: ATPIII criteria, but lower prevalence in women than men (23.9 *vs.* 32.4%) using the WHO criteria (64). Nevertheless, MetS prevalence increases consistently with age between the ages of 12 to 60 yr in the United States (Fig. 1) and across the globe, independent of sex (27, 28, 44, 65).

Studies that have compared age-related increases in prevalence among different definitions have observed variable prevalence estimates after the sixth or seventh decades (26, 28). Much of this variability in these later decades of life may be due to a survival effect, because those most susceptible to obesity-related mortality have likely died by this point (66). Finally, whether prevalence estimates plateau or drop off steeply after the age of 60 yr also varies according to the MetS definition being used (26, 28, 52).

2. MetS in younger populations. Current literature supports the notion that the presence of the MetS in youth may be an important predictor of future risk for diabetes and CVD (67). Landmark studies from the Bogalusa Heart Study demonstrated that cardiovascular risk factors present in childhood are predictive of coronary artery disease in adulthood (68, 69). For example, LDL-C and BMI measured in childhood were found to predict carotid intima-media thickness in

Fig. 1. Prevalence of the MetS across age groups and gender in various countries. The MetS prevalence continues to increase with age into the sixth decade, with prevalence in women catching up to and then exceeding that in men after the age of 60 yr in the United States and across the globe (27, 28, 44, 55, 65).

young adults (70). There is substantial evidence that obesity is the main determinant of insulin resistance in children (71) and that it increases the risk not only for the MetS in adulthood (72) but also for CVD and T2D later in life (73–76).

A major problem with identifying the MetS in children and adolescents is that there are no established criteria in this population. In fact, a recent review found 27 publications that used 40 different definitions of the MetS in children and adolescents (77). The uniqueness of pediatric growth patterns, effects of hormonal changes of puberty on insulin sensitivity and lipid profile, and the impact of ethnic background on components of the syndrome make such criteria difficult to establish. The reported prevalence of MetS in youth, therefore, varies according to the age and population under study and the definition being used (Table 6) (71, 78–82). Cook *et al.* (79) estimated the prevalence of the MetS in 2430 U.S. adolescents using NHANES 1986–1994 data by modifying the NCEP:ATPIII definition, based on reference values for physiological parameters in youth. The overall prevalence was 4.2%, 6.1% in boys and 2.1% in girls, respectively. Among obese and overweight adolescents, prevalence of the MetS was 28.7 and 6.8%, respectively. Similar to adults, prevalence of individual components of the MetS differed by race/ethnicity (*e.g.*, prevalence of elevated blood pressure was higher and prevalence of high triglyceride and of low HDL-C concentrations was lower in African-American youth compared with non-Hispanic white or Mexican-American youth). Using the same population and a similar definition but different cut points for hypertriglyceridemia and central obesity, de Ferranti *et al.* (80) obtained an overall prevalence estimate of 9.2%. In a population of 218 overweight Hispanic youth with a family history of T2D, the prevalence of the MetS ranged from 26 to 39%, depending on the definition used (83). Weiss *et al.* (82) assessed the impact of varying degrees of obesity on the prevalence of the MetS in 493 children and adolescents with BMI in the 97th percentile or above for age and gender. The prevalence of the MetS increased with the severity of obesity and reached approximately 50% in severely obese youngsters. Finally, Cook *et al.* (78) recently examined the prevalence of the MetS in 1,826 U.S. adolescents from the NHANES 1999–2002 survey using four definitions of the MetS previously used in this age group. They found that depending on the definition used, the prevalence varied between 2.0 and 9.4% in all teens and ranged between 12.4 and 44.2% in obese teens (78).

These discrepancies clearly emphasize the need for a consensus definition of the MetS in younger individuals first to understand better the prevalence but also as a potential clinical tool in identifying at-risk individuals (67, 84). The IDF Task Force on the Epidemiology and Prevention of Diabetes has recently developed a definition primarily for those 10 yr and older but less than 16 yr of age (67). MetS can be diagnosed in this age group by abdominal obesity (≥90th percentile) and the presence of two or more other factors, including hypertriglyceridemia (≥1.7 mmol/liter), low HDL-C (≤1.03 mmol/liter), elevated blood pressure (≥130 mm Hg systolic or ≥85 mm Hg diastolic), or increased blood glucose (≥5.6 mmol/liter). For those less than 6 yr of age, there were insufficient data to make a recommendation. For children between the ages of 6 and 10 yr, they suggested that the MetS
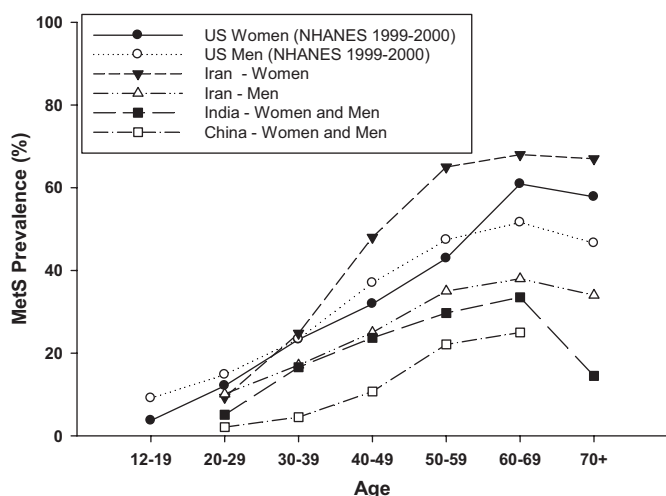
TABLE 6. Prevalence of MetS in children and adolescents among various cohorts

Population	Ref.	n	Criteria	Prevalence
NHANES (1988–1994), youths (12–19 yr old)	79	2430	ATP III ($\geq$3): WC $\geq$90th %; IFG; TG $\geq$150 mg/dl; HDL <40 mg/dl; BP $\geq$90th % or medication	4.2%; BMI $\geq$95th %, 28.7%
NHANES (1988–1994), youths (12–19 yr old)	80	1960	ATP III ($\geq$3): WC $\geq$75th %; TG $\geq$70th %	9.2%
Overweight Hispanic youth (BMI $\geq$85th %; 8–13 yr old) with family history of T2D	81	126	ATP III ($\geq$3): HDL <10th %; IGT	38%
Multiethnic/multiracial youths (4–20 yr old)	82	490	ATP III and WHO ($\geq$3): BMI z-score $\geq$2; IGT; TG $\geq$95th %; HDL <5th %; BP $\geq$95th %	38.7% in moderately obese; 49.7% in severely obese
NHANES (1999–2002), youths (12–19 yr old)	78	1826	Cook *et al.* (79)	9.4%
			Cruz *et al.* (81)	2.0%
			Weiss *et al.* (82)	2.4%
			Adult NCEP (1)	5.8%

BP, Blood pressure; TG, triglycerides.

not be diagnosed but that a strong message regarding weight reduction should be made in those with abdominal obesity. Finally, they recommended that the adult criteria be used for those 16 yr or older.

Important to note in the study of the MetS in youth is that there are racial/ethnic differences in the prevalence of the MetS, as well as differences in the prevalence of individual components of the syndrome. For example, insulin resistance is greater among African-American compared with non-Hispanic white youth (85–88). Goran *et al.* (85) reported that Mexican-American and African-American children were both more insulin resistant than non-Hispanic white children, to a comparable degree and independent of obesity, although underlying physiological compensatory mechanisms differed between African-American and Mexican-American youth. However, although African-American youth are more insulin-resistant, the prevalence of the MetS is lower in African-American youth (2%) than Hispanic (5.6%) and non-Hispanic white youth (4.8%) (79), suggesting that African-American youth may be less likely to develop obesity-related clustering of MetS components than non-Hispanic white youth.

Duncan *et al.* (62) examined trends in the prevalence of MetS in U.S. adolescents aged 12–19 yr using NHANES data (1998–1994 and 1999–2000) and the pediatric definition developed by Cook (79). The overall prevalence of a MetS phenotype among U.S. adolescents increased from 4.2% in NHANES III (1988–1992) to 6.4% in NHANES 1999–2000 ($P < 0.001$). The trend was evident in both sexes and in all three major race/ethnic groups analyzed in this study (Fig. 2). Based on population-weighted estimates, the study estimated that more than 2 million U.S. adolescents currently have a MetS phenotype. The MetS was most frequent in obese adolescents, with a prevalence of 32.1%, compared with only 7.1% for overweight adolescents. Given the increasing prevalence of overweight and obesity in youth (89) and the strong relationship between obesity and the MetS, it is not surprising that the prevalence of MetS has increased over the past decade among U.S. adolescents.

Interestingly, the risk of developing T2D in youth with the MetS is currently unknown. This is partially attributed to the

difficulty of diagnosing T2D in children and to the lack of a standard definition of the MetS definition in youth (67). Despite this, it is estimated that approximately 92% of the adolescent population that has T2D also has the MetS (90, 91). It has also recently been shown that the incidence of T2D in adulthood is increased 3-fold in those with the MetS as children (92). Further research is necessary to understand better the link between the MetS in youth and the development of T2D.

E. Prevalence estimates by socioeconomic status, tobacco, alcohol, and level of education

Few studies have evaluated the impact of SES outcomes on the prevalence of MetS. In the NHANES 1988–1994 cohort, multivariable adjusted odds ratios (OR) and 95% confidence intervals (CI) for the MetS were reported for select SES and lifestyle outcomes (23). Risk was increased in women (OR, 1.8; 95% CI, 1.2–2.6) and men (OR, 1.5; 95% CI, 1.1–2.2) who
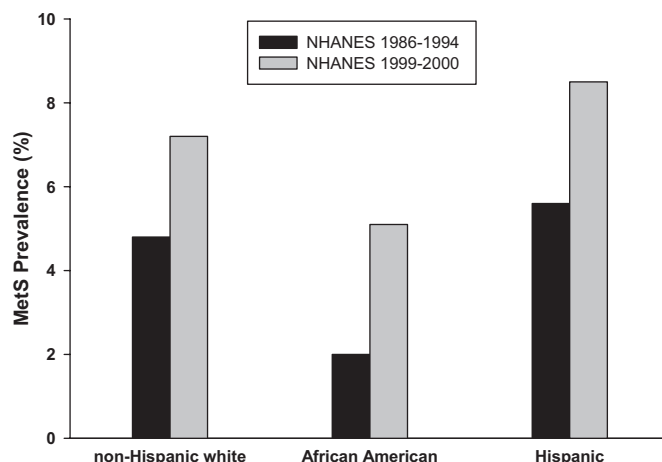
FIG. 2. The prevalence of the MetS among adolescents. Prevalence of the MetS among U.S. adolescents (age 12–19 yr) increased from 4.2% in NHANES III (1988–1992) to 6.4% in NHANES 1999–2000 ($P < 0.001$) in both sexes and in all three major race/ethnic groups analyzed (62).

were current smokers compared with those who never smoked (23). In men only, the OR for MetS was increased (OR, 1.7; 95% CI, 1.2–2.5) in those who had heavy (>60% total calories) compared with moderate (40–60% total calories) carbohydrate intake, and the OR for MetS was increased for physical inactivity (OR, 1.4; 95% CI, 1.0–2.0) (23). In women only, the OR for MetS was decreased (OR, 0.8; 95% CI, 0.6–1.0) in those who reported regular (1 drink per day) compared with moderate (<1 drink per day) alcohol intake, and the OR was increased (OR, 1.5; 95% CI, 1.0–2.3) in those who reported a lower (≤$15,000/yr) compared with a higher (>$25,000/yr) household income (23). Level of education was not related to OR for MetS in women or men in this NHANES cohort (23). However, the association between SES and MetS within the United States appears to be confounded by race and ethnicity. Among African-American women and men (Pitt County Study, n = 1195), higher educational status (at least high school graduation) was associated with reduced risk of MetS (OR, 0.63; 95% CI, 0.48–0.83), compared with lower educational status (less than high school graduation) (93).

Although there is a paucity of global epidemiological studies assessing the impact of SES on MetS prevalence, there are some data to suggest a similar relation between MetS and SES in other westernized nations as is seen within the United States (55, 56, 60, 61). An inverse association between level of education and risk of MetS has been observed in middle-aged Swedish women (94), as well as Finnish women and men (95). Among British civil servants (Whitehall II cohort, n = 7,013), women and men had a 2- to 3-fold increased risk of MetS if they were in the lowest (compared with the highest) employment grade quintile: women, OR, 2.8; 95% CI, 1.6–2.9; men, OR, 2.2; 95% CI, 1.6–2.9 (96). In these three European studies, adjusting for other behavioral risk factors (*e.g.*, smoking and alcohol intake) did not alter the association between the SES outcomes and MetS (94–96). In Korea, the association between SES and MetS was evident only in women. Relative to women with lower education and income, Korean women with higher education and income levels had a lower risk for MetS (97). In Korean men, there was no significant relation between the prevalence of MetS with education or income levels (97). Furthermore, a separate Korean study demonstrated interactions between SES (*i.e.*, education, income) and behavioral (*i.e.*, smoking, alcohol intake, exercise) outcomes, suggesting that health behaviors differentially impact incidence of MetS across SES levels (98).

In addition to SES, urban *vs.* rural location may play a role in prevalence of MetS in developing nations. Abdul-Rahim *et al.* (46) found that Palestinians with T2D living in an urban area had a 17% greater likelihood of meeting NCEP:ATPIII MetS criteria than those living in a rural area. Furthermore, men in urban areas of Cameroon had a 7.3-fold greater risk of developing MetS, whereas women had a 5.9-fold increased risk (99). Similar trends have been observed in China and Russia (49, 100, 101). However, not all nations with developing economies exhibit differences in MetS prevalence between urban and rural areas (52, 102).

F. Changes in prevalence following intervention

Prevalence estimates of MetS may be modifiable by intervention. The Diabetes Prevention Program (DPP) conducted *post hoc* analyses to address this possibility by evaluating changes in the prevalence of MetS (NCEP:ATPIII 2001 criteria) after treatment with either lifestyle (diet + exercise-induced weight loss) or metformin (103). They evaluated the incidence of new MetS cases and resolution of existing MetS cases compared with placebo treatment in participants (n = 3234) of the DPP trial. Because IGT was a primary inclusion criterion for entrance into the DPP trial, the majority (53%) of the participants met the criteria for MetS at baseline (103). Incidence of MetS was reduced by 41% in the lifestyle group and by 17% in the metformin group compared with placebo (103). Among participants who met the MetS criteria at baseline, by 3 yr MetS resolved in 18% of placebo, 23% of metformin, and 38% of the lifestyle group (103). Whether these treatment effects apply to a non-IGT population remains unknown. However, in a small study of obese (BMI ≥30 kg/m^2) older (age ≥65yr) women and men randomized to a similar lifestyle intervention (n = 17) or a control group (n = 10) for 26 wk, MetS resolved in 10 of 15 cases in the treatment group compared with no cases in the control group (103, 104). Whether reducing the incidence of MetS leads to a reduction in T2D and CVD-related morbidity and mortality remains unknown.

IV. Pathophysiology

As previously discussed, the primary purpose of identifying the MetS was to identify a clustering of features that were associated with increased CVD risk. As the term syndrome implies, a specific causative etiology to the MetS is not clear, nor was a common, unifying pathophysiological cause of the MetS necessarily intended. Nevertheless, abdominal adiposity and insulin resistance appear to be at the core of the pathophysiology of the MetS and its individual components. Thus, the purpose of this section is to review how abdominal adiposity and insulin resistance may contribute to the pathophysiology of the MetS.

A. Insulin resistance: a conceptual prologue

Insulin is a pleiotropic molecule that has effects on amino acid uptake, protein synthesis, proteolysis, adipose tissue triglyceride lipolysis, lipoprotein lipase activity, very low-density lipoprotein (VLDL) triglyceride secretion, muscle and adipose tissue glucose uptake, muscle and liver glycogen synthesis, and endogenous glucose production. Individuals are generally defined as insulin sensitive or insulin resistant by their response to an oral or iv glucose or insulin stimulus (105). Characteristics of the insulin-sensitive phenotype include a normal body weight (106) without abdominal or visceral obesity (5, 107), being moderately active (108), and consuming a diet low in saturated fats (109). Alternatively, insulin-resistant individuals demonstrate impaired glucose metabolism or tolerance by an abnormal response to a glucose challenge, elevated fasting glucose levels and/or overt hyperglycemia, or reductions in insulin action after iv ad-

ministration of insulin (euglycemic clamp technique) with decreased insulin-mediated glucose clearance and/or reductions in the suppression of endogenous glucose production. In general, the characteristics of this phenotype are more likely to include being overweight or obese (106, 110), being sedentary (108), and consuming a diet high in total or saturated fats (109).

Insulin sensitivity, however, is not a simple dichotomy of being insulin sensitive or insulin resistant, but rather exists on a continuum. Moreover, the ability of the pancreas to secrete insulin in response to a glucose challenge may also reflect insulin resistance at the level of the β-cell. To define this, Bergman (111) proposed the disposition index, a quantitative measure that describes the relationship between β-cell sensitivity and insulin sensitivity (112). In metabolically normal individuals, changes in insulin sensitivity are accompanied by compensatory alterations in the response of the β-cell to glucose. In practice, disposition index is defined as the product of the insulin sensitivity index and β-cell function as measured by the acute insulin response to glucose, a relationship that is typically plotted as an inverse hyperbola. The movement along the continuum is more complicated than the model implies, and the molecular mechanism(s) by which insulin sensitivity and β-cell function are coregulated to create a homeostatic environment are not well understood.

B. Obesity as a "driving force" in the prevalence of insulin resistance

The worldwide increase in the prevalence of obesity in the recent decades is startling and is likely a cause of the rising incidence of insulin resistance and the MetS (7, 8, 113–115), as well as CVD and T2D (7). Although not all overweight or obese individuals are metabolically unhealthy, the majority are insulin resistant (116). Indeed, many experts assert that the MetS would never have been put forth if the obesity epidemic had not become the public health concern that it is today (113). In particular, the combination of obesity, physical inactivity, and consumption of an atherogenic diet is believed to lead to insulin resistance (117). In this state of insulin resistance, normoglycemia is initially maintained by a modest increase in β-cell mass and/or an increase in insulin secretory capacity (8, 118). Although the mechanism for this compensation is unclear, there is recent evidence supporting glucose signaling as a dominant force in this process (119); it is also acknowledged that genetic factors may be involved (120, 121). However, the loss of insulin secretory capacity in the natural history of T2D is likely an admixture of β-cell dysfunction in addition to reductions in β-cell mass (122). If the increasing β-cell function and/or mass is successful long-term as a compensatory mechanism to obesity and insulin resistance, T2D could be prevented for an undetermined amount of time, despite hyperinsulinemia as a consequence.

C. Insulin resistance in adipose tissue

Adipose tissue insulin resistance appears to be important to the pathophysiology of the MetS (7, 8, 113, 123, 124). Specifically, a larger, expanded adipose tissue mass often

results in an increased turnover of free fatty acids (FFAs) (125, 126) (Fig. 3). In the setting of insulin resistance and expanded adipose tissue triglyceride stores, the process of FFA mobilization (lipolysis) from stored adipose tissue triglyceride is accelerated (7, 127). Under normal conditions, insulin inhibits adipose tissue lipolysis; however, in the setting of insulin resistance, insulin is unable to properly suppress lipolysis, resulting in relatively more FFA being liberated into the plasma (113). Although it is well accepted that this process is mediated by hormone-sensitive lipase (HSL) (128), recent evidence points to adipose triglyceride lipase as playing an additional role; and collectively these two hormones account for 95% of triglyceride hydrolysis (129). In obese subjects, insulin resistance and hyperinsulinemia are strongly associated with decreased adipose triglyceride lipase and HSL mRNA and protein expression, an effect found to be independent of fat mass (130). There is also evidence supporting a genetic predisposition for insulin resistance and T2D linked to the HSL gene (131).

Not only does insulin resistance appear to cause FFA to rise, but elevated FFA levels also appear to cause insulin resistance. Substantial evidence has accumulated to suggest that the visceral depot contributes to increased FFA turnover and insulin resistance (5, 132–136). Specifically, visceral adipocytes are more sensitive to catecholamine-stimulated lipolysis than sc adipocytes (137). Because the venous drainage of the visceral adipose tissue depot is directly into the portal system (136), it has been hypothesized that in visceral obesity the liver is bathed with fatty acids and consequently becomes insulin resistant ("portal theory") (113, 138).

Another manner in which adipose tissue contributes to the pathophysiology of the MetS is through the excessive release of proinflammatory cytokines. The source of these cytokines in adipose tissue is debated, with controversy surrounding the relative roles of adipocytes *vs.* monocyte-derived macrophages (139, 140). Since the earliest report of the presence of monocyte-derived macrophages in human adipose tissue by Ferrante and colleagues (141), it is now clear that larger fat cells also produce more cytokines (142). Not only are circulating cytokines from adipose tissue important to insulin action in other tissues such as the liver or skeletal muscle, but paracrine effects of the cytokines may also modify insulin action locally in adipose tissue (143, 144).

D. Insulin resistance in the liver

The liver plays a major role in substrate metabolism. Increases in FFA flux have been shown in numerous models to impair hepatic insulin action (138). This includes increases in hepatic glucose output, the synthesis of proinflammatory cytokines, and major changes in lipoprotein metabolism. In the liver, the increased FFA flux must be oxidized or stored. Insulin, under normal physiological conditions, increases the gene expression of a number of enzymes central to triglyceride biosynthesis (145), but also reduces VLDL triglyceride and apolipoprotein (apo) B production and secretion, an effect largely attributable to reductions in adipose tissue lipolysis (146). Another intrahepatic effect of insulin is to enhance apo B degradation (147). In the liver of insulin-resistant patients, FFA flux is high, triglyceride synthesis and
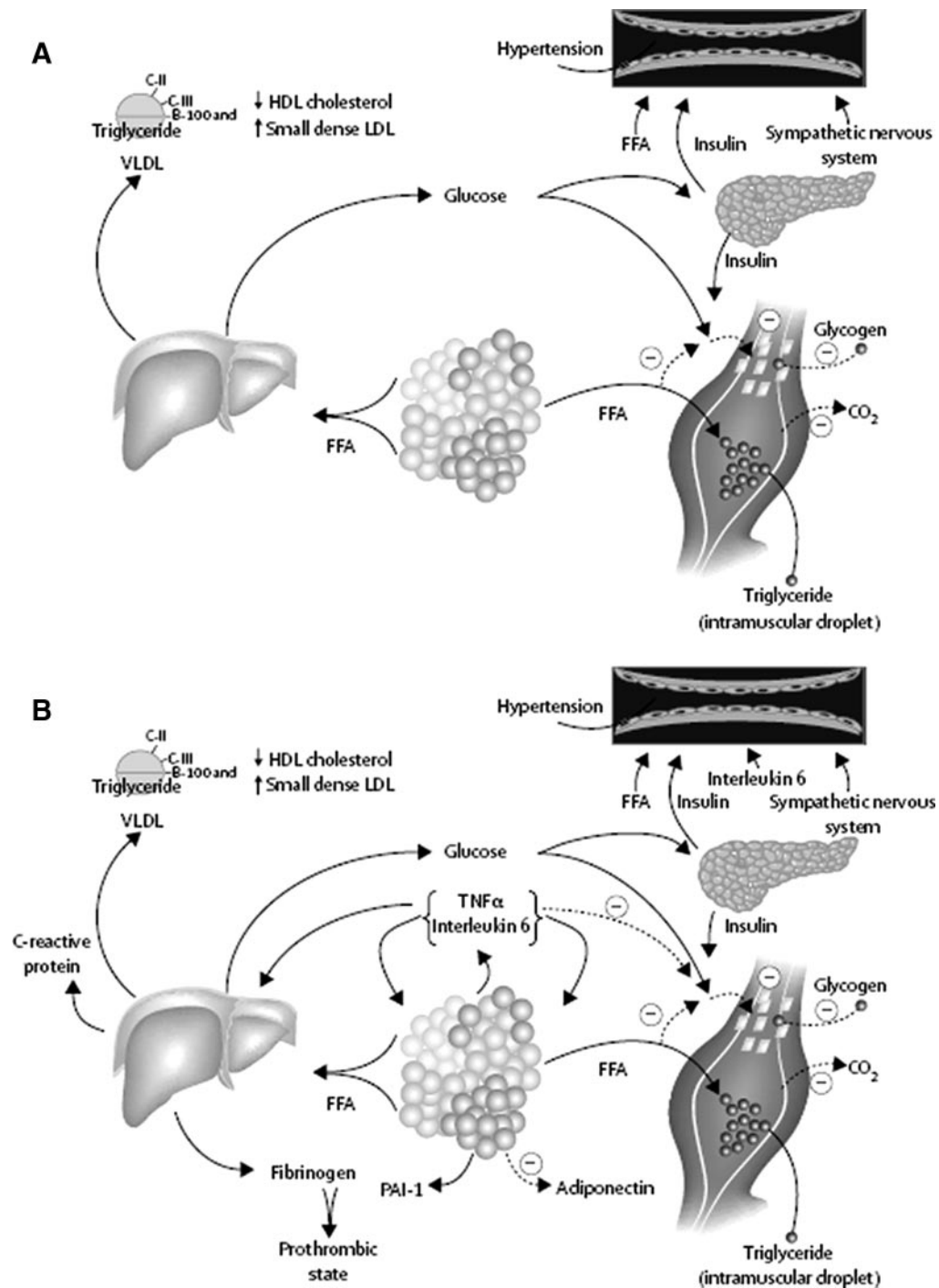
FIG. 3. Pathophysiology of the Metabolic Syndrome and insulin resistance. A, FFA are released in abundance from an expanded adipose tissue mass. In the liver, FFA result in increased production of glucose and triglycerides and secretion of VLDL. Associated lipid/lipoprotein abnormalities include reductions in HDL-C and increased density of LDL. FFA also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation. Elevated circulating glucose and to some extent FFA increase pancreatic insulin secretion, resulting in hyperinsulinemia. Hyperinsulinemia may result in enhanced sodium reabsorption and increased sympathetic nervous system activity and may contribute to hypertension, as might increased levels of FFA. B, Superimposed and contributory to the insulin resistance produced by excessive FFA is the paracrine and endocrine effect of the proinflammatory state. Produced by a variety of cells in adipose tissue, including adipocytes and monocyte-derived macrophages, the enhanced secretion of IL-6 and TNF-α among others results in more insulin resistance and lipolysis of adipose tissue triglyceride stores, resulting in increased circulating FFA. IL-6 and other cytokines also are increased in the circulation and may enhance hepatic glucose production, the production of VLDL by the liver, and insulin resistance in muscle. Cytokines and FFA also increase the production of fibrinogen and PAI-1 by the liver, complementing the overproduction of PAI-1 by adipose tissue. This results in a prothrombotic state. Reductions in the production of the antiinflammatory and insulin-sensitizing cytokine adiponectin are also associated with the metabolic syndrome and insulin resistance. [Reproduced from R.H. Eckel *et al.*: *Lancet* 365:1415–1428, 2005 (113) with permission from Elsevier.]

storage are increased, and excess triglyceride is secreted as VLDL (148).

For the most part, it is believed that the dyslipidemia associated with insulin resistance is a direct consequence of increased VLDL secretion by the liver (147). This may explain why increases in plasma apo B are variably associated with the MetS in the absence of increases in LDL-C (149). In addition to overproduction of VLDL by the liver, alterations in lipoprotein lipase (LPL) have been associated with the MetS. In a large family-based population of Mexican-Americans who were genotyped at six polymorphisms in the LPL gene that define the most common haplotypes in the population, specific LPL haplotypes showed linkage to glucoregulatory aspects of insulin action (150). Other reports linking the LPL gene to the MetS have been published (120, 151, 152). Although there is also evidence that an inverse relationship exists between pre-heparin LPL mass and insulin resistance or the MetS (153, 154), there is little evidence at present that reductions in post-heparin LPL activity (the active enzyme) occur in the MetS (155, 156). This may be a consequence of the tissue-specific regulation of LPL by insulin (157).

Hypertriglyceridemia is typically associated with reductions in HDL-C. This in part relates to the transfer of cholesteryl ester from the core of triglyceride-rich lipoproteins to HDL-C, a process catalyzed by cholesteryl ester transfer protein (CETP) (7, 113, 158). This generates a smaller, triglyceride-rich HDL-C that is a better substrate for hepatic lipase, which results in a particle that is more rapidly cleared by the kidney (159). CETP gene polymorphisms influence plasma CETP activity and plasma HDL-C concentrations, a relationship that in several reports has been associated with the presence of abdominal obesity and some features of the insulin resistance syndrome (160–162). In the setting of hypertriglyceridemia, LDL-C particles are also triglyceride-enriched, small, and dense. Evidence supports an association of small dense LDL-C with CVD (163, 164). Of interest, the MetS has been associated with increased CETP mass in men, and possibly reduced LDL-C particle diameter in addition to reduced HDL-C (165). As previously noted, hepatic lipase plus another member of the lipase gene family, endothelial lipase, have moderate to substantial phospholipase activities, respectively, and are important in HDL-C catabolism. Moreover, endothelial lipase is linked to the proinflammatory state (166). Evidence also relates increases in hepatic lipase to CVD events (167).

Hepatic steatosis is related not only to insulin resistance but also to the MetS. This includes simple deposition of excessive hepatic fatty acids as triglycerides in the liver as well as a more advanced and inflammatory lesion, nonalcoholic steatohepatitis (NASH) (168). Recent studies emphasize the role of insulin resistance, oxidative stress, lipid peroxidation, and cytokines in the development of NASH. At present, therapies of hepatic steatosis directed at improving insulin action implicate the importance of insulin resistance in the etiology of excessive hepatic fat accumulation (169).

E. Insulin resistance in muscle

In muscle, increased plasma FFA disrupt the glucose-fatty acid cycle (125, 170, 171). The predominant defect in insulin action in skeletal muscle relates to an inhibitory effect of this increase in plasma FFA on insulin-mediated glucose transport (172–174). It has also been hypothesized that triglyceride accumulation in skeletal muscle plays a direct role in the etiology of insulin resistance (124). There is also evidence that the degree of whole body insulin sensitivity is inversely correlated with im triglyceride content (124, 175) (Fig. 3). Yet, muscle triglyceride may only be a marker of other related mediators of insulin resistance in muscle, *e.g.*, ceramide (176). Moreover, after insulin sensitivity is improved by exercise or weight reduction, muscle triglyceride content changes little if at all (177, 178).

F. Hypertension and insulin resistance

The relationship between insulin resistance and hypertension has been established (179–181) and relates to several potentially different mechanisms. First, it is important to note that insulin is a vasodilator when given iv to people of normal weight (182), with secondary effects on sodium reabsorption in the kidney (183). Evidence indicates that sodium reabsorption is increased in whites but not Africans or Asians with the MetS (184). In the setting of insulin resistance, the vasodilatory effect of insulin can be lost (185), but the renal effect on sodium reabsorption preserved (186). Fatty acids themselves can mediate relative vasoconstriction (187). Moreover, the infusion of fatty acids into the portal vein activates the sympathetic nervous system and elevates blood pressure in rodents (188). Insulin also increases the activity of the sympathetic nervous system (189), an effect that might also be preserved in the setting of insulin resistance (190). However, when assessed by concentrations of fasting insulin or the homeostatic model assessment (HOMA) (191), insulin resistance contributes only modestly to the increased prevalence of hypertension in the MetS (192). Because adipose tissue is a source of angiotensinogen (193), it is not a surprise to note the association of hyperaldosteronism with hypertension and the MetS (194). Recent evidence also suggests that elevations in adipocyte-derived resistin and leptin may contribute to the pathogenesis of hypertension in patients with insulin resistance (195, 196).

G. Other contributors to insulin resistance (nocturnal FFA flux: sympathetic nervous system)

In response to any kind of stress, emotional and physical, lipolysis is stimulated via β_1 receptors, thus liberating FFA from adipose tissue (197). It has further been demonstrated that in the setting of obesity, sympathetic nervous system activation is exaggerated, adding to the rise in FFA concentration (198–200). In diet-induced obese canines, there is evidence of an apparent pulsatile release of FFA from the visceral depot and a consequential, sustained elevation of nocturnal FFA in response to a moderate fat feeding (138, 201). Whether or not a similar response occurs in humans remains unclear, but it is possible that these fatty acid patterns, diet- and physiologically-induced, play a causal role in the development of insulin resistance and the MetS.

H. Proinflammatory molecules, ER stress, and their roles in insulin resistance and the metabolic syndrome

1. Proinflammatory molecules. It is well documented that the MetS is associated with an elevated inflammatory state (202). This is evidenced by the presence of elevated concentrations of inflammatory molecules including C-reactive protein (CRP), TNFα, plasma resistin, IL-6, and IL-18 (203–207), consistent with the increase in adipose tissue mass characteristic of the MetS. Conversely, as is seen in obesity, levels of the antiinflammatory adipokine adiponectin are depressed in the MetS (204, 205, 207). In addition, as the number of the MetS components an individual exhibits increases, inflammatory markers, including CRP (208, 209), TNFα (205), IL-18 (210), and plasminogen activator inhibitor-1 (PAI-1) activity (211) also increase. Individual inflammatory markers are also associated with singular components of the MetS, as detailed below.

CRP is a general marker of inflammation, making it suitable to assess in individuals with the MetS. Elevated levels of CRP are associated with increased WC (208), insulin resistance (212), BMI (213, 214), and hyperglycemia (204, 208) and are increased with the number of the MetS components. In addition, it has been demonstrated that regardless of the presence or degree of the MetS in an individual, CRP levels independently predicted the occurrence of future CVD events (209). Because the MetS has been linked with a greater chance of future CVD events (215), CRP levels may be an important independent predictor of unfavorable outcomes in the MetS.

TNFα mRNA is expressed to a significantly greater degree in the adipose tissue of obese humans in comparison with those who are lean. This difference is abated with weight loss, thereby supporting the observations of elevated TNFα in the MetS (216). The degree of TNFα mRNA adipose tissue expression is positively correlated with plasma insulin, indicating that the amount of TNFα present in adipose tissue may be related to insulin resistance (216). Plasma TNFα is also positively associated with fasting insulin and insulin resistance (HOMA), as well as body weight, WC, and triglycerides; a negative association exists between plasma TNFα and HDL-C (205). TNFα neutralization has differential effects on critical adipokines and body composition indices; thus, it improves inflammatory markers and total adiponectin in patients with the MetS without improving insulin sensitivity (217).

Resistin is expressed in adipocytes and, most notably, inflammatory cells in humans (218). It has been linked to obesity, T2D, inflammation, and atherosclerosis, although the results of animal and human studies have been at variance. Serum resistin is highly heritable and has some common genetic background with traits related to insulin resistance, reinforcing the hypothesis that this adipokine may play a pathogenic role in insulin resistance-related abnormalities, including the MetS, T2D, and CVD (219). Elevated resistin levels in the MetS have been observed, and plasma resistin is positively associated with WC (203), systolic blood pressure (203, 208), and triglycerides (203, 208), whereas it is negatively associated with HDL-C (203, 208). Resistin shows significant BMI-dependent associations with insulin resis-

tance and factors linked with obesity and inflammation in patients with T2D (220).

IL-1β genetic variants are associated with measures of chronic inflammation and risk for the MetS, and genetic influences are more evident among subjects with low (n-3) polyunsaturated fatty acid (PUFA) intake (221). IL-1β reduces insulin receptor substrate-1 (IRS-1) expression at a transcriptional level through an ERK-dependent mechanism and at a posttranscriptional level independently of ERK activation. By targeting IRS-1, IL-1β is capable of impairing insulin signaling and action and may thus participate in concert with other cytokines in the development of insulin resistance in adipocytes (222).

IL-6 is released by both adipose tissue and skeletal muscle in humans (92, 223) and, despite its role as both an inflammatory and an antiinflammatory molecule, has been shown to be positively associated with BMI, fasting insulin, and the development of T2D (224, 225) and negatively associated with HDL-C (226). Elevated IL-6 correlates temporally with increases in AMP kinase activity in multiple tissues (227) and has potential systemic impact on both glucose and lipid metabolism (228). The detriment in insulin signaling mediated by IL-6 is thought to occur at the level of IRS-1 because myotubes incubated with IL-6 have demonstrated a reversal of IRS-1 tyrosine phosphorylation induced by insulin (229).

IL-10 is a major antiinflammatory cytokine that has been associated with insulin resistance, obesity, MetS, and T2D (230, 231). IL-10 gene polymorphisms are also identified in the polycystic ovary syndrome (232). Serum IL-10 levels are significantly correlated with IL-6, CRP, and TNF-α levels, but not with adiponectin in healthy individuals. However, IL-10 is significantly correlated with adiponectin, especially in the subjects with the MetS. Thus, IL-10 may be involved in the inflammatory network of the MetS (207, 233).

The pleiotropic proinflammatory cytokine IL-18 plays a role in the inflammatory cascade, promoting both TNFα and IL-6 production (234). It is positively associated with BMI, WC, triglycerides, systolic and diastolic blood pressure, fasting glucose and insulin, and negatively associated with HDL-C in a nondiabetic Australian population (210). The GC genotype of the IL-18 −137 G/C polymorphism and the circulating IL-18 levels are independently associated with raised blood pressure, and fasting IL-18 levels are associated with the other metabolic risk factors for CVD in normal-weight and obese black South African women (235). A common IL-18 haplotype is associated with higher BMI in individuals with T2D and CVD (236). An inverse correlation between IL-18 and the antiatherogenic adipokine adiponectin has been reported in obesity, insulin resistance, CVD, and the MetS (237). IL-18 suppresses adiponectin expression in 3T3-L1 adipocytes via a novel signal transduction pathway involving ERK1/2-dependent nuclear factor of activated T-cells, cytoplasmic, cacineurin dependent 4 (NFATc4) phosphorylation (238). A report from the large population-based Dallas Heart Study showed that in univariate analysis, IL-18 levels were associated with traditional CVD risk factors and particularly with components of the MetS. In multivariate analyses, IL-18 remained associated with multiple components of the MetS but not with coronary artery calcium or aortic plaque (239).

Visfatin (also known as pre-B-cell colony-enhancing factor) is an adipokine that is highly expressed in visceral fat. Plasma visfatin has been reported to correlate with the degree of visceral adiposity in humans (240) and has been proposed as a surrogate marker for visceral fat accumulation in obese children (241, 242). There is a significant association between plasma visfatin and visceral visfatin mRNA expression (243). Associations between circulating visfatin and characteristics of the MetS, therefore, may be directly related to an expanded visceral adipose mass or as a result of increased expression of visfatin in visceral adipose tissue. Plasma visfatin levels are elevated in individuals with the MetS (244) and are associated with several components of the MetS. Serum visfatin is positively associated with BMI (245), and visfatin mRNA expression in visceral adipose tissue is associated with BMI and percent body fat (243). Interestingly, results from the recent PIOSTAT study suggest that although visfatin has been postulated as a good marker of the MetS, insulin resistance and CVD risk factors are not associated with visfatin levels, and regulation of visfatin secretion occurs through biochemical pathways independent from those influenced by pioglitazone or simvastatin (246).

The antiinflammatory molecule, adiponectin, is negatively associated with body weight (205), WC (205), triglycerides (204, 205, 247), BMI (247), fasting insulin (205), insulin resistance (HOMA) (204, 205), and systolic and diastolic blood pressure (247), whereas a positive association exists between adiponectin and HDL-C (204, 205, 247, 248). Adiponectin is a powerful inducer of other proinflammatory cytokine (IL-1β, IL-6, IL-8, and TNF-α) production by adipose tissues and macrophages (249). Transgenic mice that express human adiponectin in their liver show significantly decreased weight gain associated with less fat accumulation and smaller adipocytes in both visceral and sc adipose tissues. These mice also have increased energy expenditure, longer life span, and reduced morbidity and mortality when fed a high-calorie diet (250). Of note, high molecular weight (HMW) adiponectin exhibits a significant association with central fat distribution, whereas low molecular weight adiponectin does not (251). Additionally, the HMW/total adiponectin ratio been shown to have a greater power to predict the presence of both insulin resistance and the MetS in comparison with total plasma adiponectin (252). Therefore, in addition to total adiponectin levels, measurement of HMW adiponectin may also be valuable for the prediction of the MetS.

Interestingly, in contrast to disorders typically associated with excess adiposity, adiponectin levels are elevated in classic chronic inflammatory/autoimmune diseases, *i.e.*, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, type 1 diabetes, and cystic fibrosis (253). In these patients, adiponectin levels correlate positively rather than negatively with inflammatory markers. In the MetS, however, plasma adiponectin levels are reduced (254, 255). Finally, of great interest at present is whether the primary proinflammatory defect in adipose tissue in the MetS is the large adipocyte, insulin resistance, the infiltration and activity of monoctye-derived macrophages, or the reduction in adiponectin synthesis and secretion.

2. Endoplasmic reticulum (ER) stress. The ER is responsible for the folding of unfolded proteins delivered to its lumen. Under stress conditions (ER stress), however, unfolded proteins can accumulate in the ER lumen, activating the unfolded protein response. As a result, ER chaperone gene transcription is up-regulated to increase protein-folding capacity and reduce the ER stress (256). Despite this mechanism being in place, ER stress can increase the activity of the serine/threonine kinase c-Jun N-terminal kinase (154). An increase in the activity of c-Jun N-terminal kinase can lead to serine phosphorylation of IRS-1, down-regulating insulin signaling and possibly contributing to the development of insulin resistance (257). Stimuli that contribute to ER stress may therefore also be indirectly promoting the development of components of the MetS such as insulin resistance (258).

I. Animal models of the metabolic syndrome

Animal models can be helpful in further understanding the potential pathophysiology of the MetS. Murine models in particular have become quite useful tools in recent years because the entire mouse genome is now sequenced, and a large number of transgenic and knockout models are readily available. There are a number of limitations with these models, however, that must be considered. Rodent lipid physiology, for example, is significantly different compared with humans. Rodents carry most of their cholesterol in HDL, not LDL; thus, a low level of HDL-C is an unusual finding. Blood pressure is usually not measured in these models, again limiting the use of the "human" clinical definition of the MetS. Nevertheless, there remains much to be learned from animal models that may be applicable to mechanisms of the MetS in humans.

1. Mouse models. Historically, there were a number of murine models that exhibited many of the components of the MetS, *i.e.*, leptin-deficient *ob/ob* and leptin-resistant *db/db* mice (259, 260). More recently, when *ob/ob* mice were crossed with the LDL-receptor-deficient mouse, the features of the MetS including obesity, dyslipidemia, hypertension, insulin resistance, and IGT, and/or diabetes plus hypercholesterolemia resulted in more oxidative stress and atherosclerosis (261, 262).

A number of less-well known polygenic mouse models have a mixture of components of the MetS and its associated diseases. Some of these features are summarized in Table 7. It is worth noting that mice with different genetic backgrounds have a variable propensity to develop the MetS in response to changes in diet composition (263, 264). For instance, when C57Bl/6 (B6) and 129S6/SvEvTac (129) mice were placed on a low-fat or high-fat diet for 18 wk, the 129 strain developed features of the MetS, notably obesity, hyperinsulinemia, and glucose intolerance only on the high-fat diet, whereas the B6 strain developed these features on both diets (265).

For a number of years, the Jackson Laboratory has carried out a comprehensive assessment of genetic susceptibility to the MetS in inbred mice when challenged with a high-fat, high-cholesterol diet (266). A high-throughput protocol was set up to evaluate female and male mice from 43 inbred

TABLE 7. Mouse models of the MetS

Gene	KO/Tg	Tissue	Strain background	Sex	Age	Diet environment	Obesity or WAT	Glucose tolerance/ insulin sensitivity	Lipids (TG/FFA)	Blood pressure	Phenotypes (others)	Ref.
ApoE	KO	Whole body	Apo100 and *ob/ob* (C57BL/6J)	M	7–16 wk	Chow	BW ↑	→	↑	←	Atherosclerosis	269
11-β-HSD1	Tg	WAT	FVB	M	9–18 wk	Chow and HF	WAT ↑	→	↑	←	Intra AT and portal corticosterone ↑	270, 271
LDLr	KO	Whole body	Apo100 and *ob/ob* (C57BL/6J)	M	7–16 wk	Chow	BW ↑	→	↑	←	Atherosclerosis	269
eNOS	KO	Whole body	C57BL/6J	M	10–12 wk	Chow and HF		→	↑	←	Leptin ↑, uric acid ↑, fibrinogen ↑	272
11-β-HSD1	Tg	Liver	C57BL/6J	M	24 wk	Chow and HF	WAT ↑	→	↑		Fatty liver	270, 273
STAMP-2	KO	Whole body	C57BL/6J	M	2–5 months	Chow	WAT ↑	→	↑	←	Fatty liver, V-WAT inflammation	274
PLSCR3	KO	Whole body	C57BL/6J	M	2–6 months	Chow	WAT ↑	→	↑		Leptin ↑, adiponectin →	275, 276
ATM	KO	Whole body	C57BL/6J and 129SvEvBRD ApoE−/− (C57BL/6J)	M and F		Chow and HF	WAT ↑ on HF	→ (HF)	←	↑ (HF)	apoB48 ↑, adiponectin ↓, atherosclerosis	277, 278
V1aR (vasopressin receptor 1a)	KO	Whole body	C57BL/6J and 129sv	M	8–10 wk	Chow and HF	BW ↑ on HF	→	→		Blood volume ↓, hepatic insulin resistance, ketone bodies ↑	279–281
Lepr	KO	SF-1 neurons of VMH	C57BL/6J	M and F	20 wk	HF and LF	BW ↑ on HF, WAT ↑ on LF	→	↑		Hepatosteatosis, leptin ↑	282
PKC-λ	KO	Muscle	C57BL/6J and FVB	M and F	5 months	Chow and LF	WAT ↑	→	↑		Hepatosteatosis, Islet b cell hyperplasia	283, 284
Aromatase (ArKO)	KO	Whole body	C57BL/6J	M and F	10 wk to 3 months	Chow	BW ↑, WAT ↑	→	↑		Hepatic steatosis, adipocyte hyperplasia and hypertrophy	285–287
FGFR4	KO	Whole body	129sv–C57BL/6	M and F	4–6 months	Chow and HF	WAT ↑	→	↑		Fatty liver ↓ on HF	288
NEIL1	KO	Whole body	C57 BL/6J	M and F	6–10 months	Chow	BW ↑	→	↑		Leptin ↑ fatty liver, kidney defect	289
IL-6	KO	Whole body	C57BL/6J	M and F	3–9 months	Chow, exercise	BW ↑, WAT ↑	→	↑ (FFA)		Leptin ↑, AMPK ↓ at rest, exercise effect →	227, 290, 291
PPARγ	KI	DN hetero	129Sv/J	M and F	3–11 months	Chow and HF	BW ↑ on HF	↓ HF	↑		Reduced muscle glucose uptake on HF, WAT/ BAT morphology change	292, 293
Mas	KO	Whole body	FVB/N	M	9 wk	Chow		→	↑		Leptin ↑	294

(*Continued*)

TABLE 7. (Continued)

Gene	KO/Tg	Tissue	Strain background	Sex	Age	Diet environment	Obesity or WAT	Glucose tolerance/ insulin sensitivity	Lipids (TG/FFA)	Blood pressure	Phenotypes (others)	Ref.
LPL	Tg	Skeletal muscle	FVB/N	M	4–6 months	Chow and HF		↓	↑	ND	Fiber-type switching in skeletal muscle, cold-induced thermogenesis ↑	295–297
Wrn	KO	Whole body	C57BL/6J	M	6–10 months	HFS	BW ↑	↓			Fatty liver, pancreatic islet hyperplasia	298
4E-BP1/4E-BP2	KO	Whole body	BALB/c	M	24 wk	Chow and HF	BW ↑, WAT ↓	↓ HF			Adipocyte size ↑, liver TG ↑, leptin ↑	299
MC4-R	KO	Whole body	C57BL/6J	M and F	3–24 wk	Chow and HF	WAT ↑	↓			Fatty liver, leptin ↑, food intake ↑	300–303
Pomc	KO	Neuron	C57BL/6J 129 × 1;129S6	M and F	6–30 wk	Chow	BW ↑	↓			Defect in adrenal function	304
Pomc	KO/Tg (tg in pituitary)	Neuron	C57BL/6J DBA/2, 129 × 1;129S6	M and F	6–30 wk	Chow	BW ↑, WAT ↑	↓			Leptin ↑, food intake ↑, oxygen consumption ↑	305
NPY	Tg	Noradrenergic neurons	C57BL/6J	M and F	3–6 months	Chow	WAT ↑, BW-	↓			Ghrelin ↑, no hyperphagia, liver TG ↑	306
ALMS1	KO	Whole body	NOD and C57BL/6J	M and F	4 months	Chow and HF	BW ↑	↓			Islet hyperplasia, islet cysts, male sterile, Alstrom syndrome, steatohepatitis on HF, diabetes	307–309
ERα	KO (RNAi)	VMH	C57BL/6J or Swiss–Webster mice	F	12–30 wk	Phytoestrogen-free diet	BW ↑, WAT ↑	↓			Hyperphagia, energy expenditure ↓	310
FABP5 (mal1)	Tg	WAT	C57BL/6J KK/Ta	M M	24 wk 10–22 wk	HF HF	V-WAT ↑	↓ ↓			Fatty liver, adiponectin ↓, TNF-α ↑	311 312
			BALB/c	F	11–13 wk	Repeated stress		↓	↑		Lean body mass ↓, leptin ↑, acidosis ↑, cortisol ↑, thyroid ↓, aa turnover ↓	313
			NZBWF1	F	36 wk	Chow	BW ↑, V-WAT ↑	↓			SLE, leptin ↑, macrophage infiltration in WAT	314
			NZO SMXA5, (SM/J&A/J)	M M	6 wk 20 wk	Chow Chow and HF	BW ↑ BW ↑	↓ ↓	↑	↑	Enlarged islets	315 316–318
			A(vy) Agouti viable yellow (B6)	M	2–8 months	Chow	BW ↑, WAT ↑	↓			Leptin ↑, Agouti-colored coat	319

KO, Knockout; Tg, transgenic; HF, high fat; LF, low fat; BW, body weight; WAT, white adipose tissue; TG, triglycerides; ND, not determined; AMPK, AMP kinase; SLE, systemic lupus erythematosus; RNAi, RNA interference; SF-1, steroidogenic factor 1; HFS, high-fat and high-sugar diet; VMH, ventromedial hypothalamus; M, male; F, female; AT, adipose tissue; aa, amino acid; V-WAT, visceral white adipose tissue; DN hetero, dominant negative; KI, knock-in.

strains for 10 traits including all the major criteria of MetS while mice consumed the diet for 18 wk. A few strains of mice developed a phenotype with a plethora of metabolic abnormalities remarkably similar to the human MetS (strains *CAST/EiJ*, *CBA/J*, and *MSM/Ms*). Other strains had a more limited phenotype, *i.e.*, severe obesity (*AKR/J* and *KK/HIJ*) *vs.* protection from obesity (*WSB/EiJ*); severe dyslipidemia (*MOLF/EiJ*) *vs.* no dyslipidemia (*CZECHII/EiJ* for males and *D2* for females); and severe insulin resistance (*KK/HIJ*) *vs.* being spared from insulin resistance (*A/J*). Overall, the discrepant phenotypes within the same environmental exposures may prove useful in dissecting the genetic and related molecular mechanisms underlying the MetS and its components (267).

Many other murine models of the MetS have resulted from modifications of single genes. Although some of these models have been summarized in a previous review on the MetS (268), it is our intent in this review to provide an extensive list of the murine models of the MetS and characterize each of the models over the period of phenotypic development. The mouse models listed in Table 7 are characterized by the number of MetS components they demonstrate: glucose intolerance/insulin resistance; abnormalities in lipids (increased triglycerides and/or FFA); and increased blood pressure. Models with all three components are listed in Table 7 first (269–273), followed by those with two (227, 274–297), and finally those with only insulin resistance (298–311). The final mouse grouping is animals with a polygenic background that meet the criteria for the MetS as stated (312–319). Details for each of the models including murine strain, gender, age, environmental exposure including diet, and components of the MetS phenotype plus related structural and/or functional abnormalities when present are all provided.

2. Rat models. A number of models of the MetS have been identified in rats. The Zucker fatty rat was among the first identified (320). Subsequently, a number of studies have been published to examine the impact of diet on the phenotypic development of the MetS (321–326). Wistar Ottawa Karlsburg W rats (*WOKW*) develop all components of the MetS. Genetic analysis of this rat model has identified potential major quantitative trait loci (QTL) for glucose metabolism on chromosome 3, dyslipidemia on chromosomes 4 and 17, and obesity on chromosomes 1 and 5 (327). Moreover, the severe insulin resistance predominant in epididymal adipose tissue of these rats was associated with a 10-fold decrease in adipocyte adiponectin gene expression and decreased peroxisome proliferator-activated receptor (PPAR)-λ gene expression, but increased FOX01 gene expression compared with control rats (328). Moreover, the MetS in *WOKW* rats was associated with impaired coronary vasodilatation due to altered adrenoceptor sensitivity (329).

Another example of the MetS in rats is the corpulent (*JCR: LA-cp*) rat that like *db/db* in mice is a homozygous mutation in the leptin receptor (330). These rats are obese, insulin resistant, and hypertriglyceridemic. *JCR:LA-cp* rats, however, are prone to atherosclerosis (331–333) and also appear to be a good model to study the contribution of postprandial lipemia to the atherosclerotic process. In

these rats, lymphatic chylomicron apoB48, chylomicron size, fasting and postprandial plasma apo B48 area under the curve are all elevated (334).

The Prague hereditary hypertriglyceridemic (*hHTG*) rat was developed as a model of hypertriglyceridemia. Although these rats are not obese, they are hypertensive, insulin resistant, and glucose intolerant (335, 336). Using F2 hybrids, several QTL have been identified for hypertension and hypertriglyceridemia (337). Another model of the MetS in rats that includes hypertension is the Lyon hypertensive rat (*LH*). These rats also have obesity, dyslipidemia, and an increased insulin/glucose ratio. This rat strain has been used to identify linkage of body weight, blood pressure, and renal, metabolic, and endocrine phenotypes (338). This is a renin-dependent model of hypertension in which low-dose (non-antihypertensive) angiotensin-converting-enzyme inhibitor therapy affords significant and durable renal protection. A total genome scan in the offspring of an F2 intercross between the hypertensive and normotensive Lyon strains has identified a series of QTL for the MetS, body weight, blood pressure, lipid metabolism, and renal function (339, 340). Other hypertensive rat models of the MetS include *SHR/NDmc-cp(cp/cp)* (341) and *SHROB* (spontaneously hypertensive, obese rat) (342).

3. Other animal models. Of interest to pet owners and veterinarians alike is the fact that obesity in dogs and cats has increased in recent years (343), and dogs in particular are models of the MetS. The canine obesity model closely recapitulates the relationship between human visceral adiposity and insulin resistance. The work of Bergman *et al.* (138) supports the portal theory of insulin resistance, in which FFA from visceral adipose tissue directly enter the liver and unfavorably modify insulin action. Sympathetic nervous system hyperactivity in this model of obesity may also contribute to excessive FFA release, hypertension, and insulin resistance. As noted previously, a nocturnal increase in plasma FFA levels may account for both insulin resistance and compensatory hyperinsulinemia.

Obesity is common in cats and is a risk factor for diabetes. The prevalence of diabetes has increased concomitantly with the increase in obesity, and diabetes is now seen in approximately 0.5–1% of cats (344). Cats develop a form of diabetes that is similar to T2D in humans, characterized by islet amyloid accumulation and loss of β-cell mass (345). From more recent studies in felines, it appears that glucose metabolism in cats is similar to that in humans; however, lipid metabolism is quite different (346). This may explain why the MetS in cats is less frequent than in dogs and is not frequently studied.

4. Primate models. Historically, nonhuman primates (NHPs) have been used for a variety of studies on diabetes mellitus. Spontaneous, natural forms of diabetes have been well documented in several species, and diabetes has also been induced in NHPs with drugs and diets. Hyperglycemia and impaired glucose clearance are also commonly associated with hyperlipidemia in primates (347).

Old World NHPs first develop obesity and then insulin resistance. Like humans, when either a relative or absolute

deficiency in insulin production occurs, fasting glucose concentrations increase, and diabetes follows. NHPs with diabetes have detrimental changes in plasma lipid and lipoprotein metabolism and concentrations, lipoprotein composition, and glycation of proteins, all of which likely contribute to an accelerated rate of atherosclerosis development. The prevalence and heritability of obesity and risk factors associated with the MetS in a pedigreed colony of *Vervet* monkeys has been reported recently (348). *Vervet* monkeys demonstrated obesity, insulin resistance, and associated changes in plasma lipids even while consuming a low-fat (chow) diet. Female monkeys were at a higher risk for central obesity and dyslipidemia.

Rhesus monkeys have also been used to study metabolic diseases. During healthy aging, rhesus monkeys demonstrate decreases in insulin sensitivity and reductions in HDL-C. In monkeys that develop diabetes, significant decreases in glucose tolerance were evident by middle age (age, ~14 yr), with elevations in fasting insulin and then a progressive decline in insulin secretion with aging (349). With aging, rhesus monkeys with diabetes also demonstrated dyslipidemia and shifts in lipoprotein particle size and number as measured by nuclear magnetic resonance (350). In humans, Bjorntorp and Rosmond (351) were among the first to suggest that the MetS was caused by stress. In a model of early-life stress using variable foraging demand, food insecurity was imposed on NHP mothers for 16 wk, initiated when their nursing offspring were 3–5 months of age. Although variable foraging demand does not restrict food availability or the infant's growth, this modification in nutrient access during rearing, however, did result in a range of neurobiological abnormalities in the offspring including greater weight gain, BMI, abdominal circumference, and glucagon-like peptide-1, and decreased glucose disposal rates during a hyperinsulinemic-euglycemic clamp (352).

J. Genetic determinants of the metabolic syndrome in humans

Increasing evidence suggests that there is genetic basis for the MetS. As with most complex traits, however, the associations are quite weak, and the replication of findings has been poor. Some recently published reviews have summarized the results from multiple genome-wide scans involving different cohorts (353–355). From these studies, familial aggregation is most evident for the individual components of the MetS; however, some studies suggest that specific genes, such as those that encode for 11β-hydroxysteroid dehydrogenase, adiponectin, and the β3-adrenergic receptor, may also predispose to the development of the MetS (356–358). Furthermore, it has been suggested that the risk of the MetS may be modified by dietary fatty acid composition (359).

Of the five subphenotypes defining MetS, all are known to have strong genetic components (typically 50–80% of population variation). For example, in a study among a population of 163 individuals from Yucatan, Mexico, which has a high prevalence of obesity, T2D, and dyslipidemia, a polymorphism in the insulin gene was associated with the presence of at least one abnormality related to the MetS (360).

A genome-wide scan for glucose homeostasis in subjects without diabetes has been carried out as part of the Insulin Resistance Atherosclerosis Study (IRAS) family study (361). Significant evidence for linkage of insulin sensitivity, disposition index, and acute insulin response to glucose to different regions on chromosome 11 and 12 was observed. These results provide impetus for future positional cloning of QTL to identify the genetic determinants of the MetS.

Another study investigated the heritability of determinants of the MetS among healthy Arabs of the Oman Family Study (362). Results from this study indicated that weight, BMI, and HDL-C level were under significant genetic influence, whereas other determinants such as insulin resistance, abdominal obesity, diastolic blood pressure, and triglyceride levels seemed to be more environmentally driven.

The prevalence rates of T2D and CHD in the Ontario Oji-Cree tribe are among the highest in the world. Studying 515 adult and 115 adolescent Oji-Cree subjects revealed that increased WC and depressed HDL-C were the most prevalent MetS components, whereas increased blood pressure was the least prevalent (363). Furthermore, different functional polymorphisms in candidate genes were found to associate with the MetS in adults (AGT T174M, GNB3 825C>T, APOC3-455T>C) and more so than in adolescents (FABP2 A54T). In a separate multiethnic study, the APOC3-455T>C promoter polymorphism was also found to be associated with an approximately 2-fold increased risk of the MetS (364).

Studies defining genetic predispositions have typically focused on older populations with MetS. A recent study in younger populations (365) found a much stronger association of the PPAR-α *L162V* locus and triglycerides in males than previously reported in older and less healthy populations. Specifically, the V allele increased triglycerides by 78% ($P = 0.004$), and this single polymorphism accounted for 3.8% of all variation in serum triglycerides ($P = 0.0037$).

The Kiel Obesity Prevention Study (KOPS) examined the common genetic background that contributes to the clustering between insulin resistance, central obesity, and other MetS traits. Their findings suggested that a common genetic background contributed to the clustering of different MetS components and central obesity or insulin resistance. Common genetic influences favor central obesity as a major characteristic linking other traits (366).

A most recent report focused on the endothelial nitric oxide synthase (eNOS) gene and its role in MetS. Previous studies suggested that endothelium-derived nitric oxide facilitates skeletal muscle glucose uptake, and eNOS null mice present with many phenotypes of the MetS including insulin resistance, hypertension, and hypertriglyceridemia (367). By using haplotype tagging single nucleotide polymorphism analysis, it was suggested that genetic variation at the eNOS locus was associated with features of MetS (368). Similar single nucleotide polymorphism analysis in different populations also revealed lipid (LPIN1) gene variants (369) and polymorphism at the IL6ST (gp130) locus (370) to be associated with the MetS.

V. Risks of Metabolic Syndrome

A. Cardiovascular disease

One of the primary observations regarding the clustering of metabolic disorders was the association of these features with increased CVD risk. It is well accepted and established that multiple risk factors confer greater risk than a single risk factor. In fact, the findings that led to the development of the Framingham Risk Score (FRS) are based on this observation. The NCEP:ATPIII emphasized that the risk for CVD can be further reduced by the modification of risk factors beyond LDL lowering (1). Thus the MetS was identified as a clustering of factors that further increase the risk for CVD.

The vast majority of studies have found that patients with the MetS have more CVD and are at increased risk for developing CVD (29, 371–386). A recent meta-analysis by Gami *et al.* (387) that included 36 different reports found that the overall relative risk for incident CVD events and death for individuals with the MetS was 1.78 (95% CI, 1.58–2.00). Despite the power of the large sample size of this meta-analysis, there are some concerns of confounding due to the inclusion criteria of the selected studies. A frequently quoted study examining this issue is from the Kuopio Ischemic Heart Disease Risk Factor Study. Finnish men without CVD were followed for approximately 11 yr, and those with the MetS were three to four times more likely to die of CHD, 2.6 to three times more likely to die of CVD, and two times more likely to die from all causes (371). In another report, U.S. adults without prior CVD from the NHANES were followed for approximately 13 yr. For those with the MetS, the risk factor-adjusted proportional-hazards regression for CHD mortality was doubled (375). Using the Framingham database, the age-adjusted relative risks for CVD and CHD in men with the MetS were 2.88 and 2.54, respectively, with those in women being slightly lower (2.25 and 1.54, respectively) (388). Scandinavian men and women with the MetS from the Botnia Study had a 3-fold increase in risk for CHD and stroke (372), whereas the age-adjusted risk of fatal CVD in men and nonfatal CVD in women was increased 2-fold in Dutch adults in the Hoorn Study (382). The Atherosclerosis Risk in Communities (ARIC) study, which included more minorities, also found a relative risk of CHD of 1.5 and 2 in men and women with the MetS, respectively (379). The presence of the MetS in patients with preexisting CHD is also associated with an increased risk for CVD events and mortality (375, 389). In fact, the MetS is associated with greater risk of CVD in patients with preexisting CHD compared with those without known CHD (RR, 2.68 *vs.* 1.94) (387). Obese individuals and those with preexisting diabetes also have a doubling of CVD risk when the MetS is present (377, 390). McNeil *et al.* (391) found that older individuals (mean age, 72 yr) with the MetS were 20–30% more likely to experience a CVD event than those without. Finally, as one would expect, the more components or features of the MetS that are present, the greater the CVD risk (373, 384, 392).

There are just a few exceptions to these findings. The Casale Monferrato Study, a study in an Italian cohort of older individuals with T2D, found that the MetS did not predict CVD above and beyond the risks attributed to T2D (393). The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), another study of older individuals aged 70–82 yr, also failed to show an association between the MetS and increased risk of CVD (394). WC, however, was not measured in PROSPER, and HDL-C and diastolic blood pressure (modestly) were the only components that predicted incident CVD; neither BMI, nor systolic blood pressure, LDL-C, or triglycerides were associated with CVD risk. Because the prevalence of MetS plateaus in the 60s, this may not be a study that resolves the MetS/CVD outcome controversy. A study in a cohort of nondiabetic American Indians, The Strong Heart Study, also found no association between either insulin sensitivity or MetS and incident CVD (395). Event rates were quite low overall in this cohort, as has been shown in other studies of American Indians, potentially impacting the power to detect differences. Finally, in a study of individuals with known stable CHD, the MetS was associated with increased total mortality and CVD mortality in women but did not appear to be associated with excess risk of CVD mortality in men (396). Again, WC was not measured in this study, which may have attenuated the relationship especially in men. The mean BMI of those with the MetS was actually lower (27 kg/m^2) than the inclusion criteria (>30 kg/m^2) described in the methods, suggesting further methodological problems with the identification of those with or without the MetS. Overall, though, it appears that there is greater evidence supporting the association between the MetS and CVD risk, even in very high-risk populations.

An important question that arises regarding the association between the MetS and CVD is whether the CVD risk in the MetS is greater than the sum of the risk of the individual risk factors. This question has been reviewed and debated elsewhere (14, 397). The Framingham experience has certainly long suggested that multiple risk factors increase CVD risk more than the sum of the individual risk factors (398). A recent meta-analysis found that the risk for CVD is still increased in people with the MetS, even after controlling for the component risk factors (RR, 1.54; 95% CI, 1.32–1.79) (387). Conversely, there are several studies that suggest that the risk of the MetS is not greater than the sum of its parts (373, 379, 382, 399). Another important issue is whether the MetS offers greater prediction of CVD risk than previously established risk assessments such as the FRS (44). Analysis of the ARIC study suggested that the MetS did not improve CHD risk prediction beyond that predicted by the FRS (379). Wannamethee *et al.* (383) also found the FRS to be a better predictor of CHD and stroke than the MetS. On the other hand, *post hoc* analysis of the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) showed that individuals with the MetS had increased risk for major coronary events irrespective of their FRS (374).

The ability of the MetS to predict the incidence of CVD may differ according to how the MetS is defined. The 10-yr CVD risk in the Hoorn Study was assessed using different definitions of the MetS. The NCEP:ATPIII definition was associated with a 2-fold increase in CVD, whereas the risk was slightly less using the WHO, EGIR, and AACE definitions (382). The NCEP:ATPIII definition was also associated with a 2-fold increased risk for CVD compared with the IDF

definition when several American and European cohorts were examined (400). The meta-analysis by Gami *et al.* (387) found the WHO definition to be associated with slightly greater risk than the NCEP:ATPIII definition (2.06 *vs.* 1.67). On the other hand, the NCEP, WHO, and IDF MetS definitions all showed similar CVD risk in follow-up of the San Antonio Heart Study (25).

B. Type 2 diabetes mellitus

The prevalence of T2D has tripled in the last 30 yr (401). Currently, diabetes afflicts more than 20 million people in the United States (402). T2D is a complex disease caused by both environmental and genetic factors. It is marked by chronically elevated blood glucose concentrations, which result from defects in insulin production, insulin action, or a combination of both. Although insulin resistance is considered the hallmark of prediabetes, defects in insulin secretion are regarded as the key pathophysiological characteristic of T2D. Although T2D is a heterogeneous disease, most patients with T2D have insulin resistance and the MetS before onset of T2D (403). In fact, insulin resistance, hyperinsulinemia, dyslipidemia, and obesity precede the progression to T2D in 75 to 85% of patients (404).

Numerous studies have examined the ability of the MetS to predict T2D. The presence of the MetS increases the risk (115, 405) and is highly predictive of new-onset T2D (394, 406, 407). The risk for incident T2D is up to five times higher in individuals with the MetS compared with those without the syndrome (397, 408). Interestingly, the presence of both the MetS and insulin resistance has an additive effect because these patients exhibit a 6- to 7-fold increased risk for T2D (385).

The ability of the MetS to predict the incidence of T2D differs according to how the MetS is defined (408). The NCEP:ATPIII and IDF definitions consider elevated fasting plasma glucose as an essential, but not required, criterion for defining the presence of MetS. The WHO definition, however, requires the presence of IFG and/or IGT. The effect of varying definitions of the MetS on the risk for T2D may be significant because the risk for T2D conferred by either IFG or IGT is higher than that conferred by other individual components of the syndrome (409). Furthermore, IFG and IGT have been shown to predict the development of diabetes, independent of other components of the MetS (268). The Hoorn study found that in patients without the MetS, 33% of those with IFG only and 64.5% of those with the combination of IFG and IGT developed diabetes over a 5.8–6.5 yr follow-up (410). Additionally, Hanson *et al.* (407) found that hyperinsulinemia was the strongest predictor of diabetes incidence. This led many investigators to question whether the syndrome's ability to predict diabetes is due to a single factor (*i.e.*, insulin resistance) or whether it represents an additive effect of multiple metabolic abnormalities.

A number of major studies have published data on the effectiveness of the MetS to predict the incidence of diabetes. The Insulin Resistance Atherosclerosis Study found that IDF and NCEP:ATPIII MetS definitions predicted incidence of diabetes as well as the WHO definition, despite the first two not requiring the use of an oral glucose tolerance test or a

measure of insulin resistance (411). Laaksonen *et al.* (406) compared the WHO and the NCEP:ATPIII definitions in a cohort of Finnish men and found that the WHO definition was the most sensitive of the definitions because it detected over four fifths of prevalent and two thirds of incident cases of diabetes, all with good specificity (0.78–0.80). Subjects in the Framingham Offspring Study demonstrated that the presence of the MetS (as defined by NCEP:ATPIII criteria) accounted for approximately half of the new diabetes cases over an 8-yr follow-up period (388). The San Antonio Heart Study evaluated NCEP:ATPIII and a modified-WHO (without an oral glucose tolerance test) definition and found that the presence of IGT alone and the NCEP definition had similar and greater sensitivities for identifying patients at risk for T2D than the modified WHO definition (52, 53, and 43%, respectively). Combining IGT with the NCEP and modified WHO definitions increased the sensitivity 71 and 66%, respectively (412).

The ability of the MetS to predict diabetes risk has also been compared with the Diabetes Predicting Model and the FRS. Stern *et al.* (413) found that, in the San Antonio Heart Study population, the MetS was inferior to the Diabetes Predicting Model for determining incidence of diabetes. On the other hand, the FRS, which was developed to predict the risk of CHD, was inferior to the MetS for predicting incidence of diabetes in men from the British Regional Health Study (383).

Finally, the presence of the MetS in women with gestational diabetes mellitus (GDM) substantially increases the risk of developing T2D. GDM alone significantly increases a woman's risk for subsequently developing T2D (414, 415). The conversion of GDM into T2D varies between 6 and 92%, depending on diagnostic criteria, racial/ethnic background of the subject sample, and duration of surveillance (416). The presence of the MetS further increases the progression from GDM into T2D. In a 9.8-yr follow-up study, 481 women with prior GDM who were treated with diet alone were compared with 1000 age-matched control women. The prevalence of the MetS was three times higher in the prior GDM group when compared with controls, and this persisted after adjustment for age and BMI. As much as 67% of the GDM women were glucose intolerant *vs.* only 19% in the control group, and the prevalence of the MetS was double in the prior GDM group *vs.* the control group (417). These findings are in line with a similar study by Verma *et al.* (418), in which the prevalence of the MetS was three times higher in GDM women *vs.* controls after an 11-yr follow-up.

VI. Associated Conditions

There are a number of conditions associated with the MetS that deserve brief attention here. Some of these conditions are directly associated with the underlying excess adiposity and insulin resistance associated with the MetS.

A. Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) includes a range of pathological features from mild steatosis to NASH to cirrhosis. A presumptive diagnosis of NAFLD can be made

in patients with elevated liver enzymes and/or fatty liver by imaging in the absence of other causes of liver disease, although a definitive diagnosis can only be made by liver biopsy (419). The prevalence of NAFLD ranges from 3 to 36% of the general population, depending on how it is defined (420, 421). It has been suggested that 95% of obese individuals and up to 70% of those with T2D have some form of NAFLD (420). The prevalence of NAFLD is also increased in children with obesity and insulin resistance (422). In addition, the presence of NAFLD is a strong predictor of the MetS (421), and liver fat correlates to all of the components of the MetS (423). In those patients with the MetS, liver fat content is significantly increased up to 4-fold higher than those without the MetS (423), and the incidence of NAFLD has shown to be increased 4-fold in men and 11-fold in women with the MetS (424).

Fat deposition in the liver has been shown to be primarily due to an increased influx of fatty acids to the liver, most likely as a result of the increased lipolysis associated with obesity and insulin resistance and as a result of increased hepatic *de novo* lipogenesis (425). Reduced fatty acid oxidation and mitochondrial dysfunction and decreased export of fat further contribute to the accumulation of liver fat (420, 426). In addition, a number of transcription factors and adipokines appear to play an important role in the development of NAFLD (427). For example, in certain models of obesity, sterol regulatory element-binding protein 1c is up-regulated, potentially resulting in increased conversion of glucose to fatty acids and triglycerides (426). PPAR-α, a nuclear receptor important in fatty acid uptake and oxidation, has been shown to be underexpressed in animal models of NAFLD (427). Adiponectin concentrations are reduced in individuals with NAFLD, and the administration of adiponectin reverses NAFLD in experimental models (428). Although insulin resistance is associated with fat accumulation in the liver, fat accumulation in the liver appears to result in hepatic insulin resistance, suggesting a "dynamic" process (426). Furthermore, it has been shown that pure hepatic insulin resistance, as demonstrated in the liver insulin receptor knockout mouse model, is sufficient "to produce the dyslipidemia and increased risk of atherosclerosis associated with the MetS" (429). NAFLD, which may be a result of insulin resistance but may also be a cause of insulin resistance, may then be central to the pathophysiology of the MetS. Finally, it is less clear why some individuals with NAFLD progress to NASH and potentially to cirrhosis. Genetic factors are likely important, as are the roles of cytokines such as TNF-α and oxidative stress (420, 426).

B. Polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) is a clinical syndrome that is associated with anovulation, androgen excess, and insulin resistance. Not only do women with PCOS suffer from problems with fertility and clinical stigmata of androgen excess, but they also suffer from consequences of insulin resistance, such as a significant risk for the development of T2D (430) and CVD risk factors (431). There is, therefore, significant overlap between PCOS and the MetS. There have been debates on whether PCOS may in fact be in the con-

tinuum with the MetS. The MetS is common in women, especially obese women, with PCOS (432). The prevalence of PCOS is also rising, with rates reported as high as 28% in overweight/obese women (433). The pathophysiology of the PCOS, like the MetS, is also unclear and highly debated. The ovary, hypothalamic-pituitary axis, and insulin resistance all are thought to have a role in this condition (434). The insulin resistance and obesity that are frequently found in women with PCOS have been implicated in significant risk for CVD and metabolic disorders. Greater than two thirds of women with PCOS have some degree of glucose intolerance and are therefore at high risk for developing diabetes if they do not already have it (430, 435). Women with PCOS clearly have a higher prevalence of CVD risk factors (436, 437). Although it is not clear whether women with PCOS have a greater risk for CVD events, they certainly have evidence of greater risk for subclinical CVD (436, 438).

C. Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a potentially serious consequence of obesity and is associated with increasing BMI. There is also an association between insulin resistance and OSA (439, 440). OSA has also been shown to be associated with increased inflammation (441) and reduced adiponectin concentrations (442, 443). Individuals with OSA are more likely to have the features of the MetS than those without OSA, even when adjusted for obesity (444–446). In addition, disordered sleep in general is associated with weight gain and insulin resistance (439, 447–450). Some have even suggested that OSA should be considered as a manifestation of the MetS (448).

D. Hypogonadism

As women with PCOS are at greater risk for the MetS, there is also a relationship between the MetS and male gonadal and erectile dysfunction. Men with the MetS appear to have a greater prevalence of hypogonadism (451, 452). Conversely, hypogonadism is a risk factor for the development of the MetS and T2D (453). In addition, features of the MetS improve with testosterone replacement (454). The MetS has also been shown to be independently associated with a greater prevalence of erectile dysfunction (455–458).

The prevalence of MetS increases in women after the menopause, but whether this is the result of aging *per se* or the result of changing hormonal milieu is unclear. Furthermore, it is unclear whether the menopause-related increases in insulin resistance and dyslipidemia are the result of estrogen deficiency directly or occur secondary to increases in abdominal adiposity (459). Indeed, increases in abdominal adiposity may precede changes in insulin action and dyslipidemia, because visceral fat begins to increase during the menopausal transition (460). Nevertheless, estrogen replacement in postmenopausal women has been shown to improve many components of the MetS, such as abdominal adiposity, HDL-C, and fasting glucose (461–464) and to lower the incidence of T2D (462, 465, 466). Thus, declines in sex steroids likely contribute to the increased prevalence of the MetS in women after menopause.

E. Lipodystrophy

Lipodystrophies are inherited or acquired disorders characterized by the loss of selective adipose tissue depots. The pathogenesis of the lipodystrophies is complex and has been recently reviewed elsewhere (467, 468). These patients, especially those with partial and generalized forms of lipodystrophy, generally have severe insulin resistance and often share the features of the MetS, putting these individuals at risk for T2M, dyslipidemia, NAFLD, and CVD. Highly active antiviral therapy for the treatment of HIV-infected patients has been associated with the development of severe metabolic disturbances and "acquired" lipodystrophy (469, 470). These metabolic disturbances include hypertriglyceridemia, low HDL-C, and insulin resistance reminiscent of the MetS. The prevalence for the MetS in these patients, however, is actually lower than in the general population due in part to the low WC in this population (469).

F. Microvascular disease

Although the MetS is clearly associated with CVD, it is less clear whether patients with the MetS are at greater risk for microvascular disease independent of diabetes. Approximately 8–10% of individuals with IFG and IGT but without diabetes, most of whom have the MetS, have retinopathy (471, 472). The MetS has also been shown to be associated with an increased risk of chronic kidney disease (473–475) and microalbuminuria (476–478). Moreover, the MetS has been found to be associated with increased risk for neuropathy (479). For those individuals with diabetes, the MetS appears to be associated with increased risk for all types of microvascular disease (480, 481), although a recent *post hoc* analysis of the United Kingdom Perspective Diabetes Study did not find the MetS to be associated with a greater risk for microvascular disease in individuals with T2D (482).

VII. Therapeutics

A discussion on the therapeutic options for managing the MetS must be prefaced with the understanding that there are no randomized controlled trials published to help guide specific recommendations for managing the MetS. In addition, because it is unclear whether there is a unifying pathophysiological mechanism resulting in the MetS, it is unclear whether the MetS can be treated in and of itself. The following discussion will therefore center on treating the individual components of the MetS, with the overall goals of reducing the risk for or preventing CVD and T2D as outlined in Table 8. Nevertheless, concentrating therapeutic efforts on treating the excess adiposity and insulin resistance associated with the MetS may provide the most overall success in attaining these goals. In addition, certain therapeutic options may impact more than one component of the MetS. The following discussion will be divided into lifestyle modification, pharmaceutical therapy, and surgery.

A. Lifestyle modification

1. Diet. It is well established that weight loss is beneficial for treating all of the components of the MetS, including excessive adiposity, dyslipidemia, hypertension, insulin resistance, and hyperglycemia (483). The magnitude of weight loss need not be drastic; the Finnish Diabetes Prevention Study showed that lifestyle intervention with modest weight loss significantly reduced the prevalence of the MetS (OR, 0.62; 95% CI, 0.40–0.95) compared with the control group (484). A 41% reduction in the incidence of the MetS was also seen with the intensive lifestyle intervention of the DPP (485). In addition, a weight loss as small as 5–10% of body weight can significantly reduce triglycerides and increase HDL-C (486). Furthermore, both hypertensive individuals and individuals at risk for developing hypertension can see a significant reduction in blood pressure with a modest weight loss (487–489). Fasting blood glucose, insulin, and hemoglobin A1c can also be decreased with modest weight loss (490); interestingly, a 7-d negative energy balance without measurable weight loss has also been shown to improve insulin sensitivity (491). Notably, the DPP demonstrated that weight loss was the number 1 predictor of reduction in the incidence of diabetes (492). In fact, for every kilogram of weight loss,

TABLE 8. Therapy of MetS risk factors

Therapeutic target	Goals and recommendations
Abdominal obesity	5–10% Weight loss or weight maintenance
	Lifestyle modification with diet and increased physical activity
	Pharmacological weight loss therapy
	Bariatric surgery
Insulin resistance/hyperglycemia	Prevention or delay of progression to type 2 diabetes
	Lifestyle modification and weight loss as described above
	Pharmacotherapy
	Treatment of diabetes
	Appropriate glycemic control
Metabolic dyslipidemia	
Primary target: LDL-C	LDL-C lowering as per NCEP:ATPIII goals (see Table 9)
Secondary target: non-HDL-C	If TG ≥200 mg/dl, lower non-HDL-C to <30 mg/dl plus the LDL-C goal
Tertiary target: HDL-C	If HDL-C <40 mg/dl in men or <50 mg/dl in women, consider therapy for HDL-C raising
Elevated blood pressure	Goal BP is <140/90 mm Hg (<130/80 mm Hg if diabetes or CKD present)
Prothrombotic state	Consider low-dose aspirin for high-risk patients
Proinflammatory state	No specific goals; treat all of the above risk factors

TG, Triglycerides; BP, blood pressure.

the risk of diabetes development was decreased by 16%. A decrease in caloric intake is an avenue by which to promote a chronic negative energy balance resulting in weight loss. Although the macronutrient classification of the eliminated calories is of lesser importance when addressing overall energy balance, the type of macronutrients habitually consumed can influence the health of the individual with MetS.

a. Carbohydrate. Currently, the United States Department of Agriculture (USDA) and the Institute of Medicine (IOM) recommend a carbohydrate intake of 45–65% of total caloric intake (USDA, 2005). This recommendation is appropriate for most populations because total carbohydrate consumption has not been shown to be associated with the development of T2D or the MetS (493–495). Due in part to the recent rise in the popularity of low-carbohydrate diets, there has been interest in the effect of carbohydrate intake on serum lipid levels. Investigations into this question have consistently reported that carbohydrate intake is positively associated with total cholesterol, LDL-C, and triglycerides and negatively associated with HDL-C (496, 497). In addition, lower carbohydrate diets have been associated with improved carbohydrate metabolism in those with insulin resistance and/or T2D (498). Although weight loss has been shown to be greater with lower carbohydrate diets in the short term (499–501), the effects on long-term weight loss have been mixed (502–505).

Dietary carbohydrate can be placed into two categories: simple and complex. It is the latter that should comprise the bulk of the carbohydrate intake, whereas simple carbohydrates, especially in the form of added sugars, should be limited (USDA, 2005). Common sources of added sugars in the diet include soft drinks, cakes, cookies, pies, fruit drinks, dairy desserts, and candy (506). Although added sugars are chemically identical to naturally occurring simple sugars (*e.g.*, sugars found in fruit), concern is warranted regarding the lack of nutrients found in foods laden with added sugars. It has been shown that individuals who consume a greater percentage of calories as added sugars consume significantly less vitamins and minerals (507).

The glycemic index has received considerable attention in terms of classifying which carbohydrates are "good" or "bad" for disease risk. Low glycemic index foods (*i.e.*, those that are minimally processed) have been shown to improve components of the MetS including hyperlipidemia and hyperglycemia (508), whereas a higher glycemic index has been shown to be positively associated with insulin resistance and MetS prevalence (495). Therefore, a diet high in complex, unrefined carbohydrates with an emphasis on fiber (14 g/1000 calories consumed daily) and low in added sugars (<25% of caloric intake) is recommended for individuals with or at risk for the MetS. This type of diet was recommended for participants in the lifestyle intervention group of the DPP (*i.e.*, high carbohydrate, low fat); participants decreased their percentage fat intake by an average of 6.6% over a 1-yr period (492). This dietary change contributed to weight loss, which, as previously noted, was the primary predictor of the decrease in diabetes incidence in the study. Moreover, a lower glycemic load was associated with a reduced risk of CVD in the Nurses' Health Study (509). Interestingly,

though, diet soda but not "regular" soda was found to be a predictor of the MetS in the ARIC study (510).

b. Protein. Data regarding appropriate protein intakes for patients with the MetS are sparse. The ARIC study, however, recently found that meat intake was associated with MetS incidence (510). With the exception of patients with nephropathy, a protein intake within the recommendations for the general population is acceptable: a protein intake of 10–35% of total caloric intake is recommended by the IOM (http://health.gov/dietaryguidelines/dga2005/report/HTML/D1_Tables.htm).

c. Fat. Since NHANES 1971, the average percentage fat intake in the United States has decreased from 36.9 to 32.8% in men and from 36.1 to 32.8% in women (511), thus bringing fat intake within the recommended range of intake (*i.e.*, 20–35%; USDA/IOM). Despite these reductions, there has been a marked increase in obesity and the MetS over the same time period (512). Like carbohydrate, it may be the type of fats that are consumed, rather than the total amount, that has a greater effect on components of the MetS. Several studies have shown no effect of increased fat intake (20 to 40% of caloric intake) on insulin sensitivity (513–516), although some conflicting results have been reported (517). Interestingly, it has been shown that obese insulin-resistant women lost more weight on a 16-wk high-fat (40%), low-carbohydrate (40%) diet, whereas obese insulin-sensitive women lost more weight on a low-fat (20%), high-carbohydrate diet (60%) (518). Therefore, the degree of insulin resistance may determine what macronutrient composition is most appropriate to promote weight loss.

Evidence points toward the type of fat that is consumed having an effect on insulin sensitivity. Saturated fat has consistently been shown to be positively associated with fasting insulin levels (517, 519, 520). The substitution of unsaturated fats for saturated fats in the diet has been shown either to have no effect on (521–525) or to improve (109, 526–528) insulin sensitivity. Given the observed association between saturated fat intake and insulin levels, it is prudent to recommend a reduction in saturated fat intake (<7% of caloric intake) and in increase in the unsaturated fatty acids, specifically linoleic (5–10% of caloric intake) and α-linolenic (0.7–1.6% of caloric intake), as is promoted by the 2005 USDA Dietary Guidelines. These guidelines are also applicable in the case of CVD because investigators began researching this relationship as early as the 1960s. Both serum cholesterol and overall CVD risk have been shown to be improved by type of dietary fat, *i.e.*, a reduction in saturated fat and an increase in unsaturated fat, more so than total fat intake (529–532). The Nurses' Health Study investigators reported that a 5% increase in saturated fat intake was associated with a 17% increase in coronary risk, whereas monounsaturated and polyunsaturated fat intakes were inversely related to coronary disease (533).

d. Sodium. In addition to the effects of diet on weight loss, other "diet-related" lifestyle modifications can have a significant impact on blood pressure regulation (534). A clear positive association has been shown between sodium intake and blood pressure, with excessive sodium intake associated

with hypertension (535, 536). In addition, sodium restriction has been shown to be an important strategy in the prevention and treatment of hypertension (536–539). The Dietary Approaches to Stop Hypertension (DASH) diet showed that lower sodium intake reduced blood pressure in patients with high-normal blood pressure and mild hypertension (539). Furthermore, sodium restriction has also been associated with reduced CVD events (540) and congestive heart failure (541). Guidelines therefore recommend that daily sodium intake should be restricted to no more than 65–100 mmol (534, 542). In addition to sodium restriction, increased potassium intake has also been shown to improve blood pressure, especially in the setting of high sodium intake (543). Guidelines have recommended the intake of foods enriched with potassium, such as fruit and vegetables, with a goal of 90–120 mmol of potassium per day (534, 544).

In summary, dietary intake clearly has an impact on all of the components of the MetS. Although each case should be treated individually, it is prudent to recommend a diet low in saturated fat, higher in unsaturated fats, high in complex carbohydrates, and low in sodium.

2. Physical activity. A lifestyle intervention designed to increase physical activity and decrease, or possibly maintain, body weight is another important approach for global CVD risk modification. Higher cardiorespiratory fitness (*i.e.*, aerobic capacity) and increased self-reported physical activity have been shown to be inversely related to CVD mortality and to incidence of IGT and T2D (545–547). Although it is difficult to separate out the effect of exercise, independent of weight loss, increased physical activity appears to reduce CVD risk and incidence of T2D (546, 548–550). Thus, it should not be surprising that physical activity has been shown to predict incidence of MetS in a dose-dependent manner; lower levels of activity increased incidence of MetS and higher levels of physical activity protected against the development of MetS (551, 552). Furthermore, the odds of having the MetS were almost doubled in adults reporting no moderate or vigorous physical activity compared with those reporting engaging in at least 150 min/wk (553). Higher cardiorespiratory fitness also predicted lower incidence of MetS in middle-aged women and men followed for an average of 5.7 yr (554). Physical activity and cardiorespiratory fitness likely protect against development of the MetS through their effects on each of the individual components. Exercise is particularly effective at reducing insulin resistance and has also been shown to improve dyslipidemia and hypertension, albeit to varying degrees. Whether or not physical activity is accompanied by a change in body weight (particularly abdominal adiposity) is an important mediator in its ability to modify each of the components.

a. Aerobic exercise and abdominal adiposity. When negative energy balance (*i.e.*, caloric deficit) and weight loss are the same between groups of individuals undergoing dietary restriction, either with or without exercise, fat mass (whole-body and abdominal) is reduced to the same extent (555). However, even in the absence of weight loss, exercise has been shown to reduce visceral adipose tissue (556–558). A recent systematic review of the literature supports a dose-response effect of aerobic exercise volume on visceral adi-

posity, but the ability of exercise to reduce visceral adipose tissue was less robust in those with metabolic disorders (*e.g.*, T2D, dyslipidemia) (559). Thus, it remains unclear whether a dose-response of exercise on central adiposity holds true in MetS. Nevertheless, during weight maintenance (*i.e.*, energy balance), regular exercise appears to play an important role in abdominal fat loss (556–558) and prevention of weight regain in those who have successfully lost weight (560, 561).

b. Aerobic exercise and insulin resistance. Insulin resistance has generally been considered to be an important underlying pathology of the MetS. Although there are no definitive criteria for categorizing an individual as insulin resistant or insulin sensitive, the majority (~78%) of people who have the MetS are relatively more insulin resistant (*i.e.*, upper tertile of steady-state plasma glucose during insulin suppression) (562). Exercise improves glucose homeostasis by enhancing glucose transport and insulin action in working skeletal muscle. Not only does muscle contraction stimulate uptake of glucose through non-insulin-dependent mechanisms during exercise, but sensitivity to insulin-mediated glucose uptake is greatly improved immediately after exercise (563, 564). Although a single bout of aerobic exercise will normally not acutely improve glucose tolerance in an insulin-resistant individual with T2DM, glucose uptake during exercise is increased, and glucose and insulin response to a meal immediately after exercise is improved (565). However, in obese and T2D individuals, this acute effect of exercise on insulin-stimulated glucose uptake does not appear to persist beyond 24 h after the last bout of exercise (566). Additionally, repeated bouts of exercise that are accompanied by improvements in cardiorespiratory fitness (*i.e.*, aerobic exercise training), but no change in body weight, do not appear to improve insulin-mediated glucose uptake beyond the effect of the last bout of exercise (567). Thus, for continued benefit of exercise on insulin action, an individual would need to follow the AHA and American College of Sports Medicine recommendation to exercise at least 30 min/d most days of the week (568). There is evidence to suggest that aerobic exercise training may need to be accompanied by weight loss for a persistent effect on glucose tolerance and insulin action beyond the immediate postexercise effects (569, 570).

c. Aerobic exercise and dyslipidemia. Current NCEP:ATPIII recommendations maintain LDL-C reduction as the primary treatment goal for CVD risk reduction, but also recommend that therapeutic lifestyle changes (*e.g.*, physical activity, weight management) be implemented in those individuals with the MetS with the aim of treating elevated triglycerides and low HDL-C (571). Although aerobic exercise training has generally been shown to increase HDL-C and to decrease triglycerides, results are mixed particularly for an effect on LDL-C (572–576). The variable results of previous studies are impacted by the characteristics of the cohort being studied, including: baseline lipid/lipoprotein profile, degree of overweight/obesity (and changes in body composition over time), age, sex, and disease (*e.g.*, T2D). Nevertheless, beneficial effects of exercise training on lipids and lipoproteins are routinely observed and may have additional impact when combined with dietary modification and weight loss (577).

Furthermore, exercise has an acute effect on postprandial triglyceride excursions, possibly providing additional anti-atherogenic protection (578).

d. Aerobic exercise and hypertension. A recent meta-analyses of randomized, controlled trials studying the effect of aerobic exercise on blood pressure suggests that exercise reduces systolic and diastolic blood pressure by approximately 3.8 and 2.6 mm Hg, respectively (579). Although the effect of aerobic exercise on blood pressure is small, and not routinely observed in all studies, there may be added benefit when combined with dietary modification (*i.e.*, DASH diet) and/or weight loss (580).

e. Resistance exercise and the metabolic syndrome. As with cardiorespiratory fitness, greater muscle strength has been associated with decreased risk of developing MetS in men, suggesting that there may be a role for resistance training in the prevention of MetS (581). This association between resistance training and the MetS, however, is attenuated after adjusting for cardiorespiratory fitness (581), emphasizing the interrelatedness of the two functional measures. Nevertheless, resistance exercise has been shown to improve many of the individual components of MetS. Although resistance training has little effect on lipids, it can improve glycemic control and insulin sensitivity (582, 583) and may reduce blood pressure (584). Furthermore, resistance training may indirectly affect metabolic improvements through reductions in abdominal fat (582, 583). Prospective lifestyle interventions designed to evaluate the combined effects of resistance and aerobic exercise on MetS will add important information to this area (585).

B. Pharmaceutical therapy

1. Excess adiposity. Central adiposity is a core component of the MetS and may be one of the key elements in the pathophysiology responsible for the development of the MetS and its components. It therefore seems logical to target weight loss aggressively. As discussed above, lifestyle interventions resulting in modest weight loss can result in significant clinical benefits. Lifestyle modification, however, is too often met with failure and frustration. The National Institutes of Health guidelines for the treatment of obesity recommend consideration of pharmaceutical therapy for weight loss for individuals with a BMI of at least 30 kg/m^2 or for those with a BMI of at least 27 kg/m^2 and comorbidities associated with their excess weight. The majority of patients who meet the criteria for the MetS will therefore meet the criteria for considering pharmaceutical weight loss therapy.

It is beyond the scope of this paper to review pharmacotherapy for weight loss, and this topic has been reviewed elsewhere recently (586–589). Currently, only sibutramine and orlistat are Food and Drug Administration approved for long-term use. Studies have shown that pharmacological therapy for weight loss results in improvements in the individual components of the MetS (586). In addition, a 4-yr randomized controlled study of orlistat showed a significant reduction in the progression to diabetes in high-risk individuals (590). The long-term benefits of these agents in reducing CV risk in those with the MetS, however, have not yet

been clearly established. Nevertheless, these agents should be considered as a potential valid treatment option.

2. Insulin resistance/hyperglycemia. Insulin resistance is another core component of the MetS that potentially deserves specific attention when discussing pharmacotherapy. As discussed above, weight loss and lifestyle modification independent of weight loss can lead to clinically meaningful improvements in insulin sensitivity and should be considered the primary therapeutic options for treating insulin resistance. The difficulties and frustrations associated with weight loss efforts and lifestyle modification have driven the demand for using pharmaceutical agents that target insulin resistance more directly. The exact role of using these agents, however, is less clear. There are now several randomized, controlled trials showing that agents that target insulin resistance can help prevent the progression to T2D in individuals with IGT. It must be remembered, however, that these studies have not directly targeted individuals with the MetS. It is unclear whether these agents truly prevent the progression to T2D or simply treat glucose intolerance or mild hyperglycemia. In addition, it is unclear from these studies whether these agents improve CVD outcomes. Therefore, as with weight loss medications, the goals for the use of agents targeting insulin resistance must be kept clear.

Metformin, which has a primary mechanism of action of reducing hepatic glucose production, has been shown to reduce the progression of diabetes from IGT by approximately 31% in the DPP, of which 53% had the MetS (591). Incidence of the MetS was also reduced by 17% in the metformin-treated group of the DPP, which was driven primarily by improvements in WC and fasting glucose (485). Other cardiac risk factors, however, did not improve with metformin to the same degree as with the intensive lifestyle intervention (592). Long-term follow-up would suggest that metformin is in fact treating IGT and not necessarily "preventing" progression to T2D (593). From a safety perspective, though, no concerns emerged with 5 yr of follow-up. Now that metformin is available in generic form, the cost may not be prohibitive although no formal cost effectiveness studies have been performed. Despite the potential attractiveness of this agent for patients with the MetS, there are still many unresolved issues. What dose should be used? How long should this therapy last: indefinitely? Does metformin reduce the risk for CVD outcomes? The United Kingdom Diabetes Prospective Study (UKPDS) and its 10-yr follow-up report suggests the answer is "yes," but this outcome was measured in patients with T2D, not the MetS (594, 595).

Thiazolidinediones have been shown to improve insulin sensitivity. There are now several studies showing their potential for "preventing" T2D in high-risk individuals (596–598). Of note, the TRIPOD study showed that troglitazone could slow the progression to T2D in high-risk women with recent history of GDM (597). There appeared to be a lasting effect of troglitazone on slowing diabetes progression even when the agent was discontinued. More recently, the DREAM study showed that rosiglitazone also slowed the progression to T2D in patients with IGT by about 60% (598). Again, these studies were not performed in patients with the MetS specifically, and more recently there has been concern

regarding potential increased risk in CVD outcomes, especially with rosiglitazone (599–601). Although thiazolidinediones increase body weight, they are associated with a reduction in waist-to-hip ratio and improvements in other components of the MetS, including blood pressure, triglycerides, HDL-C, and liver-related transaminases (598).

In the STOP-NIDDM trial, acarbose, a drug that affects carbohydrate absorption and is approved for the treatment of T2D, was also shown to reduce the progression to T2D in individuals with IGT (602). This trial also showed that acarbose treatment was in fact associated with reduced CVD and hypertension (603). The main limitation of the use of this agent is its poor patient tolerability.

3. Dyslipidemia. The "metabolic" dyslipidemia is characterized by elevated concentrations of triglycerides, low levels of HDL-C, and small, dense LDL-C particles. Dyslipidemia, especially elevated LDL-C, is a major modifiable risk factor for CVD, and proper management has been shown to significantly reduce CVD events and deaths (604). This has prompted the guidelines to recommend reaching appropriate LDL-C concentrations as the primary goal. Although it is necessary to state the importance of implementing therapeutic lifestyle changes in patients with the MetS (*e.g.*, increased physical activity and decreased saturated fat and cholesterol intake), a portion of MetS patients will require drug therapy to achieve lipid goals.

a. Treatment goals. The NCEP:ATPIII guidelines have identified elevated LDL-C as the primary target of cholesterol-lowering therapy, after which other components of dyslipidemia should be addressed (1). The LDL-C goal is dependent upon a person's absolute risk for CHD, meaning the higher the risk, the lower the goal as outlined in Table 9. The majority of MetS patients will be of moderately high to high risk. The guidelines recommend that LDL-C goals should be set at less than 130 mg/dl with the option of targeting less than 100 mg/dl in moderately high-risk individuals. Target goals should be set at an LDL-C less than 100 mg/dl in high-risk patients with the option of aiming for less than 70 mg/dl in the "very high-risk" patient (605). The NCEP:ATPIII guidelines recommend setting a secondary lipid goal for non-HDL-C. Specifically, for individuals with

triglycerides of at least 200 mg/dl, after achieving LDL-C goals, the goal should be to decrease non-HDL-C (LDL-C + VLDL-C). The goal for the non-HDL-C is 30 mg/dl greater than LDL-C (1). A primary lipid target to reach this goal will be either further LDL-C lowering or triglyceride lowering. Perhaps another secondary goal should reflect atherogenic particle number instead. Atherogenic particle number can be estimated by non-HDL-C (recommended by the NCEP:AT-PIII as discussed above), LDL particle number, or apo B. It is beyond the scope of this review to discuss the relative merits of each of these biomarkers as targets for lipid management in the MetS. A tertiary lipid goal should be for HDL-C. Although the NCEP:ATPIII guidelines classify low HDL-C as less than 40 mg/dl in both men and women, there is no specific target goal for HDL-C because there is insufficient evidence to specify a therapy goal. Similarly, because the guidelines classify hypertriglyceridemia as triglyceride concentrations of at least 150 mg/dl, no specific triglyceride goals have been set.

b. Statins. Because LDL-C lowering is the primary treatment goal of the metabolic dyslipidemia, the use of LDL-C-lowering agents such as the 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins has become the standard first-line therapy. Due to their minimal drug-drug interactions and side effects, statins are considered to be the most effective class of drugs for reducing LDL-C concentrations (604). Depending on the dose and the specific type of statin used, LDL-C reductions of 15 to 60 mg/dl are observed (606). Statins increase HDL-C by 5–10%, with greater increases seen in individuals with lower HDL-C and elevated triglycerides (607–609), and reduce triglyceride concentrations by 7–30% primarily with moderate to high doses (607–609). Non-lipid-lowering or pleiotropic effects of statins have also been implicated in their beneficial effects on inflammation, endothelial function, and CVD events (610, 611). Statins are highly effective in decreasing CVD mortality and morbidity, but despite the number of primary and secondary prevention trials showing benefits in reducing CVD outcomes with statin therapy, there are no published trials to date that have specifically targeted patients with the MetS. The study that most resembles a primary prevention trial of

TABLE 9. Goals for LDL-C lowering (605)

Risk category	LDL-C goals	Recommendations

Lower risk
    0–1 Major risk factor
 	
    10-yr risk <10%
	<160 mg/dl	Lifestyle modification
		Consider pharmacotherapy if LDL-C
		    ≥190 mg/dl after lifestyle modification

Moderate risk
    ≥2 major risk factors
 	
    10-yr risk <10%
	<130 mg/dl	Lifestyle modification
		Consider pharmacotherapy if LDL-C
		    ≥160 mg/dl after lifestyle modification

Moderately high risk
    ≥2 Major risk factors
 	
    10-yr risk 10–20%
	<130 mg/dl
	Optional <100 mg/dl
		Lifestyle modification
		Consider pharmacotherapy if LDL-C
		    ≥130 mg/dl or optionally ≥100 mg/dl
		    after lifestyle modification

High risk
    CHD or CHD risk
    equivalents
	<100 mg/dl
	Optional <70 mg/dl
		Lifestyle modification
		Consider pharmacotherapy if LDL-C
		    ≥100 mg/dl or optionally ≥70 mg/dl
		    after lifestyle modification

CVD in patients with the MetS is the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm trial (612). In this study, individuals with hypertension and at least one other CVD risk factor were randomized to atorvastatin or placebo. Regardless of their baseline lipids, the treatment arm showed a significant reduction in CVD events. *Post hoc* analysis of the Treating to New Targets study found that intensive lowering of LDL-C in patients with both CHD and the MetS was associated with a reduction in major CVD events (613). Thus, at present the evidence strongly supports attention directed toward lowering LDL-C before addressing the lipid components of the MetS (614).

c. Other LDL-C lowering agents. Bile acid sequestrants (BAS) and cholesterol absorption inhibitors (CAI) lower LDL-C by decreasing absorption of intestinal bile acids and cholesterol, respectively. BAS result in 15 to 30% reductions in LDL-C (615). The only clinically available CAI, ezetimibe, has been shown to result in 15–25% reductions in LDL-C (616). Although BAS and CAI are both effective as monotherapy, greater benefits are obtained when used in combination with statins, an effect that may be due to their complementary mechanisms of action (617–619). BAS have been shown to reduce the risk for major coronary events (620), whereas ezetimibe has only been shown to reduce potential cardiac risk in patients with the MetS (620, 621). The recent Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study, although not an outcome study, demonstrated no effect of ezetimibe on carotid intima media thickness in patients with familial hypercholesterolemia despite a 17% lower level of LDL-C (622).

d. Fibrates. Fibrates are an effective therapy for reducing serum triglyceride concentrations and therefore non-HDL-C. Fibrates decrease triglycerides by 25–50%, with greater reductions in individuals that are hypertriglyceridemic (623). Fibrates also increase HDL-C by 5–15% and reduce LDL-C by 0–30%, although LDL-C may be increased in patients with low HDL-C and elevated triglycerides (604). The decrease in triglycerides may transform small, dense LDL-C into more normal-sized LDL-C (624). The Helsinki Heart Study, a primary prevention study, found that fibrate therapy with gemfibrozil significantly reduced the incidence of CVD (625, 626), but this was not specifically in patients with the MetS. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), a secondary prevention study, also showed that gemfibrozil significantly reduced CVD, especially in obese individuals with diabetes (627). Other clinical fibrate trials, such as the Bezafibrate Infarction Prevention (BIP) and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) studies, however, have found less favorable effects (628, 629); therefore the evidence for cardioprotection is not as robust as it is for statins. Combination therapy of fibrates plus statins in high-risk individuals attains the target for non-HDL-C better than statins alone. However, no clinical trials to date have compared statins against the combination of statins plus fibrates on CHD outcomes (604, 629). The potential benefits of combining these agents must be weighed against the increased risk of myopathy (630). *Post hoc* analyses of some of these fibrate studies, however, suggest that individuals with the MetS may derive greater benefits than those without the MetS (631).

e. Niacin. Niacin has favorable effects on essentially all of the abnormalities of the metabolic dyslipidemia. It is considered the most effective agent for raising HDL-C (15 to 35%) and increasing HDL particle size (632). Niacin significantly lowers triglycerides (20 to 50%) and LDL-C (5–25%) (604). Niacin also causes beneficial changes in lipoprotein subclasses because it has been shown to reduce the proportion of small, dense LDL particles while increasing large, more buoyant LDL particles and larger HDL particles (633–635). Combination therapy of niacin and a statin produces greater effects on lipid levels than does either agent given alone (636). The primary limitations for the use of niacin include flushing (most often associated with immediate-release niacin) and hyperglycemia (637–640).

f. Omega-3 fatty acids. Supplementation with marine omega-3 PUFAs may be indicated in MetS patients presenting with combined dyslipidemia. Two to 4 g of omega-3 PUFAs per day have been shown to reduce fasting and postprandial serum triglycerides by 20 to 40%, an effect that is most profound in individuals with elevated levels of triglycerides (641–643). The long-chain PUFAs, eicosapentaenoic acid and docosahexaenoic acid, appear to be equally effective in reducing serum triglyceride concentrations (644). Omega-3 PUFAs have little or no effect on HDL-C (645, 646) but can lead to 5–10% elevations in LDL-C levels (647). Studies examining the use of statins and omega-3 PUFA in treating combined dyslipidemia have found significant reductions in serum triglycerides without adverse affects on LDL-C (648, 649). In the JELIS study, the addition of eicosapentaenoic acid to a statin therapy significantly decreased the incidence of primary end points of major coronary events (*e.g.*, sudden cardiac death and fatal or nonfatal myocardial infarction) (650). Additional benefits of high-dose omega-3 PUFAs for patients with the MetS are improvements in inflammatory state (651), decreased platelet aggregation (652), reductions in blood pressure (653), enhanced endothelial function (654), and potential antiarrhythmic effects (655). Despite these benefits, the NCEP:ATPIII guidelines recommend that more definitive clinical trials are necessary before recommending high intakes of omega-3 PUFAs (1).

4. Elevated blood pressure/hypertension. Management of elevated blood pressure and hypertension is another key target in CVD risk reduction in the MetS patient, although there are no clear guidelines for blood pressure management specific to this population. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has recommended that the target blood pressure should be less than 140/90 mm Hg in those without diabetes or chronic kidney disease (CKD) and less than 130/80 mm Hg for those with diabetes or CKD (656). As with management of dyslipidemia, the primary therapeutic intervention for blood pressure management should be lifestyle modification, as discussed above, but many patients will require pharmacological therapy to reach blood pressure goals. It has been proposed that angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor

blockers should be the first-line classes of agents in the MetS, especially in the setting of diabetes or CKD (657, 658). Certainly these classes of agents have been shown to be effective in reducing the incidence of albuminuria or progression of nephropathy in patients with diabetes (659). Although a number of trials have shown that ACE inhibitors and angiotensin receptor blockers may reduce the risk for diabetes (660), a more recent study designed to examine this issue directly found that the ACE inhibitor ramipril did not prevent the progression of diabetes in persons with IFG or IGT (661). The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that treatment with a thiazide-type diuretic in patients with the MetS results in superior CVD outcomes compared with treatment with calcium channel blockers, α-blockers, or ACE inhibitors despite the less favorable metabolic profile associated with thiazide diuretics (662, 663). The ALLHAT and the UKPDS have shown that agents such as thiazide diuretics and beta-blockers lower the risk for CVD events even in patients with diabetes (664, 665). These agents, however, have also been associated with increased risk for diabetes (663, 664). Certainly the majority of patients who need antihypertensive therapy will likely need more than one agent for proper blood pressure control (542).

5. Prothrombotic state. The MetS is associated with elevated levels of coagulation factors such as fibrinogen and PAI-1 (666). Although low-dose aspirin is frequently recommended to patients with MetS (667, 668), there are no specific studies of the use of aspirin or other antiplatelet agents for the primary prevention of CVD in individuals with the MetS specifically. Long-term use of aspirin therapy has been advocated in the secondary prevention of CVD (669), and some have recommended aspirin in high-risk patients with the MetS, especially those with CVD (670). Until there are more data, however, the use of aspirin in the primary prevention of CVD should remain as an "individual clinical judgment" (669).

6. Proinflammatory state. The MetS is associated with elevated markers of inflammation. Elevated levels of CRP, a systemic marker of inflammation, have been shown to be associated with greater risk for CVD in patients with MetS (209). There are, however, no currently recommended direct therapies targeting inflammation. Lifestyle modification and weight loss result in reduced CRP concentrations (671, 672), as does the treatment of the other associated comorbidities such as dyslipidemia, elevated blood pressure, and insulin resistance/hyperglycemia (673, 674).

C. Bariatric surgery

Perhaps the most promising treatment of multiple risk factors within the MetS in the context of severe obesity lies in bariatric surgery. The data supporting the safety and efficacy of bariatric surgery have been reviewed previously (675). Titles in the literature reflect optimism about its role in resolving many health risk factors and in attenuating at least a portion of the epidemics of obesity, diabetes (676, 677), and perhaps the MetS (678). Bariatric surgery has been found to be associated with the improvement and resolution of mul-

tiple comorbidities associated with obesity, including hypertension, T2D, NAFLD, OSA, cardiopulmonary failure, CVD, arthritis, PCOS, dyslipidemia (exclusive of hypercholesterolemia), hyperuricemia, and infertility (676, 679–688). The seminal study of Pories *et al.* (676) highlighted the resolution of aberrances in glucose metabolism (IGT, T2D) over a 14-yr follow-up period. This observation was substantiated in the Swedish Obese Subjects study in which a decrease in the incidence of T2D was seen at 2 yr (including a reversal of previously diagnosed diabetes and prevention of new onset diabetes). In an extension of the study of Pories and colleagues, the reduction in incidence of T2D was from 31.8 to 8.6%, whereas the incidence increased from 56.4 to 87.5% in the control group (689). In a recent meta-analysis of 22,094 morbidly obese patients who underwent bariatric surgery, T2D resolved in 76.8% of cases and improved in 86.0% of cases (680). In a more recent study, patients with T2D randomized to laparoscopic adjustable gastric banding had a greater than 5-fold increase in "remission" of their diabetes as compared with conventional diabetes therapy (690). More specifically to the MetS, improvements in the metabolic profile have also been documented as an effect of the surgery (677, 682, 691, 692), presumably due to the redistribution of adiposity (693). Most recently, 10-yr follow-up data from the Swedish Obese Subjects study (n = 4047 severely obese subjects) showed an overall reduction in mortality in patients who had the surgery compared with the control group (694). And in a recent retrospective cohort study (n = 7925), mortality in the surgery group was reduced by 40% over 7.1 yr, particularly from deaths due to CVD, diabetes, and cancer (695). Thus, bariatric surgery appears to be beneficial on many levels in treating numerous risk factors of the MetS in severely obese people who qualify for the surgery, and it should be considered as a valid treatment option for the MetS patient.

VIII. Unanswered Questions

Despite the great interest in the MetS, many unanswered questions remain. There has been much debate and controversy over whether there is a unifying pathogenesis of the MetS. Although abdominal adiposity and insulin resistance appear to be at the core of the development of the MetS, it is still not clear whether all of the components are directly related to these conditions. How should the MetS best be defined is another important question that deserves considerable attention. As is evident from the number of different definitions proposed by different groups (NCEP:ATPIII, WHO, IDF, AACE, *etc.*), there is not a consensus on how best to define the MetS. This issue is important to resolve for a number of different reasons. Without a consensus definition, it is difficult to perform research on the MetS, and this creates confusion for the clinicians. Should a marker for the prothrombotic state or inflammation be added? In addition, whatever the components, should they all be considered equal in their importance or risk prediction? This is reflected by some definitions requiring some, but not all, components to be present. In addition, whether the MetS should reflect more of a continuum of risk as opposed to a "present" or

"absent" situation has also been debated (696). In fact, it is unclear whether these cutpoints should be based on biological or statistical endpoints. How many of the factors should actually be present to make the diagnosis also needs better scientific rationale. How should the MetS best be treated? Beyond favorable lifestyle modification, most would agree that treating each of the individual components of the MetS is important. It is less clear, however, what the goals of treatment for the individual components should be for patients with the MetS. For example, should lipid or blood pressure goals be treated more aggressively than IGT in those with the MetS? It is also unclear whether targeting a more unifying pathophysiological process such as abdominal adiposity or insulin resistance should be recommended at this time.

IX. Summary and Conclusions

The MetS is a clustering of components or risk factors associated with an increased risk for CVD and T2D. A consensus definition of the MetS has been difficult to develop, but it is an important consideration for the groups involved and continues to be a "work in progress." Although the prevalence of the MetS depends on the definition used and population studied, it has clearly been increasing globally. The MetS is not exclusive to adults. In fact, the prevalence of the MetS in younger populations is increasing in parallel with childhood obesity. This will likely be associated with increased risk for CVD and T2D in adulthood. Most studies show that the MetS is associated with an approximate doubling of CVD risk and that the risk for incident T2D is more than five times higher in individuals with the MetS compared with those without the syndrome. In addition, the MetS is associated with a number of other comorbidities such as NAFLD, sleep disorders, reproductive tract disorders, and microvascular disease.

Specific guidelines for the treatment of the MetS and/or its components have not yet been established. In addition, because it is unclear whether there is a unifying pathophysiological mechanism resulting in the MetS, it is unclear whether the MetS can be treated in and of itself. It is our opinion that lifestyle modification and weight loss should be at the core of treating or preventing the MetS and its components. It is well established that weight loss with diet and physical activity is beneficial for treating all of the components of the MetS, including excessive adiposity, dyslipidemia, hypertension, insulin resistance, and hyperglycemia. In addition, there is some consensus on treating the individual components of the MetS with the overall goals of reducing the risk for or preventing CVD and T2D. Nevertheless, concentrating therapeutic efforts on treating the excess adiposity and insulin resistance associated with the MetS may provide the most overall success in attaining these goals. In addition, pharmacotherapy and surgery for weight loss also have an important role. Pharmacotherapy targeting a number of the components of the MetS, in addition to aggressive management of LDL-C and therapy for the prothrombotic state, has also been generally accepted as appropriate management of these high-risk patients. There is more controversy over pharmacotherapy targeting insulin resistance and hyperglycemia. Finally, a number of unanswered questions regarding the MetS remain, including questions regarding the definition, pathogenesis, and treatment of the MetS.

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