Abdominal obesity and metabolic syndrome

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Metabolic syndrome is associated with abdominal obesity, blood lipid disorders, inflammation, insulin resistance or full-blown diabetes, and increased risk of developing cardiovascular disease. Proposed criteria for identifying patients with metabolic syndrome have contributed greatly to preventive medicine, but the value of metabolic syndrome as a scientific concept remains controversial. The presence of metabolic syndrome alone cannot predict global cardiovascular disease risk. But abdominal obesity — the most prevalent manifestation of metabolic syndrome — is a marker of 'dysfunctional adipose tissue', and is of central importance in clinical diagnosis. Better risk assessment algorithms are needed to quantify diabetes and cardiovascular disease risk on a global scale.

Metabolic syndrome is associated with an increased risk of type 2 diabetes and cardiovascular disease (CVD)[1–8]. Although there is a debate surrounding the concept of metabolic syndrome[9–11], it is recognized as a major and prevalent CVD risk factor by bodies such as the World Health Organization (WHO)[12], the National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATP III)[13] and the International Diabetes Federation (IDF)[14].

After an initial attempt by the WHO to define metabolic syndrome on the basis of certain criteria that included an insulin resistance marker, the NCEP–ATP III proposed simple screening tools and cut-off values to help identify patients who are likely to have features of metabolic syndrome and be at increased relative risk of type 2 diabetes and CVD[13]. The five screening variables used to identify those with metabolic syndrome are waist circumference, circulating levels of triacylglycerols and of high-density lipoprotein (HDL)-cholesterol, fasting glycaemia and blood pressure. A meta-analysis of the prospective studies that have used these criteria has shown that the presence of metabolic syndrome increases the risk of type 2 diabetes and CVD[15].

The recommendation to measure waist circumference rather than body mass index (BMI) recognized the important part played by abdominal obesity in metabolic syndrome. By singling out waist circumference, the NCEP-ATP III recommendation acknowledged that health professionals and clinicians are struggling with a demographic explosion: more and more patients are overweight or obese and show the related metabolic effects of an affluent, sedentary lifestyle characterized by excess consumption of highly processed, energy-dense food of poor nutritional value. The parallel rapid growth of overweight and obese individuals and of type 2 diabetes is striking[16], and led to the coining of the term 'diabesity'[17–20] to emphasize the link between these two conditions. Type 2 diabetes might be a significant CVD risk factor, but the independent contribution of the hyperglycaemic state of type 2 diabetes to CVD risk is rather weak. This hyperglycaemic state is only the tip of a huge dysmetabolic iceberg, mostly resulting from a combination of factors found in overweight and obese patients with excess abdominal fat and insulin resistance[2].

The existence of metabolic syndrome implies a shift from a pathophysiological concept based on metabolic abnormalities resulting from an insulin-resistant state to an epidemiological construct based on abdominal obesity and crude correlates of the features of insulin resistance. Some investigators argue that there is no rationale for the existence of metabolic syndrome and that insulin resistance is the key culprit increasing CVD risk (on top of traditional risk factors) in obese individuals[7,9–11]. Non-Caucasian populations may be more or less prone to abdominal and visceral fat accumulation[21–26] and to the development of metabolic abnormalities, and it has been proposed that the publication of specific waist circumference cut-offs to define abdominal obesity in various ethnic groups is not supported by solid epidemiological and metabolic data.

Beyond excess body weight

Although obesity is a risk factor for insulin resistance and type 2 diabetes, and a significant risk factor for CVD, not every obese patient is insulin resistant[27] or at high risk of diabetes and CVD. This explains why obesity has been an ill-defined modifiable CVD risk factor compared with others such as hypertension, smoking and cholesterol (high low-density lipoprotein (LDL)/low HDL). But, for any given amount of total body fat, the subgroup of individuals with a selective excess of intra-abdominal, or visceral, adipose tissue is at substantially higher risk of being characterized by insulin resistance and by the features of metabolic syndrome[28,29]. Although excess visceral fat accumulation is associated with various atherogenic and diabetogenic abnormalities[28–32], an important question has been whether visceral fat is a causal factor or simply a marker of a dysmetabolic profile.

Pathophysiology of visceral obesity

There is ample evidence that an impaired non-esterified fatty acid (NEFA) metabolism could contribute to the insulin-resistant state observed among individuals with visceral obesity. Hypertrophied intra-abdominal adipocytes are characterized by a hyperlipolytic state that is resistant to the antilipolytic effect of insulin[33,34]. The resulting NEFA flux to the liver may impair liver metabolism, leading to increased hepatic glucose production. Hepatic insulin resistance is associated with decreased apolipoprotein B degradation and increased production of triacylglycerol-rich lipoproteins. A high-fat diet promoting visceral adiposity in a canine model of diet-induced visceral obesity can induce hepatic insulin resistance with respect to glucose production, whereas the sensitivity of peripheral tissues seems to be less affected by the diet-induced increase in visceral adiposity[35]. Although trivial differences in fasting NEFA levels have sometimes been observed in response to this high-fat regimen, there was a marked increase in the 24-hour NEFA

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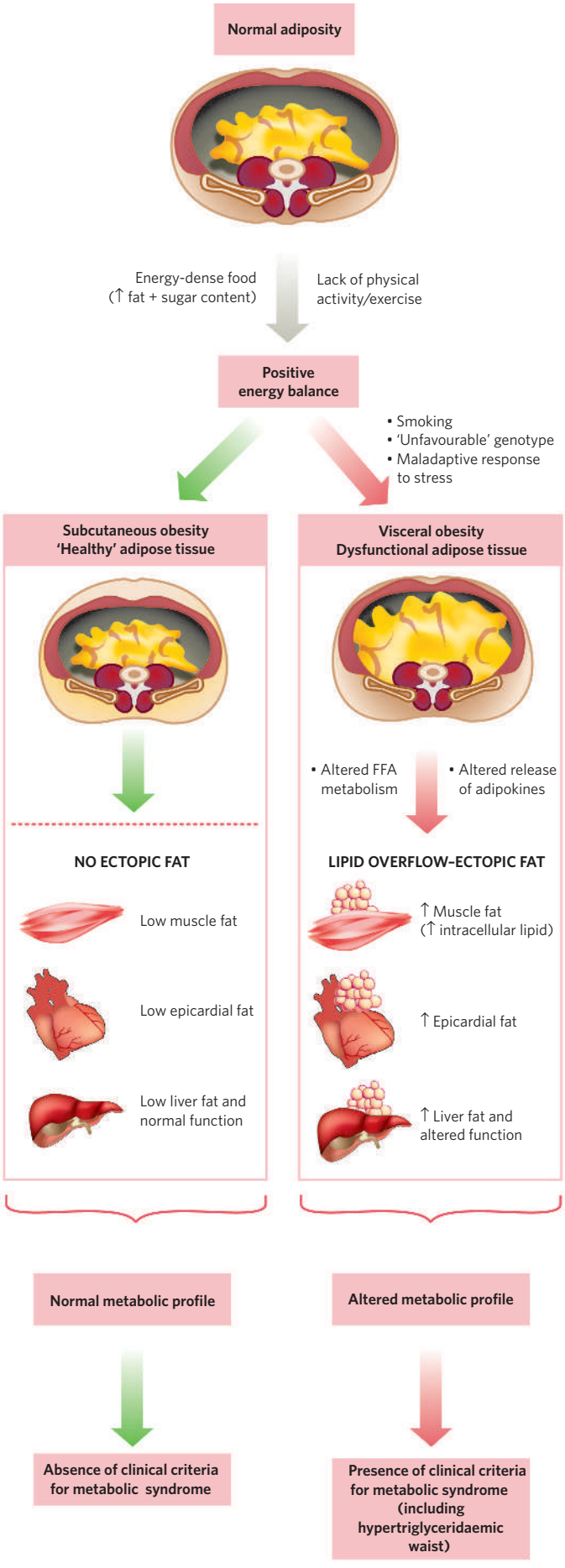

Figure 1 | The lipid overflow–ectopic fat model. Excess visceral fat accumulation might be causally related to the features of insulin resistance, but might also be a marker of a dysfunctional adipose tissue being unable to appropriately store the energy excess. According to this model, the body's ability to cope with the surplus of calories (resulting from excess caloric consumption, a sedentary lifestyle or, as is often the case, a combination of both factors) might, ultimately, determine the individual's susceptibility to developing metabolic syndrome. There is evidence suggesting that if the extra energy is channelled into insulin-sensitive subcutaneous adipose tissue, the individual, although in positive energy balance, will be protected against the development of the metabolic syndrome. However, in cases in which adipose tissue is absent, deficient or insulin resistant with a limited ability to store the energy excess, the triacylglycerol surplus will be deposited at undesirable sites such as the liver, the heart, the skeletal muscle and in visceral adipose tissue — a phenomenon described as ectopic fat deposition. Factors associated with a preferential accumulation of visceral fat and with features of insulin resistance include, among others, smoking, the well-documented genetic susceptibility to visceral obesity[94] and a neuroendocrine profile related to a maladaptive response to stress[30]. The resulting metabolic consequences of this 'defect' in energy partitioning include visceral obesity, insulin resistance, an atherogenic dyslipidaemia and a pro-thrombotic, inflammatory profile. These are defining features of metabolic syndrome. This constellation of abnormalities can be detected by the clinical criteria for metabolic syndrome, the two simplest being the simultaneous presence of increased waist girth and fasting triacylglycerol levels, a condition that has been described as 'hypertriglyceridaemic waist'[85].

profile of these viscerally obese dogs. It was therefore proposed[35] that such an increase in NEFAs could be a stimulus for insulin secretion and could have an important role in the aetiology of insulin resistance, particularly as it relates to hepatic carbohydrate and lipid metabolism.

In humans, although there is a correlation between visceral fat accumulation and portal delivery of NEFAs to the liver, most portal NEFAs originate from the systemic circulation. This suggests that other factors might explain the altered metabolic profile of viscerally obese patients[36]. There is evidence that adipose tissue is not only specialized in the storage and mobilization of lipids but that it is also a remarkable endocrine organ releasing numerous cytokines, including, among many others, proinflammatory molecules such as interleukin (IL)-6 and tumour necrosis factor-α (TNF-α). In obesity, there is evidence of macrophage infiltration in adipose tissue[37], which could contribute to the inflammatory profile that has been reported in abdominally obese patients[38]. Plasma levels of C-reactive protein (CRP), an inflammatory marker that is predictive of a risk of myocardial infarction possibly greater than that estimated by traditional risk factors[39], are increased in patients with visceral obesity[40].

The protein adiponectin[41,42] is abundant in the blood, and is specifically derived from adipose tissue. As opposed to proinflammatory adipokines, adiponectin levels are reduced in obese individuals, particularly among patients with excess visceral adiposity[43]. Adiponectin has been found to have many effects *in vitro* that are compatible with improved insulin signalling and potential protection against atherosclerosis[44,45]. The reduced adiponectin levels observed in viscerally obese patients could therefore be one of the key factors responsible for their atherogenic and diabetogenic metabolic risk factor profile. Abdominally obese patients with an excess of visceral adipose tissue have elevated plasma CRP concentrations accompanied by elevated IL-6 and TNF-α levels and by reduced adiponectin concentrations[43,46]. However, although low adiponectin levels are a salient feature of visceral obesity, whether this adipokine has a central role in the altered metabolic risk profile of patients with visceral obesity remains uncertain. Overall, these results are consistent with an important endocrine function of the expanded visceral adipose depot not only leading to altered NEFA metabolism but also to a proinflammatory profile[47] that might contribute to the insulin resistance and altered glucose homeostasis of viscerally obese patients[48].

Both the altered NEFA metabolism and the endocrine function hypotheses imply that visceral adipose tissue is causally involved in the pathophysiology of the metabolic syndrome that is often found in

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patients with visceral obesity. However, another possibility (which does not exclude a contribution from the two mechanisms described above) is that excess intra-abdominal fat accumulation represents a marker of the relative inability of subcutaneous adipose tissue to act as an 'energy sink' when an individual has to handle a calorie surplus due to excess energy intake and/or reduced energy expenditure[49] (Fig. 1). Such a relative deficit in the capacity of subcutaneous fat to store excess energy would result in increased accumulation of fat at undesired sites such as the liver, the skeletal muscle, the heart and even in pancreatic β-cells, a phenomenon that has been described as ectopic fat deposition[50]. Consistent with this theory is the fact that transgenic mice that are essentially fatless owing to the expression of A-ZIP/F-1 protein — which blocks the activity of several transcription factors — also show liver and muscle insulin resistance and eventually develop diabetes[51,52]. Surgical implantation of adipose tissue in these mice improves the insulin sensitivity of their liver and muscles[51,52], consistent with the idea that subcutaneous fat is a metabolic sink to buffer an energy surplus. In humans, the severe insulin-resistant state found in patients with lipodystrophic conditions[53] is also consistent with the role of subcutaneous adipose tissue as a depot buffering the energy excess[54]. In accordance with this hypothesis, treatment with glitazones increases subcutaneous fat deposition[55], which might help to explain the beneficial effects of this class of drug on muscle and liver insulin sensitivity.

Thus, the insulin-resistant, dyslipidaemic state found in patients with the features of metabolic syndrome might be only partly explained by the peculiar metabolic and endocrine properties of the expanded visceral adipose tissue. Visceral obesity might also be a marker of defective fat partitioning between the adipose tissue, the skeletal muscle, the liver and the heart.

On the basis of the association between abdominal, especially visceral, adiposity and the presence of the features of metabolic syndrome, the measurement of waist circumference has been proposed as a crude anthropometric correlate of abdominal and visceral adiposity[12–14]. But measuring waist girth has its limitations, which are discussed below.

Clinical criteria

The five simple criteria and cut-off values proposed by the NCEP–ATP III panel[2,13] and endorsed by the IDF[14] to diagnose the likely presence of metabolic syndrome were reached through expert consensus and interpretation of the literature. The criteria are: increased waist circumference with population-specific cut-off values; increased triacylglycerol levels or treatment for hypertriglyceridaemia; low HDL-cholesterol concentration or treatment for this condition; elevated blood pressure or treatment for hypertension; and elevated glucose concentration or treatment with a hypoglycaemic agent. These criteria and values have not been validated for their ability to discriminate optimally for individuals with both metabolic syndrome and a related increase in CVD risk. This is particularly crucial for the assessment of CVD risk associated with excess visceral adiposity in non-Caucasian populations, an area in which much work is needed. Despite this limitation, prospective observational studies have generally shown that individuals who meet the clinical criteria for metabolic syndrome are at increased risk of CVD events and type 2 diabetes compared with individuals without the syndrome[15]. Using different cut-offs or metabolic syndrome markers might improve identification of patients at increased risk. For instance, an elevated fasting blood glucose concentration, which is often referred to as a 'prediabetic' state, is more useful for predicting type 2 diabetes risk[56–60] than CVD risk[61–63].

Since their publication, the conceptual definition of metabolic syndrome has often been confused with the five proposed clinical criteria. These criteria are merely surrogate variables to help identify a subgroup of high-risk individuals likely to be characterized by key features of the metabolic syndrome: abdominal obesity, insulin resistance, high triacylglycerol–apolipoprotein B, low HDL-cholesterol, small, dense LDL dyslipidaemia, a pro-thrombotic state and an inflammatory profile. These clustering features are the most prevalent form of the metabolic syndrome as defined by NCEP–ATP III[64]. This constellation of abnormalities might be accompanied by hypertension and/or type 2 diabetes, depending on the individual's genetic susceptibility.

Despite some limited evidence[56,65], it remains uncertain whether all possible combinations of three of the five NCEP-ATP III criteria similarly increase CVD risk. This warrants further attention.

Limitations

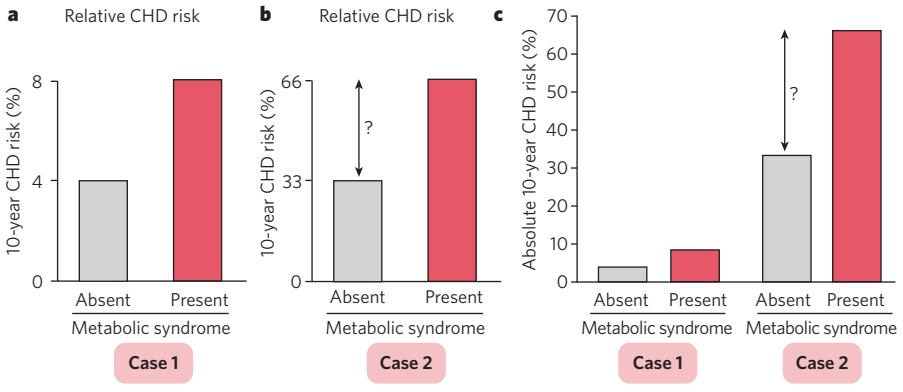
One limitation of metabolic syndrome is that although it leads to an approximately twofold increase in relative CVD risk[15], it should not replace the need to assess overall cardiovascular risk taking into account well-established CVD risk factors such as age, gender, smoking, blood pressure, cholesterol (or LDL-cholesterol) and diabetes[10]. It has also

Box 1 | Assessment of global CHD risk

Meeting the clinical criteria for the metabolic syndrome does not necessarily equal a very high absolute risk of CVD. Consider the following two cases.

The first case (panel **a**) is a 30-year-old nondiabetic man with normal blood pressure, who has never smoked and has an LDL-cholesterol concentration of 3.00 mmol l^{-1}. The patient has a waist girth of 104 cm, fasting plasma triacylglycerol levels of 2.50 mmol l^{-1}, and an HDL-cholesterol concentration of 0.85 mmol l^{-1}. Although this patient is diagnosed as having metabolic syndrome (its presence presumably doubling his risk of CHD), his Framingham score — which estimates 10-year CHD risk on the basis of traditional risk factors — is low (4%). This is because the patient is young and does not have the traditional risk factors, with the exception of a low HDL-cholesterol concentration, a prevalent correlate of abdominal obesity. A twofold increase in risk due to the presence of metabolic syndrome therefore produces an absolute CHD risk of only 8%.

Let us now consider the second case (panel **b**), who meets exactly the same NCEP–ATP III metabolic syndrome criteria as the first (nondiabetic, waist girth of 104 cm, fasting plasma triacylglycerol levels of 2.50 mmol l^{-1} and an HDL-cholesterol concentration of 0.85 mmol l^{-1}). However, this patient is 55 years of age, smokes one pack of cigarettes per day, has untreated hypertension (170/95 mmHg) and has an LDL-cholesterol concentration of 4.10 mmol l^{-1}. Under the Framingham model, this patient is at much greater absolute risk of CHD than the patient in case number 1 (33% compared with 4%), irrespective of metabolic syndrome. Thus, the same theoretical twofold increase in CHD risk due to metabolic syndrome would generate a much higher absolute CHD risk in the second patient (66%) than the first (8%). This is illustrated by panel **c**.



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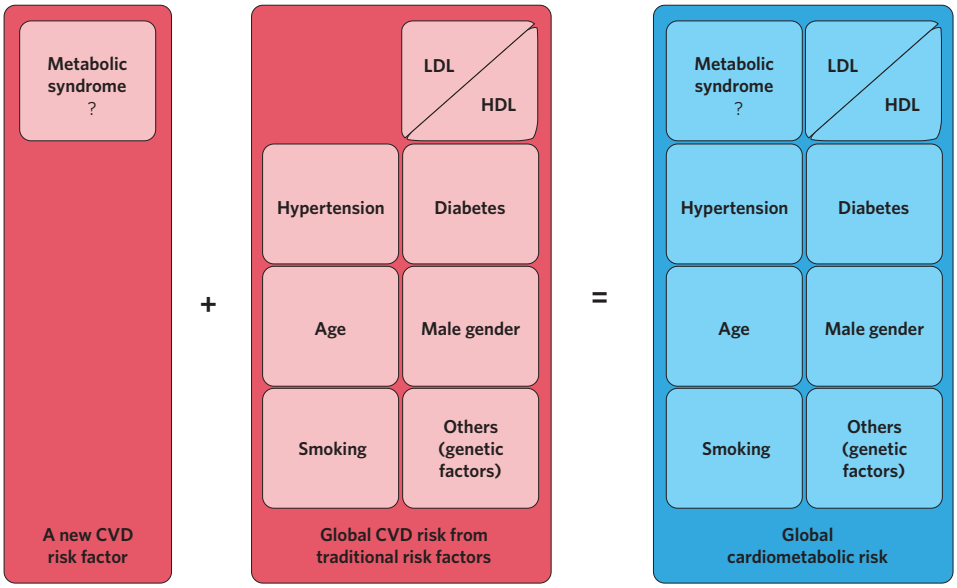

Figure 2 | Factors contributing to global cardiometabolic risk. Cardiometabolic risk is the overall risk of CVD resulting from the presence of metabolic syndrome but also of traditional risk factors such as lipids (LDL and HDL), hypertension, diabetes, age, male gender, smoking and other unknown risk factors (including genetic factors that cannot be assessed in clinical practice most of the time). According to this model, metabolic syndrome does not replace the need to assess global CVD risk, but may eventually have to be considered in global risk assessment. Whether metabolic syndrome is an independent factor that adds significantly to the global CVD risk as assessed with traditional risk factors is uncertain and much debated in the literature. The controversy over its added value is highlighted by the question mark.

been argued that current risk-assessment algorithms such as the Framingham Heart Study calculator of coronary heart disease (CHD) risk[66] largely capture the risk associated with metabolic syndrome[67,68]. The Framingham Heart Study calculator, for instance, considers some elements of metabolic syndrome, such as blood pressure and HDL-cholesterol levels. Although the presence of clinical criteria for metabolic syndrome is predictive of an increased relative CVD risk, the absolute risk of CVD is mainly determined by the presence or absence of traditional risk factors. Therefore, meeting the clinical criteria for metabolic syndrome does not necessarily equal a very high absolute risk of CVD. The two cases presented in Box 1 illustrate this point.

When assessing the absolute CVD risk of patients who meet the clinical criteria for metabolic syndrome, it is necessary first to pay attention to traditional risk factors. This is one of the key criticisms of metabolic syndrome and its relevance to clinical practice[9,10]. A lively debate is currently ongoing as to whether metabolic syndrome enhances our understanding of global CHD risk as assessed by available algorithms such as the Framingham[66] or PROCAM[69] (Prospective Cardiovascular Münster study) risk calculators. Conflicting and mostly negative results have been reported[67,68,70], and further studies are needed. But some evidence suggests that when sophisticated markers of metabolic syndrome — such as fasting insulin and apolipoprotein B levels, and LDL size — are measured, their presence increases CVD risk beyond that which would be calculated using traditional CVD risk algorithms[71]. For the time being, it is important to emphasize that the diagnosis of metabolic syndrome does not necessarily entail a high absolute risk of CVD. Rather, such a diagnosis should be a cause for concern, as it identifies an individual with a dysfunctional metabolism who needs to change his or her lifestyle and lose weight, especially abdominal fat. Thus, diagnosis of metabolic syndrome does not automatically identify a candidate for pharmacotherapy, nor should it detract from the importance of pharmacological management of traditional risk factors in accordance with current guidelines[1,9].

Evolving guidelines

The IDF working group proposed metabolic syndrome criteria that conformed with NCEP–ATP III recommendations[13,14]. The IDF committee placed special emphasis on abdominal obesity and the measurement of waist circumference. Their guidelines proposed that increased waist circumference was a necessary criterion to identify patients at risk of having metabolic syndrome. Furthermore, in light of compelling evidence that the waist girth cut-off value proposed for men by NCEP–ATP III (102 cm) was too high, particularly in some ethnic populations, the IDF guidelines reduced critical waist values to 94 cm in men and 80 cm in women, noting that factors such as ethnicity and age substantially affect the relationship of waist to abdominal visceral fat deposition and related abnormalities. Given that most patients with metabolic syndrome have an excess of abdominal fat, it was a step forward when increased waist girth was included in the IDF guidelines as the first criterion to identify individuals likely to have metabolic syndrome. But the focus on abdominal obesity has been criticized by some who feel that insulin resistance is the syndrome's central component[7,10], given that there are forms of insulin resistance not related to excess abdominal fat[53,54,72].

This debate has caused confusion in the media and the medical field, and it is unfortunate that major organizations have been unable to reach a consensus to emphasize that the most prevalent form of insulin resistance is found among patients with an excess of abdominal fat[29]. Of course, smoking is a confounding factor in the abdominal obesity–insulin resistance association, as smokers have more abdominal adipose tissue than non-smokers even after adjustments for markers of total adiposity[73,74]. Smoking is also associated with insulin resistance and low HDL-cholesterol levels[75]. However, metabolic studies conducted exclusively on non-smokers have confirmed the very significant relationship between abdominal adiposity and an atherogenic and diabetogenic metabolic risk profile[28,29,76,77]. This supports the idea that smoking is not the main factor responsible for the elevated CVD risk of abdominally obese individuals.

Challenging waist

Another criticism of metabolic syndrome has been the relevance or appropriateness of lowering waist circumference cut-off values used to define abdominal obesity in the recent IDF guidelines[14]. In some parts of the world, this reduction in waist circumference cut-offs has considerably increased the number of patients being diagnosed with metabolic syndrome. Some have even seen this as an attempt to increase the number of patients who would be eligible for pharmacotherapy[1,9]. To close this debate, clinical endpoints (incidence of diabetes and CVD) and prospective international epidemiological data with proper body-fat distribution and metabolic markers are urgently needed to quantify the risk associated with features of metabolic syndrome in various populations of the world. For instance, a study conducted in Greenland Inuit had indicated that this population might be less prone to developing metabolic syndrome in the presence of obesity than Caucasian whites[78]. However, no imaging data of visceral adiposity were obtained in this study. In addition, the available evidence suggests that the definition of obesity is markedly different in Asia compared with North America or Europe[23].

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Some ethnic populations are more or less susceptible to visceral fat accumulation for a given amount of total body fat[21–26]. The definition of high-risk abdominal obesity must, therefore, be tailored to various world populations. This issue is a serious roadblock to properly quantifying the prevalence of metabolic syndrome and its clinical sequelae. To this end, modern metabolic epidemiology studies are needed with comprehensive metabolic measurements and proper assessment of regional body fatness using imaging techniques. These studies should quantify abdominal subcutaneous and visceral adipose tissue and ectopic fat deposition, as well as assess relevant metabolic markers so that the relationship of metabolic parameters and clinical events to the size of these regional fat deposits can be more accurately measured.

For now, the numerous papers published on metabolic syndrome's estimated worldwide prevalence must be interpreted with great caution as they may be misleading. For this reason, the IDF committee has identified knowledge gaps in their recommendations[14]. On this basis, the recently reported 'new' IDF waist-girth criteria should be considered a work in progress, and will have to be validated for their ability to discriminate optimally for the subgroup of individuals who have features of metabolic syndrome and are at increased risk of CVD.

The current epidemic of type 2 diabetes and metabolic syndrome is a direct result of our energy-dense diet and affluent sedentary lifestyle. Because such a lifestyle increases the likelihood of individuals eating more than they need, this positive energy balance leads to abdominal obesity and insulin resistance in the presence of an unfavourable genotype and other permissive factors (such as smoking and a maladaptive response to stress). Failure to consider high-risk abdominal obesity as the most prevalent form of metabolic syndrome will unfortunately confuse many physicians and their patients. Furthermore, it would detract from the attention that should be given to weight loss, which has been reported to induce a substantial mobilization of abdominal and visceral adipose tissue among high-risk abdominally obese patients[77,79]. Such selective mobilization of abdominal/visceral fat has been suggested to be an important factor in explaining why moderate weight loss improves the metabolic profile of most patients with metabolic syndrome[79–83].

Strengths and weaknesses

Not all patients with an increased waist girth have the features of metabolic syndrome, leading some to question its usefulness[7]. Although the finding is not surprising, it has supported the assertion that abdominal obesity is not a component of the syndrome. However, an increased waistline may be the consequence of excess subcutaneous abdominal adiposity, a situation sometimes observed even in very obese patients with a normal risk-factor profile[84]. Once waist circumference has been assessed as a first step, the presence or absence of hypertriglyceridaemia might help to distinguish high-risk visceral obesity from lower-risk subcutaneous obesity (Fig. 1). An increased waist circumference alone is therefore not sufficient to identify a high-risk abdominally obese patient with excess visceral adipose tissue. Clinical markers of an altered metabolic risk profile, such as clinical criteria for metabolic syndrome (the simplest being increased triacylglycerol levels), must also be present to suggest the presence of high-risk visceral obesity[85–87]. Once classical and metabolic risk factors have been taken into account, there is little evidence that waist circumference alone is an independent risk factor for CVD.

If we consider the pathophysiology of the most prevalent form of metabolic syndrome, then the most prevalent correlate of the metabolic syndrome epidemic is abdominal obesity. Thus, after accounting for the consequences of abdominal obesity (such as insulin resistance, atherogenic dyslipidaemia, hypertension, hyperglycaemia, a pro-thrombotic state and an inflammatory profile), waist circumference is unlikely to predict CVD events. But should we stop assessing abdominal obesity and put the worldwide obesity epidemic on the back burner? The answer to this question is an emphatic 'no'. In the presence of the clinical criteria of metabolic syndrome, an increased waist circumference does provide relevant pathophysiological information insofar as it defines the prevalent form of the syndrome resulting from abdominal obesity.

But a key issue remains unsolved: the identification of high-risk abdominally obese patients in various populations of the world. Even for the US population, there was no scientific rationale behind the waist circumference cut-offs of 102 cm in men and 88 cm in women. These waist girth values corresponded to a BMI of 30 kg m^{-2} in men and women, and were simply taken from an earlier European study[88]. Other cut-offs have been proposed on the basis of metabolic markers and disease states[57,85,87,89]. As mentioned above, the relationship of total adiposity to visceral fat deposition and to metabolic complications may vary between populations. The available data suggest that blacks are more prone to subcutaneous fat accumulation for a given BMI than are whites[21,22,25,26], whereas Asians are quite prone to visceral fat accumulation[23,24], which may explain their greater propensity to develop diabetes at relatively low BMI values. We therefore need to establish the relationship of anthropometry to visceral and subcutaneous adiposity in various populations, and to study a comprehensive set of metabolic syndrome markers in order to quantify their relationship to specific clinical events such as type 2 diabetes and CVD.

The future of global cardiovascular disease risk assessment

Better global risk-assessment algorithms are needed to quantify diabetes and CVD risk resulting from the presence of classical risk factors and the presence of abdominal obesity or insulin resistance-related metabolic markers. The term 'cardiometabolic risk' has been coined by organizations such as the American Diabetes Association[90] and the American Heart Association[91] to describe the overall risk of developing type 2 diabetes and CVD[92,93], and this idea may potentially reconcile both supporters and detractors of the metabolic syndrome concept. As illustrated in Fig. 2, cardiometabolic risk encompasses the global risk of CVD and type 2 diabetes associated with traditional risk factors while also taking into consideration the potential additional contribution of abdominal obesity and/or insulin resistance and of related metabolic markers (to be identified) to global CVD risk. Current evidence does not suggest that the presence of clinical criteria for metabolic syndrome adds to global CVD risk. Only additional prospective studies, which will consider the measurement of sophisticated metabolic markers and direct measurements of abdominal visceral and subcutaneous adiposity, have the potential to answer this important question. Once these results become available we should be better positioned to address the key questions of what constitutes a high-risk abdominal obesity phenotype in various regions of the world and what the main determinants of risk in different populations are.

However, a distinction must clearly be made between metabolic syndrome as a concept and the criteria used in clinical practice to identify individuals with features of metabolic syndrome. Although insulin resistance is a key component of a constellation of metabolic abnormalities, which increase the risk of type 2 diabetes and CVD, the most prevalent form of insulin resistance is associated with abdominal obesity and with 'dysfunctional' adipose tissue that cannot properly handle the energy surplus resulting from a sedentary lifestyle combined with excessive calorie consumption[49,54]. Initial indicators of high-risk abdominal obesity are an increased waist circumference along with raised fasting plasma triacylglycerol concentrations[85]. Although metabolic syndrome increases relative CVD risk, its diagnosis does not necessarily mean that a patient is at very high risk of a cardiovascular event. To properly evaluate cardiovascular risk, physicians must first consider traditional CVD risk factors. Whether the presence of the clinical criteria for the metabolic syndrome increases the risk of CVD beyond that of traditional risk factors is not yet clear. Resolving this is crucial for the optimal assessment of global CVD risk. ■

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