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Etiology and Pathophysiology/Obesity Comorbidities

Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies

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Summary

Obesity is reaching epidemic proportions with recent worldwide figures estimated at 1.4 billion and rising year-on-year. Obesity affects all socioeconomic backgrounds and ethnicities and is a pre-requisite for metabolic syndrome. Metabolic syndrome is a clustering of risk factors, such as central obesity, insulin resistance, dyslipidaemia and hypertension that together culminate in the increased risk of type 2 diabetes mellitus and cardiovascular disease. As these conditions are among the leading causes of deaths worldwide and metabolic syndrome increases the risk of type 2 diabetes mellitus fivefold and cardiovascular disease threefold, it is of critical importance that a precise definition is agreed upon by all interested parties. Also of particular interest is the relationship between metabolic syndrome and cancer. Metabolic syndrome has been associated with a plethora of cancers including breast, pancreatic, colon and liver cancer. Furthermore, each individual risk factor for metabolic syndrome has also an association with cancer. Our review collates internationally generated information on metabolic syndrome, its many definitions and its associations with life-threatening conditions including type 2 diabetes mellitus, cardiovascular disease and cancer, providing a foundation for future advancements on this topic.

Keywords: Cancer, cardiovascular disease, metabolic syndrome, type 2 diabetes mellitus.

Abbreviations: AACE, American Association for Clinical Endocrinology; ApoB, apolipoprotein B; ARIC, Atherosclerosis Risk in Communities; AusDiab, Australian Diabetes; BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; EGIR, European Group for the Study of Insulin Research; FAs, fatty acids; GLP-1, glucagon-like peptide; GWAS, genome-wide association studies; HDL, high-density lipoproteins; IDF, International Diabetes Federation; IGF-1, insulin-like growth factor receptor-1; IR, insulin resistance; LDL, low-density lipoprotein; MetS, metabolic syndrome; NCEP:ATPIII, National Cholesterol Education Program – Third Adult Treatment Panel; NHANES, National Health and Nutrition Examination; QTL, quantitative trait loci; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHO, World Health Organization.

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Introduction

The term metabolic syndrome (MetS), first coined by Haller and Hanefeld in 1975 (1), is characterized as a combination of underlying risk factors that when – occurring together – culminate in adverse outcomes, including type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) (2) and thus an approximately 1.6-fold increase in mortality (3). The major risk factors for developing MetS are physical inactivity and a diet high in fats and carbohydrates, contributing to the two central clinical features, i.e. central obesity and insulin resistance (IR). Obesity is fundamental to MetS as it appears to precede the emergence of the other MetS risk factors (4). The defining components of MetS that cluster together are obesity/central obesity, IR, hypertension and circulating hypertriglyceridaemia (dyslipidaemia) (5).

Although the increased consequential risk of T2DM and CVD is recognized by many organizations including the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP:ATPIII), the American Association for Clinical Endocrinology (AACE) and the International Diabetes Federation (IDF), a single precise definition and the contributions of the underlying components of MetS is of much debate. As detailed in Table 1, each of these groups has developed their own (granted, typically overlapping) criteria for defining MetS, with regard to thresholds for each of the variables of MetS in order to accurately identify people at a higher than average risk of developing T2DM and CVD. In 2009, however, a joint statement by the IDF Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Health Federation; International Atherosclerosis Society; and International Association for the Study of Obesity was published. This joint definition stated that obesity and IR are not pre-requisites for MetS but that three of the five components would suffice for a diagnosis of MetS, with the thresholds for measuring waist circumference (WC) requiring ethnic and nation specificity (Table 2) (6).

Methods

A literature search conducted using PubMed, Google Scholar and Trinity College Dublin library holdings was conducted up to 16 July 2014 using multiple search terms 'Metabolic syndrome', 'Prevalence of metabolic syndrome (in geographic area e.g. Asia)'. A search for each risk factor and its relation to MetS was conducted. A search for the association between MetS and CVD and MetS and T2DM was conducted and also a search of CVD and T2DM alone. 'Metabolic syndrome and cancer', 'obesity and cancer', 'dyslipidemia and cancer', 'hypertension and cancer' were also searched. Of the papers read, 56 were selected for reference in the review, seven from 1975 to 2000, 28 from 2002 to 2007 and 42 from 2008 to 2014. Information

Table 1 Criteria as set out by the different associations for MetS definition and for MetS diagnosis

WHO	EGIR	NCEP:ATPIII	AACE	IDF
High insulin level	High fasting insulin concentrations – insulin resistance	*Any three of the following:*	Impaired glucose tolerance	Central obesity = WC (ethnicity and gender specific)
+	+		+	+
Two of the following:	*Two of the following:*		*Two of the following:*	*Two of the following:*
1. Abdominal obesity WC > 37″, BMI > 30 kg m^{-2}	**1.** WC ≥ 94 cm (male) ≥80 cm (female)	**1.** WC > 40″ (male) >35″ (female)	**1.** Triglycerides ≥150 mg dL^{-1} Cholesterol – HDL <40 mg dL^{-1} (male) <50 mg dL^{-1} (female)	**1.** Triglycerides ≥150 mg dL^{-1} Cholesterol – HDL <40 mg dL^{-1} (male) <50 mg dL^{-1} (female)
2. Triglycerides >150 mg dL^{-1} Cholesterol – HDL <35 mg dL^{-1} (male) <39 mg dL^{-1} (female)	**2.** Triglycerides >2 mmol L^{-1} Cholesterol – HDL <1 mg dL^{-1}	**2.** Triglycerides ≥150 mg dL^{-1} Cholesterol – HDL <40 mg dL^{-1} (male) <50 mg dL^{-1} (female)	**2.** BP ≥ $\frac{130}{85}$ mm Hg	**2.** BP ≥ $\frac{130}{85}$ mm Hg
3. BP ≥ $\frac{140}{90}$ mm Hg	**3.** BP ≥ $\frac{140}{90}$ mm Hg or hypertensive medication	**3.** BP $\frac{130}{85}$ mm Hg		**3.** Fasting plasma glucose ≥5.6 mmol L^{-1} or T2DM
4. Microalbuminuria >30 mg g^{-1}	**4.** Fasting glucose ≥6.1 mmol L^{-1}	**4.** Fasting plasma glucose ≥110 mg dL^{-1}		

Criteria set out for the diagnosis of MetS according to a number of influential associations.
AACE, American Association of Clinical Endocrinology; BMI, body mass index; BP, blood pressure; EGIR, European Group for the Study of Insulin Resistance; HDL, high-density lipoprotein; IDF, International Diabetes Federation; MetS, metabolic syndrome; NCEP:ATPIII, National Cholesterol Education Program – Third Adult Treatment Panel; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHO, World Health Organization.

Table 2 Ethnic-specific waist circumference thresholds for abdominal obesity

Ethnicity	Male	Female
Europid	≥102 cm (≥94 cm)	≥88 cm (≥80 cm)
South Asian	≥90 cm	≥80 cm
Central and South American	≥90 cm	≥80 cm
Middle Eastern/Mediterranean	≥94 cm	≥80 cm
Sub-Saharan African	≥94 cm	≥80 cm
Chinese	≥90 cm	≥80 cm
Japanese	≥90 cm	≥80 cm

Waist circumference cut-off values for metabolic syndrome criteria as defined by ethnicity. For Europid, the literature typically reports that ≥94 cm for men and ≥80 cm for women are suitable waist circumference (WC) cut-off, while in practice a WC of ≥102 for men and ≥88 for women are more typically used.

published on the web sites of WHO, EGIR, NCEP:ATPIII, AACE and IDF were also considered.

Prevalence

The most widely accepted and clinically used definitions for MetS are those set out by WHO, NCEP:ATPIII and IDF (Table 1) (7). The existence of these three somewhat varying definitions, which differ only in small details and defining values, impedes determining the true prevalence of MetS worldwide, as well as within specific countries, genders and ethnicities. Regardless of the details of each specific definition, however, it is generally accepted by all groups that the prevalence of MetS is increasing, in accordance with increasing body mass index (BMI) and age (8). Kaur *et al*. (9) reported that the worldwide prevalence of MetS to be between 10 and 84% depending on the ethnicity, age, gender and race of the population, whereas the IDF estimates that one-quarter of the world's population has MetS. According to Pal and Ellis (10) 20% of adults in the Western world have MetS.

Despite ambiguity on the precise definition of MetS, a number of studies have been undertaken to determine – as accurately as possible – the incidence of MetS within specific countries, ethnic backgrounds and between genders. Although this review cannot claim to be comprehensive for all countries and ethnicities, a number of studies have been reviewed (as exemplified in Table 3) for Australia, China, Denmark, India, Ireland, South Korea and the United States. Evidently, MetS is a serious global issue.

United States

In the United States, data taken from the 2000 census estimated that 47 million of the U.S. adult population (accounting for 22.5% of the adult population) had MetS, according to the NCEP:ATPIII definition (11). This figure could be an underestimation, as the IDF method is now proposed to be superior at diagnosing MetS compared with the NCEP:ATPIII definition, as described below.

Table 3 Prevalence of MetS in a selection of countries worldwide

Country	*n*	Age (years)	NCEP:ATPIII	IDF
Australia (15)	11,247	≥25	24.4% male 19.9% female	34.4% male 27.4% female
China (19)	15,540	35–74	9.8% male 17.8% female	N/R N/R
Denmark (17)	2,493	41–72	18.6% male 14.3% female	23.8% male 17.5% female
India (21)	2,350	>20	17.1% male 19.4% female	N/R N/R
Ireland (16)	890	50–69	21.8% male 21.5% female	N/R N/R
South Korea (23)	40,698	20–28	5.2% male 9.05% female	N/R N/R
United States (13)	3,601	≥20	33.7% male 35.4% female	39.9% male 38.1% female

Prevalence of MetS according to age and NCEP:ATPIII or IDF definitions.
IDF, International Diabetes Federation; MetS, metabolic syndrome; NCEP:ATPIII, National Cholesterol Education Program – Third Adult Treatment Panel; N/R, not reported.

In 2011 Mozumdar and Liguori (12) compared MetS prevalence between National Health and Nutrition Examination Survey (NHANES) III data (1988–1994) (6,423 participant's ≥20 years) and NHANES 1999–2006 data (6,962 participant's ≥20 years), according to the NCEP:ATPIII definition. The data showed that the prevalence of MetS had significantly increased between the time of the first and the second surveys, considering both the unadjusted (27.9 ± 1.1 to 34.1 ± 0.8%) and age-adjusted (29.2 ± 1.0 to 34.2 ± 0.7%) data. The unadjusted ($P = 0.012$) and age-adjusted (0.046) prevalence in men had significantly increased. For women, the unadjusted and age-adjusted ($P < 0.001$) prevalence were also significantly increased from the time of the first and the second surveys. From the NHANES 1999–2006 data, Mozumdar and Liguori (12) estimated that approximately 68 million U.S. adults had MetS (i.e. 32.4 million men; 35.3 million women).

Ford (13), in 2005, identified a discrepancy between the NCEP:ATPIII and IDF definitions for diagnosing MetS. A total of 3,601 men and women aged ≥20 years were recruited from the NHANES 1999–2002 survey. In this cohort, the NCEP:ATPIII definition identified 34.5 ± 0.9% (33.7 ± 1.6% men, 38.1 ± 1.2% female) of the cohort with MetS. In contrast, the IDF definition identified 39.0 ± 1.1% (39.9 ± 1.7% male, 38.1 ± 1.2% female) of the same population to have MetS (Table 3).

In order to determine the prevalence of MetS by group, age, race and gender, a U.S. study similar to the one

described above used data from the NHANES 2003–2006 cohort for a total of 3,423 adults subdivided as three cohorts based on age, i.e. aged 20–39, 40–59 and >60 years. Here, the overall prevalence of MetS was reported as 34% based on the NCEP:ATPIII definition. Specifically for the 20–39 years age group, 20% of males and 16% of females were identified as having MetS. For the 40–59 years age group 41% of males and 37% of females had MetS, and for the >60 years age group, 52% of males and 54% of females had MetS. These results show that MetS prevalence increases with age, but with no significant difference between genders. However, when the cohort was divided into race and ethnicity, i.e. non-Hispanic white, non-Hispanic Caucasian and non-Hispanic African-American, a difference in MetS prevalence was apparent. Specifically, 25% of non-Hispanic black males were considered to have MetS compared with 37% of non-Hispanic white males, but no significant difference in MetS prevalence for the female subgroups was reported. Non-Hispanic black and Mexican–American females were approximately 1.5 times more likely to have MetS than non-Hispanic white females (8).

Australia

An Australian population-based survey ($n = 11,247$: 5,049 male and 6,198 female) termed Australian Diabetes (AusDiab) was conducted. Participants had anthropometry, blood pressure and fasting glucose levels measured and their 10-year CVD risk was calculated. In 2005, Zimmet *et al.* (14) identified 29.1% of this Australian population older than 24 years as having MetS according to the IDF criteria and 19.3% of the same population when evaluated according to the NCEP:ATPIII criteria.

Using the same AusDiab data Cameron *et al.* (15) compared MetS prevalence using four definitions, i.e. the IDF, NCEP:ATPIII, EGIR and WHO. The NCEP:ATPIII definition identified 22.1%, the WHO definition identified 21.7%, the IDF definition identified 30.7% and the EGIR definition identified 13.4% of the cohort as having MetS. Regardless of the definition of MetS considered, the prevalence of MetS increased with increasing age and was significantly higher in men than women in all groups ($P < 0.001$). It was also determined that the WHO definition was associated with greater CVD risk (15) (Table 3). Again, in both Australian studies, the IDF definition identified a higher percentage of the population with MetS than the NCEP:ATPIII definition. Furthermore, the IDF criteria identified an apparently higher prevalence of MetS than the WHO and EGIR definitions.

Europe – Ireland, Denmark

In 2009 Waterhouse *et al.* (16) compared the prevalence of MetS by the NCEP:ATPIII and IDF criteria in an Irish population. The study enrolled 1,716 participants aged 32–78 years. The IDF definition identified 21.4% (26.4% male, 14% female) of individuals as having MetS, while the NCEP:ATPIII comparative figure was 13.2% (15.8% male, 9.3% female). The NCEP:ATPIII apparently did not recognize 8.2% of MetS patients that the IDF definition identified (Table 3).

In a Danish study, termed Monitoring of Trends and Determinants in Cardiovascular Disease health survey, 2,493 participants of 41–72 years were asked to take part in the MetS study. MetS was, again, diagnosed according to the IDF and NCEP:ATPIII definitions. The IDF definition identified 23.8% of males and 17.5% of females as having MetS, while the NCEP:ATPIII definition identified 18.6% of males and 14.3% of females as having MetS (17) (Table 3).

Asia – China, India, South Korea

Zhao *et al.* (18) aimed to determine the prevalence of MetS among north-western, rural Chinese. A cohort of 2,990 participants aged 18–80 years were enrolled and MetS was identified according to the NCEP:ATPIII, IDF definitions and the NCEP:ATPIII modified for an Asian population. MetS was identified in 7.9% (male 5.4%, female 10.4%), 10.8% (male 8.1%, female 13.6%) and 15.1% (male 12.8%, female 17.4%) according to each of the three definitions, respectively. MetS had a higher prevalence in women than men, increasing with age. Here, hypertension was the most common MetS component. In a separate study, Gu *et al.* (19) identified MetS in a Chinese population according to the NCEP:ATPIII definition. Of the 15,540 participants, aged 35–74 years, the prevalence of MetS was determined to be 9.8% in men and 17.8% in women (Table 3). The data illustrate that the percentage of MetS identified by the NCEP:ATPIII method is somewhat different in both studies for the same ethnicity. This discrepancy may be due to the differences in sample size for each study (i.e. 2,990 for Zhao *et al.* [18] and 15,540 for Gu *et al.* [19]). The discrepancy may also be due to the differences in age groups studied (i.e. 18–80 years for Zhao *et al.* [18] and 35–74 years for Gu *et al.* [19]). The latter study reported the prevalence of MetS to be higher in northern China compared with southern China and was higher in urban areas than rural areas. As Zhao *et al.* (18) studied a northwest, rural area, this may explain the differences in MetS prevalence between the two studies, although both studies do show a trend that Chinese women have a higher prevalence of MetS than Chinese men.

Sawant *et al.* (20) conducted a study in the urban city of Mumbai, India, using data from the CARDIAC evaluation camp on 548 individuals who are ≥20 years. MetS was identified in 19.52% (male 25.16%, female 12.6%) of the cohort by the NCEP:ATPIII criteria. MetS was significantly

($P = 0.008$) higher in males than females. Interestingly in 95% of the cohort, at least one component of MetS was identified according to the modified NCEP:ATPIII criteria. Considering 2,350 individuals aged ≥20 years, Deepa *et al.* (21) identified MetS in 23.2% of the subjects according to the WHO definition, 18.3% according to the NCEP:ATPIII definition and 25.8% by the IDF definition, again, as previously observed in other cohorts, e.g. in the United States (13) the IDF criteria identified a highest MetS prevalence (Table 3).

Lim *et al.* (22) compared the prevalence of MetS in a South Korean population based on data from the Korean Health and Nutrition Examination Surveys from 1998, 2001, 2005 and 2007 for a total of 6,907, 4,536, 5,373 and 2,890 individuals ≥20 years from each survey, respectively. The age-adjusted prevalence of MetS was 24.9% in 1998, 29.2% in 2001, 30.4% in 2005 and 31.3% in 2007, according to the revised NCEP:ATPIII definition. Therefore, the prevalence of MetS increased with time and low-density lipoprotein (LDL) cholesterol was the most common abnormality, increasing by 13.8% in the 10-year period. This was followed by obesity (8.7%) and hypertriglyceridaemia (4.9%). In a study (23) of 40,698 South Korean participants, MetS was identified in 6.8% (5.2% male, 9.0% female) using the NCEP:ATPIII definition, whereas the definition adjusted specifically for the Asian population and WC identified 10.9% (9.8% male, 12.4% female), while the same definition modified for BMI identified 13.1% (13.2% male, 13.1% female) with MetS (Table 3). The discrepancies in the MetS prevalence figures between these two Korean studies may be due to the substantial difference in sample sizes (i.e. 2,890–6,970 for Lim *et al.* [22] and 40,698 for Lee *et al.* [23]). Furthermore, Lee *et al.* (23) studied a Korean population based in Seoul, whereas the study by Lim *et al.* (22) was a national survey and so the different regions of study may partly explain the apparent discrepancies in MetS prevalence observed.

Collating these many studies shows that MetS is a substantial international problem, regardless of the specific criteria/definition selected to determine MetS. Differences in prevalence within a given population are apparent, depending on which specific definition is used indicating a level of agreement but also that results from different studies should be compared with caution and in full knowledge of the definition that was used. To truly determine the problem of MetS throughout the world, ideally one international definition would be agreed upon and consistently used.

Genetics of metabolic syndrome

The complexity of MetS, lack of one consistent definition and differences in lifestyle factors makes the identification of a genetic component of MetS difficult (24). However, evidence for a genetic component to MetS has been suggested through linkage analysis, candidate gene approach and genome-wide association studies (GWAS).

Family and twin studies

Family and twin studies have provided a lot of information with regard to the genetics of MetS. The heritability of MetS, as defined by the NCEP:ATPIII definition, was reported to be 24% ($P = 0.006$) in 203 subjects from 89 Caribbean–Hispanic families. The heritability of each component individually was 16–60% with lipids/glucose and obesity at 44% and blood pressure at 20% (25). Another study of 293 Italian individuals from 51 families found the heritability of MetS (as defined by NCEP:ATPIII) to be 27% ($P = 0.002$). Individually, the heritability of a de-regulated blood glucose and high-density lipoprotein (HDL) cholesterol was reported to be 10 and 54%, respectively. Central obesity, hypertension and low LDL cholesterol had the highest heritability at 31% ($P < 0.001$) (26).

Linkage studies

As MetS is a complex disorder many studies have examined its individual components or combination of some of its components, rather than MetS as a whole. Linkage studies to identify genes associated with MetS have been performed and candidate quantitative trait loci (QTL) have been identified. A QTL on chromosome 3q27 was identified for 220 U.S. Caucasian individuals from 507 families (27). This encompasses genes such as the glucose transporter, GLUT2 (24). A U.S. study of 456 Caucasian individuals and 217 African-American subjects from 204 families showed evidence of linkage for elevated body fat, abdominal visceral fat, triglyceride, glucose, insulin and blood pressure (BP) and decreased HDL cholesterol on chromosome 10p11.2 and 19q13.4 in Caucasian individuals. In African-American individuals, linkage was found on chromosome 1p34.1 (28). Evidence of linkage (between weight/waist, BP, lipid factor) of MetS phenotypes was found in a U.S. study of four ethnic backgrounds (Caucasian, Mexican–American, African–American and Japanese–American). For each group several regions harboured susceptibility genes for MetS, with a strong linkage on chromosome 2q12.1-2q12 for Caucasian individuals and 3q26.1-3q29 for Mexican–Americans (29).

Genome-wide association studies

GWAS relevant to MetS have been performed by a number of research groups. In 2007, a U.K. study enrolled T2DM (1924) individuals and control subjects ($n = 2,938$). Here an single nucleotide polymorphism was identified in the first intron of fat mass and obesity-associated protein (FTO) gene on chromosome 16q that was reproducibly in T2DM

($n = 3757$) subjects and controls ($n = 5{,}346$). The study concluded that the *FTO gene* predisposes to T2DM through its effect on BMI. One hundred sixty-five of the adults who were homozygous for the risk allele weighed approximately 3 kg more and had a 1.67-fold increased odds of obesity when compared with controls (30). An association between increased BMI and FTO and other gene loci (i.e. TMEM18, KCTD15, SH2B1, MC4R, among others) has been reported for individuals of European descent (31–35) and also in Asian populations (36). It is evident from these studies that there is a genetic link to obesity through BMI. However, further research is required to fully elucidate the role of the genes such as *FTO gene obesity*.

Only four GWAS have apparently been published to date regarding MetS as a whole. In a male Indian–Asian population, MetS was identified according to the IDF definition for 2,300 individuals. In this study, no SNP was associated with MetS as a whole but many were identified for its individual components (37). In a study of 22,161 individuals of EU ancestry, where MetS was defined by NCEP:ATPIII, five SNPs in these three (APOA5, LPL and CETP) were identified as being associated with MetS. Sixteen more SNPs were identified to be associated with combinations of MetS components (38). Kristiansson *et al*. (39) also reported SNPs within the *APOA1* gene to be associated with MetS in Finnish populations of 2,637 MetS cases and 7,927 controls.

To date many SNPs have been identified to be associated with each of the components of MetS, mostly falling in or near genes involved in lipid metabolism, adiposity and IR. However, results to date only provide a limited amount of evidence for a genetic background to MetS.

Pathophysiology

Obesity

Obesity is an excess of body fat and is measured by BMI or by WC. A BMI ≥ 25 kg m^{-2} and WC ≥ 94 cm in men and ≥80 cm in women is considered overweight, whereas a BMI ≥ 30 kg m^{-2} and WC ≥ 102 cm in men and WC ≥ 88 cm in women is considered obese (40). Central obesity is considered the most common manifestation of fundamental importance for the diagnosis of MetS (Fig. 1) (41). The prevalence of obesity worldwide is reaching epidemic levels. In 2005 the WHO estimated that 1 billion people worldwide had a BMI ≥ 25 kg m^{-2} and 300 million had a BMI ≥ 30 kg m^{-2}. They also estimated that by 2015, 1.5 billion people will have a BMI ≥ 25 kg m^{-2} (42). By 2008 Finucane *et al*. (43) had demonstrated that this figure of 1 billion had risen to an estimated total of 1.46 billion people worldwide with a BMI higher than 25 kg m^{-2}; this correlated with 898 million overweight individuals and 502 million obese individuals. A recent report from the American Heart Association stated that 154–157 million adults in the United States are overweight or obese (44). MetS is, therefore, of substantial concern to the medical field and to society in general due to the worldwide increase in obesity.

Insulin resistance

In 1988 Reaven proposed the notion of syndrome X to describe the clustering of components of MetS, with IR as the common denominator (45). Although obesity is the predominant risk factor for IR and T2DM, environmental and genetic factors also contribute to the pathogenesis (46), contributing to 171 million people being diagnosed with

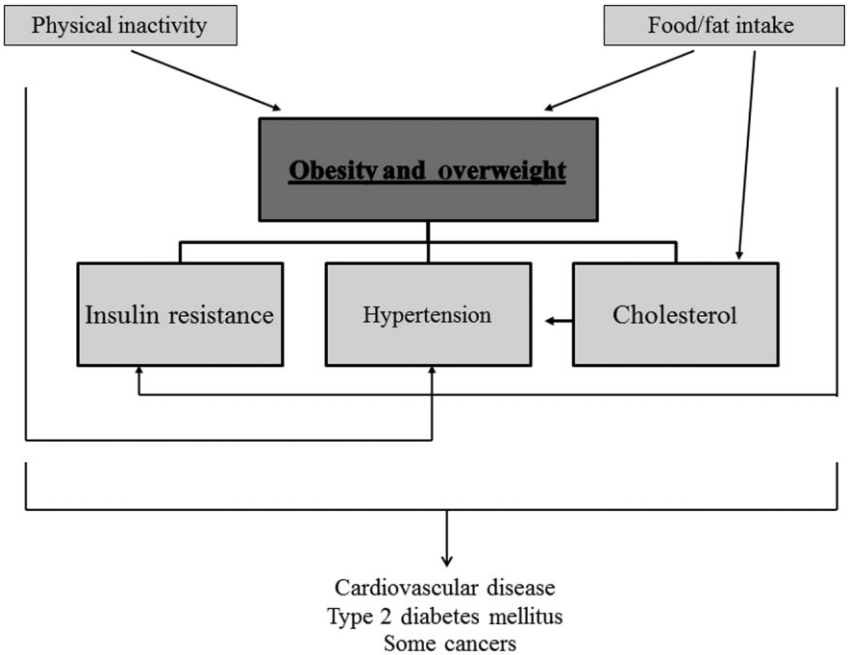

Figure 1 Interplay between the risk factors for metabolic syndrome. Overweight and obesity are central to the risk of metabolic syndrome (MetS), both predisposing to insulin resistance, hypertension and dyslipidaemia, all of which are risk factors of MetS. Arrows indicate that physical inactivity and excess food/fat intake lead to overweight and obesity, excess food/fat intake leads to hypercholesterolaemia and insulin resistance (IR), overweight and obesity lead to IR, hypertension and hypercholesterolemia.

diabetes in 2000 and projected to increase to 366 million by 2,030 (47). Thirty to 40% of the population are reported to be insulin resistant (48). In addition to contributing to IR (by an as of yet unidentified mechanism), elevated levels of fatty acids (FAs) impair β-cell function (47). IR is linked to hypertriglyceridaemia and is a driver of T2DM and also CVD (49). IR is related to several CVD risk factors, such as obesity, hyperglycaemia, hypertriglyceridaemia, low HDL cholesterol and hypertension (48). Therefore, as with obesity, IR is also an important factor in MetS.

Dyslipidaemia

In addition to obesity and IR, dyslipidaemia (an abnormal amount of lipids, e.g. cholesterol and/or fats in the blood) is a hallmark of MetS and includes the flux of FAs, apolipoprotein B (ApoB), high triglycerides, low HDL cholesterol and high small-dense LDLs (50). An association between obesity, hypertension and hypertriglyceridaemia was proposed by Albrink in the 1980s (51). From there, Albrink along with others, such as Reaven, began to demonstrate a link between dyslipidaemia and MetS (49). After several decades, the Insulin Resistance Atherosclerosis Study illustrated a direct link between IR and atherosclerosis. In addition to FAs playing a substantial role in the onset of IR in obese individuals, it was established that such FAs also have a role in the increase in triglyceride levels that lead to hypertriglyceridaemia (49). In MetS patients, dyslipidaemia may be caused by a combination of the overproduction of very-low-density lipoprotein, overproduction of ApoB, decreased breakdown of ApoB and increased catabolism of HDL cholesterol. All of these may be a consequence of IR (50). Overall, the three major components of dyslipidaemia associated with MetS are increased fasting and postprandial triglyceride-rich lipoproteins, decreased HDL and increased LDL (Fig. 2) (52).

Hypertension

As illustrated in Fig. 1, hypertension (abnormally high blood pressure) is also a central component of MetS, with approximately 85% of MetS patients suffering with this condition (53). Hypertension is usually diagnosed at a late stage in the disease, at which point consequential life-threatening diseases, such as kidney damage and heart failure, occur (54). IR and obesity have been recognized as the leading cause of hypertension (54). Fifty per cent of hypertensive people are insulin resistant (49). Obesity and IR contribute to the development of hypertension, both independently and collectively. Under normal, healthy circumstances, introduction of insulin into the bloodstream causes a release of nitric oxide and subsequent vasodilation. This is not seen in obese, insulin-resistant individuals (49). Instead, IR and thus compensatory hyperinsulinaemia activate the renin angiotensin aldosterone system with consequential vasoconstriction and hypertension (53).

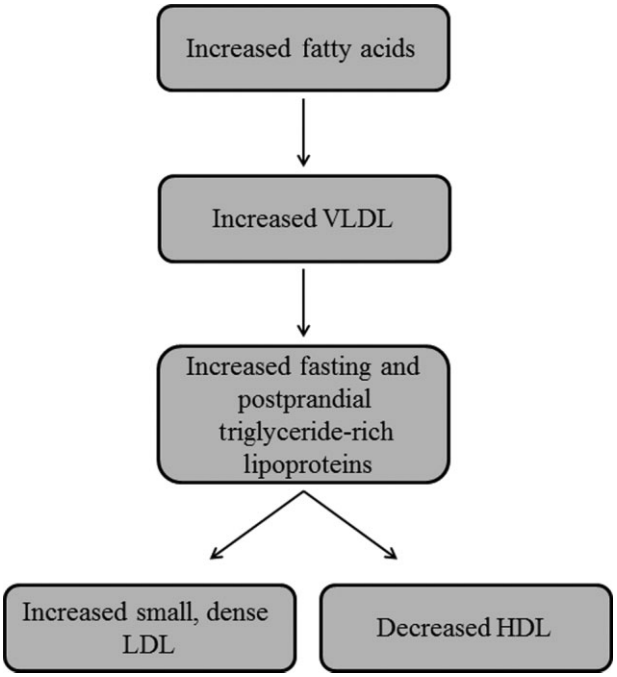

Figure 2 Process of progression from obesity and insulin resistance to dyslipidaemia. Arrows indicate that increased fatty acids lead to increased very-low-density lipoprotein (VLDL), which leads to increased fasting and postprandial triglyceride-rich lipoproteins, which leads to both increased small, dense low-density lipoprotein (LDL) and decreased high-density lipoprotein (HDL).

The NHANES 1999–2000 study in the United States, including a total of 1,677 U.S. adults aged ≥20 years, demonstrated that hypertension is the most common component of MetS in men (41%), but was the third most common component in women (37%, 52% had high WC and 43% had low HDL levels) (55).

Consequential risks associated with metabolic syndrome

It has been established that those with MetS have a five times higher risk of developing T2DM and three times higher risk of developing CVD (2). So far, however, our understanding is only as an indicator of risk and it has not yet been possible to develop an algorithm determining the personalized relative risk for a given individual developing CVD and/or T2DM (56).

Cardiovascular disease/chronic heart disease

One purpose of accurately diagnosing MetS is to at least get an indication of the increased risk of CVD (57). Although

the component factors of MetS that cluster together increase an individual's risk of CVD, it is apparent that each individual component also increases this risk (58). CVD is the leading cause of death in the Western world, accounting for 17 million deaths per year. In a Danish study focused on MetS, IR and CVD and which included 2,493 participants, 21% were defined as having MetS according to the IDF criteria and 16% were reported as having MetS according to the NCEP:ATPIII definition. After 9.4 years of follow-up, 233 deaths from the original 2,493 participants had resulted from cardiovascular (CV) events (CV death, ischaemic heart disease and stroke). This meant that the incidence of CVD deaths was 14.6% according to IDF criteria and 16.6% according to NCEP:ATPII criteria. These results taken together showed that NCEP:ATPIII definition was a significant predictor of CVD and the IDF definition was not when adjusted for IR. Of interest in this study, IR was an independent risk factor for CVD while MetS and IR were both reported to be significant predictors of CVD in the non-diabetic population. Risk of CVD from each component of MetS was not addressed (17). As this study stated, the predictive power of NCEP:ATPIII defined MetS for predicting CVD was higher than for the IDF definition. However, a study in a Greek population of 9,669 individuals and focused on comparing the predictive power of both definitions identified MetS at 43.4 and 24.5% according the IDF and NCEP:ATPIII definitions, respectively. Here the NCEP:ATPIII definition predicted a higher prevalence of CVD (23.3%) than the IDF (18.3%) (59).

Population-based research studies have analysed the increased risk of CVD among MetS patients, across ethnicities. A U.S. study spanning 8 years and involving 3,323 middle-aged individuals of mainly Caucasian ethnicity (participants were part of the Framingham offspring study, examination 4) showed that the prevalence of MetS (by the NCEP:ATPIII definition), in both men and women who did not have CVD or T2DM at baseline, increased over an 8-year period. This increase was from 21.4 to 33.9% in men and 12.5 to 23.6% in women; an increase of approximately 50% for both genders. The risk of CVD and T2DM increased in correlation with this increase in the prevalence of MetS. After 8 years 174 individuals had CVD, 107 had chronic heart disease and 178 individuals had T2DM (60). The relative risk of CVD was 2.88 in men and 2.25 in women.

Type 2 diabetes mellitus

T2DM, like MetS, is a complex heterogeneous constellation of metabolic disorders including IR, unique dyslipidaemia, obesity and hyperglycaemia (61) the most common aetiological factor being obesity (62), resulting in elevated blood glucose concentrations (5). IR, dyslipidaemia, obesity and hyperinsulinaemia all precede T2DM in 75–85% of patients. There are approximately 150 million people worldwide with the condition and this figure is projected to double by 2020 (61). In a U.S. population of 20- to 74-year-olds, a meta-analysis incorporating studies from 1976 to 1980 and 1999 to 2000 showed an increase in prevalence of total diabetes (i.e. both type 1 and type 2) from 5.3 to 8.2% and the number diagnosed with diabetes between the two time periods increasing from 41 to 83%. The increase in the prevalence of T2DM was reported to be due to the rise in obesity. An increase in mean BMI from 25.4 to 26.7 kg m^{-2} from 1980–1962 to 1999–2000 was also seen. This correlated with an increase in mean obesity from 14.5 to 26.7% during the same periods and these increases correlated with an increase in T2DM from 1.8 to 5.8% (63).

The pancreatic hormone glucagon is also substantially relevant and must be consider. Glucagon is secreted by the alpha (α) cells of the pancreas and dys-regulation of α cells may precede β cell dys-regulation in T2DM (64). Glucagon functions to increase glucose levels in the blood, antagonistic to insulin. It is dys-regulation in both type 1 diabetes and T2DM, but the effect is apparently more subtle in T2DM although there is evidence of some increased secretion and/or incomplete suppression of α cells in the majority of T2DM patients. In T2DM, the levels of glucagon are inappropriately high and appear to contribute to hyperglycaemia and abnormal glucose regulation (65). Although studies relating glucagon to MetS *per se* are lacking, of note is glucagon-like peptide-1 (GLP-1). GLP-1 is an integrin produced in the intestines that regulates both insulin and glucagon levels. In T2DM, sera levels of GLP-1 are also increased. In a Japanese study, GLP-1 was significantly ($P < 0.001$) increased in the MetS group ($n = 60$) compared with the pre-MetS group ($n = 37$). The levels of GLP-1 correlated with the number of MetS components present. Of further note, MetS patients with a high level of GLP-1 were at a higher risk for CVD, independent of diabetes (66).

Cancer as a comorbidity

Over the last several years, the prevalence of cancer and its association to MetS has been documented, but substantial epidemiological studies linking the two are lacking. From studies that have been reported on so far, MetS or its components may play a role in the aetiology, progression or prognosis of certain cancers. The American Cancer Society estimates that there are approximately 1.5 million new cancer cases per year accounting for 500,000 cancer deaths; ~20% of which are associated with obesity (67).

Cancer and obesity

Considering the components of MetS, obesity – as is stated above – is reaching epidemic proportions worldwide with

68% (72.3% male, 64.1% female) of the U.S. population being overweight or obese (68). Obesity is associated with a high incidence of cancer risk at multiple sites and is both a risk factor and poor prognostic factor for many malignancies including renal, breast, ovarian, pancreatic, endometrial and oesophageal cancers (69,70). Overweight and obesity account for approximately 20% of all cancer cases (71). An association between obesity and cancer has been established, but the mechanism(s) for this association has not been elucidated. It is known, however, that obesity contributes to IR; this leads to increased insulin levels correlating with increased levels of the growth factor insulin-like growth factor receptor-1 (IGF-1) (70). IR or oxidative stress may, therefore, be a contributing mechanism.

A study performed in the United States from 1982 to 1998 involving 900,000 men and women (404,576 men, 495,477 women), who were free from cancer at baseline found that at the time of the 16-year follow-up 57,145 deaths had occurred. The results of the study showed that men with a BMI ≥40 had a 52% higher death rate from all cancers and women with a BMI ≥40 had a 62% higher death rate from all cancers than men and women of normal weight, respectively. From these data it was concluded that 14% of all cancer deaths in men and 20% in women in the United States could be prevented if normal weight was maintained (72).

Cancer and insulin resistance

There is growing epidemiological and clinical evidence implicating IR to cancer risk, but the mechanism(s) by which IR increases cancer risk is yet to be fully elucidated, although many theories have been proposed including genetic and/or environmental factors that lead to IR, e.g. obesity and hyper-insulinaemia. Obesity leads to a number of pathophysiologies including an increase in FAs and triglycerides in the blood resulting in IR. Once IR is established, hyper-insulinaemia, hyperglycaemia and increased gluconeogenesis result. In insulin-resistant patients hyperinsulinaemia leads to mitosis of cells; mitosis is disrupted by reactive oxygen species (ROS) produced by hyperglycaemia and also increased FAs. ROS overproduction results in deoxyribonucleic acid mutagenesis and carcinogenesis. Increased gluconeogenesis results in hyperglycaemia, decreased sex hormone binding globulin, increased IGF-1 that leads to increased IGF-1 and anti-apoptosis and altogether this results in tumour initiation. Hyper-insulinaemia and increased availability of IGF-1 in insulin-resistant patients apparently have a role in tumour initiation and progression. Specifically, they stimulate ovarian synthesis of sex steroids and, in the breast and endometrium, they promote cellular proliferation and inhibit apoptosis (73). Although the exact mechanism linking cancer and IR is not known, hyperinsulinaemia and increased IGF-1 availability appear to play a role in tumour initiation and progression in insulin-resistant patients.

Cancer and dyslipidaemia

Dyslipidaemia includes high levels of LDL cholesterol and low levels of HDL cholesterol and has also been associated with increased cancer risk. During the U.S. Atherosclerosis Risk in Communities (ARIC) study from 1987 to 2000, 259 of 14,547 individuals were diagnosed with lung cancer. The individuals diagnosed with lung cancer were more likely than controls to have low levels of HDL cholesterol and to have a higher prevalence of CVD at baseline (74).

A 1-year study performed in the Edith Wolfson Medical Centre, Israel, included 204 patients aged 66.6 ± 18.9 years (107 male, 97 female), and divided according to low and high HDL cholesterol levels. Cohort 1 included $n = 108$ with HDL ≤20 mg dL^{-1}, whereas cohort 2 included $n = 96$ individuals with HDL ≥65 mg dL^{-1}. HDL levels in cohort 1 were found to inversely correlate with odds of death. Low HDL was seen more so in men (67.7%) than women (36.5%). Of the 204 individuals, 50 had been previously diagnosed with a cancer malignancy that correlated to 37 and 10.4% in cohort 1 and cohort 2, respectively. The researchers deduced that an increase of 1 mg mL^{-1} serum HDL correlated with a 2.3% decrease in cancer risk. In agreement with this notion, low HDL cholesterol has been demonstrated in colorectal, gastric, breast and prostate cancer (75), while a high LDL cholesterol is associated with a 15 times increase in haematological cancer risk (76).

Conclusion

MetS has been highlighted as a major socioeconomic problem throughout the world as the burden of MetS along with its individual risk factors, i.e. central obesity, IR, dyslipidaemia and hypertension is evident throughout all ethnicities studied. Currently, there are several definitions for MetS as set out by the IDF, WHO, AACE, among others. Because of the inconsistency in cut-off points set out by these organizations, the true prevalence is hard to determine. An internationally acceptable single definition for MetS, agreed upon by all, is urgently required to avoid confusion – keeping in mind that earliest diagnosis and intervention could alleviate the increased risk of many associated problems such as T2DM, CVD and cancer. The data illustrate that perhaps MetS may be a graded condition. Many studies show that as the number of components of MetS rises so too does the condition being studied (i.e. GLP-1 levels are increased in MetS and this increase correlates with the increase in MetS components). This would, therefore, indicate an additive effect of each MetS component contributing to full-blown MetS and also the risk of

CVD and T2DM increases with increasing MetS components. Klein *et al*. (77) identified an approximately 35-fold increase in T2DM risk for individuals with four or more components compared with those with none of the MetS components at baseline. It is possible, therefore, that a decrease in one or two of the components of MetS could potentially reduce the risk of CVD and T2DM. This would not only help save lives but would reduce the very substantial burden that each of these conditions places on the healthcare systems throughout the world. In 2012, in the United States alone the cost of T2DM was $245 billion, with CVD costs $108.9 billion annually. Cancer diagnosis and treatment are also extraordinarily large draws on the economy. Accurate and timely diagnosis and treatment of MetS – or better still, prevention – is therefore crucial to the health of the world's population but also to the global economy. Further efforts to reach a consensus on a common definition could be a substantial step on the route to progress.

Conflict of interest statement

The authors would like to declare no conflicts of interest as stated on the ICMJE form for disclosure of potential conflicts of interest.

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