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REVIEW

What about non-alcoholic fatty liver disease as a new criterion to define metabolic syndrome?

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is currently not a component of the diagnostic criteria for metabolic syndrome (MetS); however, the development of NAFLD has some common mechanisms with the development of MetS, as they share the pathophysiologic basis of insulin resistance. It is also recognized that NAFLD is the hepatic manifestation of MetS. To define MetS, the presence of at least three of the proposed criteria is required, and sometimes it is sufficient to have only one laboratory value, modified by diet or drugs, for the classification of MetS. Ultrasonographically-detected NAFLD (US-NAFLD) is more stable, only changing during the middle- to long-term. Although controversies over MetS continue, and considering that abdominal ultrasonography for diagnosing NAFLD has high specificity and guidelines to modify the natural course of NAFLD by diet composition or lifestyle have not yet been established, why should we not introduce US-NAFLD as a new criterion to define MetS?

Key words: Non-alcoholic fatty liver disease; Metabolic syndrome; Nonalcoholic steatohepatitis; Ultrasonography; Criteria

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of fat in the liver when it exceeds 5%-10% of its weight[1]. In addition to leading to major histopathological alterations, it may be associated with elevated liver enzymes and abnormal liver function, ranging from steatosis to steatohepatitis, fibrosis, and cirrhosis[2,3]. Although diagnosed worldwide, its prevalence varies, reaching approximately 20%-30% in western countries[4]. In the United States, where 25% of the adult population is obese, the disease occurs in more than two-thirds of these individuals and in more than 90% of class Ⅲ obese individuals[5]. It is estimated that 2% to 3% of the population has nonalcoholic steatohepatitis (NASH)[6,7].

Approximately 74%-90% of patients who undergo liver biopsy show alterations due to triacylglycerol accumulation[8]. The disease is highly prevalent (88.7%) in obese patients undergoing bariatric surgery[9], and the likelihood of developing steatohepatitis is increased in class Ⅲ obesity, with 15%-20% of these patients diagnosed with NASH[10].

Some studies have shown an increased prevalence and higher incidence of cardiovascular disease (CVD) in individuals with NAFLD. These studies have shown hepatic

Table 1 National Cholesterol Education Programme Adult Treatment Panel Ⅲ - 2001/American Heart Association - 2005 metabolic syndrome (diagnosis: 3 of 5)

Risk factor	Defining level (AHA 2005)
Abdominal obesity (waist, inches)	
Men	> 40
Women	> 35
Triglycerides (mg/dL)	150 (or Med)
HDL-C (mg/dL)	
Men	< 40 (or Med)
Women	< 50
BP (mmHg)	130/85 (or Med)
Fasting glucose (mg/dL)	110 (100)

AHA: American Heart Association; HDL-C: High-density lipoprotein-cholesterol; BP: Blood pressure; Med: Medium.

Table 2 International Diabetes Federation: Definitions of metabolic syndrome

Central obesity plus any two of the following four factors	
Raised triglyceride	150 mg/dL, or specific treatment for this lipid abnormality
Reduced HDL-C	< 40 mg/dL in men and < 50 mg/dL in women, or specific treatment for this lipid abnormality
Raised BP	Systolic BP 130 or diastolic BP 85 mmHg, or treatment of previously diagnosed hypertension
Raised FPG	100 mg/dL, or previously diagnosed type 2 diabetes. If above 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome

OGTT: Oral glucose tolerance test; FPG: Fasting plasma glucose; HDL-C: High-density lipoprotein-cholesterol; BP: Blood pressure.

steatosis as an independent risk factor for the development of this disease[11,12].

Metabolic syndrome (MetS), which involves the combination of risk factors for CVD such as insulin resistance, abdominal fat, dyslipidaemia, glucose intolerance, and hypertension, has often been associated with more severe liver abnormalities[13].

NAFLD is now considered to be the hepatic component of the MetS[14,15].

Conventional radiology studies used in the diagnosis of fatty liver include ultrasonography (US), computed tomography, and magnetic resonance imaging. Other than these radiological studies, there are no sensitive and low invasive screening methods for NAFLD. Alanine aminotransferase (ALT) > 30 IU/L is usually used as the cut off level for screening NAFLD[16,17]. This threshold had a sensitivity of 0.92 for detecting the fatty-fibrotic pattern proven by ultrasound among obese children[18]. However, ALT was within normal levels in 69% of those who had increased liver fat[19]. Similarly, in the Dallas Heart Study, 79% of the subjects with a fatty liver (liver fat content > 5.6%) had normal serum ALT[20]. This implies that a normal ALT does not exclude steatosis. Aspartate aminotransferase and gamma glutamyltransferase also correlate with liver fat content independent of obesity[21], but are even less sensitive than serum ALT.

It is well known that NAFLD mirrors insulin resistance, and patients with NAFLD tend to have the abnormal components of the MetS. However, the target for correctly detecting MetS has not yet been met.

METABOLIC SYNDROME: DEFINITION, IMPORTANCE AND PATHOPHYSIOLOGY

Definition

MetS identifies patients at increased risk of developing CVD and type 2 diabetes mellitus. As it is a clustering of different risk factors, and its pathogenesis is not well understood, this has given rise to the development of multiple concurrent definitions. Central obesity and insulin resistance are acknowledged as important causative factors[22-24], together with other associated conditions, including physical inactivity[25], ageing[26] and hormonal imbalance[27,28] such as polycystic ovary syndrome or testosterone insufficiency.

The concept of clustering of risk factors was first described by Reaven[29], when the term "insulin resistance syndrome" was conceived. However, as the mechanisms underlying the link to CVD risk factors remain uncertain and insulin resistance is not easily measured in clinical practice, the more recent consensus, *e.g.*, 2001 National Cholesterol Education Programme (NCEP) Adult Treatment Panel Ⅲ (ATP Ⅲ)[30] (Table 1) and the 2006 International Diabetes Federation (IDF) criteria[31] (Table 2), favours focusing on other clinical parameters that are easier to measure. It is, therefore, imperative to bear in mind that as the newer criteria do not include insulin resistance as one of its diagnostic criteria, individuals diagnosed as having the syndrome using these criteria may not necessarily be insulin resistant. This is in contrast to the 1999 World Health Organization (WHO)[32] and the 1999 European Group for the Study of Insulin Resistance[33] criteria, which emphasise insulin resistance. The IDF consensus, however, takes into account the importance of gender and ethnic differences in predicting early cardiovascular risk and may indeed be a better predictor for risk in women[34] and specific ethnic groups, *e.g.*, South Asians (Indians), who appear to be more susceptible to the development of MetS at waist circumferences below that of the NCEP/ATP Ⅲ cutpoints[35] (Table 3). It is also worth noting that the NCEP/ATP Ⅲ criteria were revised in 2004, where the threshold for fasting glucose was lowered to ⩾ 100 mg/dL (5.6 mmol/L) in concordance with American Diabetes Association criteria for impaired fasting glucose (IFG)[36]. Hence, in view of the various diagnostic criteria used, care will need to be exercised when interpreting clinical studies related to MetS.

Importance

MetS continues to be highly prevalent and contributes to a rapidly growing problem globally. About 40% of adults in the US population are estimated to have MetS by the

Table 3 Central obesity defined according to the International Diabetes Federation

Country/ethnic group	WC
Europids (In the United States, the NCEP-ATP Ⅲ values[1] are likely to continue to be used for clinical purposes)	
Male	⩾ 94 cm (37 in)
Female	⩾ 80 cm (32 in)
South Asians (based on a Chinese, Malay, and Asian-Indian population)	
Male	⩾ 90 cm (35 in)
Female	⩾ 80 cm (32 in)
Chinese	
Male	⩾ 90 cm (35 in)
Female	⩾ 80 cm (32 in)
Japanese	
Male	⩾ 85 cm (34 in)
Female	⩾ 90 cm (32 in)

[1]102 cm, 40 in, male; 88 cm, 35 in, female. NCEP: National Cholesterol Education Programme; WC: Waist circumference; ATP: Adult Treatment Panel.

age of 60 years[26,37]. At least one-fourth of the adult European population may have MetS[38-40], with a similar prevalence in Latin America[41]. MetS is also considered an emerging epidemic in developing Asian countries, including Singapore, China, Japan and South Korea, with a prevalence of 8%-13% in men and 2%-18% in women, depending on the population and definitions used[42-44].

Pathophysiology

There have been several proposed hypotheses for the development of MetS. One such widely quoted hypothesis suggests that adipose tissue dysfunction is the underlying cause, resulting in abnormal metabolism of free fatty acids and the release of adipocytokines which are responsible for the observed inflammatory changes and insulin resistance[45-47]. Adipose tissue is in itself an endocrine organ that is metabolically active, rather than purely an energy storage organ[48-51]. Adiponectin is secreted exclusively by adipocytes in adipose tissue, and low levels in individuals have consistently predicted the presence of MetS and CVD risk[52-56]. In fact, adiponectin can be measured reliably in a clinical setting; its circulating values do not umdergo diurnal fluctuation as much as other markers such as insulin, glucose or triglycerides, and only a small amount is required for its measurement, making this a potentially suitable biomarker for MetS[57,58]. Resistin[23,59,60] and visfatin[61-64] are the other adipocytokines implicated in the pathogenesis of MetS.

An alternative proposed aetiology suggests an underlying state of chronic, low-grade inflammation[65-67], leading to endothelial dysfunction and the release of inflammatory cytokines, which induce insulin resistance in adipose tissue and muscle[67,68]. Indeed, insulin-resistant individuals manifest evidence of low-grade inflammation even without an increase in total body fat[69].

Excess visceral fat accumulation may be causally related to the features of insulin resistance, but might also be a marker of dysfunctional adipose tissue which is unable to appropriately store the energy excess (Figure 1). 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 MetS. There is evidence to suggest 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 MetS. 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 the preferential accumulation of visceral fat and with features of insulin resistance include, among others, smoking, the well documented genetic susceptibility to visceral obesity[70] and a neuroendocrine profile related to a maladaptive response to stress[71]. The resulting metabolic consequences of this "defect" in energy partitioning include visceral obesity, insulin resistance, an atherogenic dyslipidaemia and a prothrombotic, inflammatory profile. These are defining features of MetS.

This constellation of abnormalities can be detected by the clinical criteria for MetS, the two simplest being the simultaneous presence of increased waist girth and fasting triacylglycerol levels, a condition that has been described as "hypertriglyceridaemic waist"[72].

It is noteworthy to stress that the identification of other risk factors might improve knowledge on the pathogenesis of NAFLD and open the way to new therapeutic approaches[73-75]. The debate surrounding the mechanisms inducing or favouring the presence/severity of NAFLD continues. In fact, some investigators have identified factors other that MetS to be associated with NAFLD[76-78].

RECENT CONTROVERSY

Although the MetS has existed in various forms and definitions for more than eight decades, only in the past 5 years has real controversy about its definition and significance emerged[79,80]. The main controversy is that the syndrome has had too many definitions and there is a lack of clarity about its role and value in clinical practice[81]. It is fair to say, with exceptions[82], that most of the published reports indicate that the syndrome does not predict cardiovascular events or disease progression any better than the sum of its components[3,83,84]. The relative value in predicting type 2 diabetes remains uncertain[85]. The controversy, however, drove the need for a single global definition. Thus, came the initiative of the IDF and the American Heart Association/National Heart, Lung, and Blood Institute, joined by the World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity[79] to develop one unified definition[86].

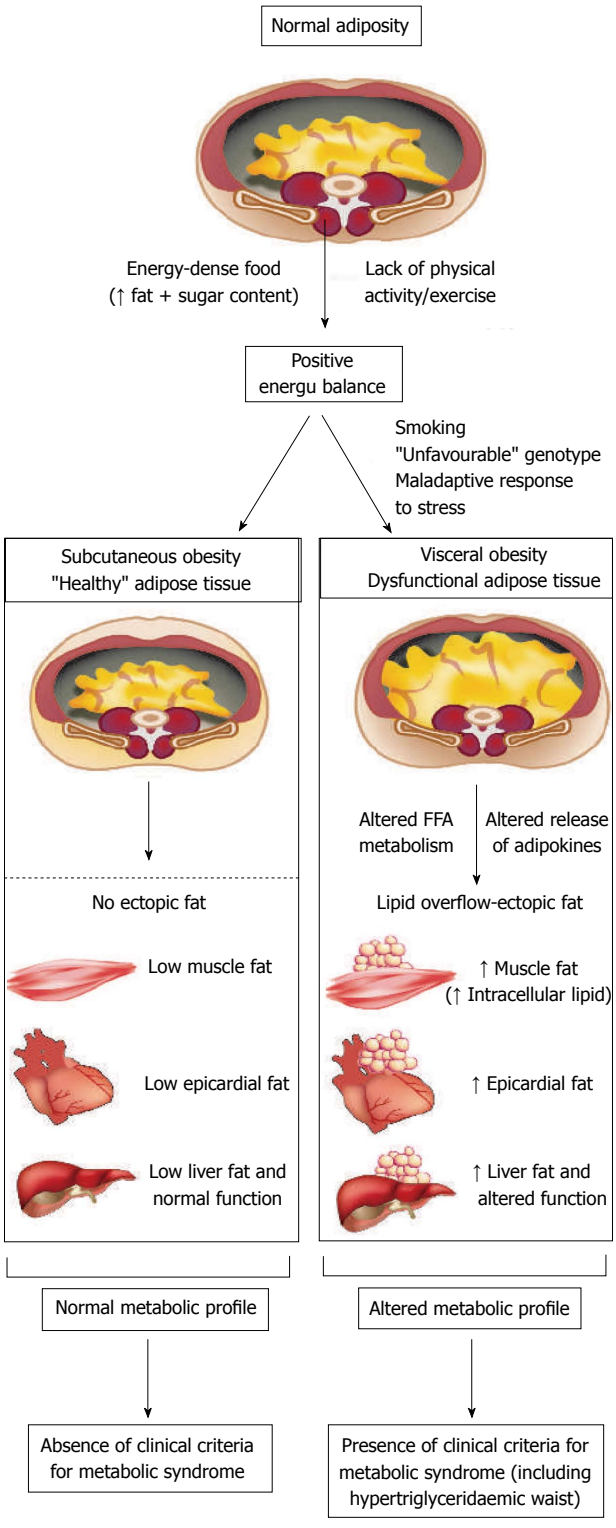

Figure 1 The lipid overflow-ectopic fat model. FFA: Free fatty acid.

The main difference between the NCEP ATP Ⅲ (National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults)[87] and the IDF definitions[88] was that the IDF had a threshold value for waist circumference as obligatory. As a major step in consensus, this obligation has been reversed so that we now have a platform for standardised reporting in epidemiological and clinical research[81]. Yet, because the relation between waist circumference and CVD and diabetes risk differs globally, the definition for the expanded waist circumference remains unsettled. In the meantime, national or regional cutpoints for waist circumference can be used.

Insulin resistance continues to explain most, if not all of the MetS. In fact, no other mechanisms have emerged that come close to justifying the individual components or their clustering. Evidence now indicates that the MetS begins with excess central adiposity[89]. When β-cell function is responsive, hyperinsulinaemia results but fasting and postprandial glycaemia often remain normal for years. However, in those genetically predisposed, defects in insulin secretion and IFG and/or impaired glucose tolerance follow[90].

Most controversial has been the mechanism of hypertension under the tent of insulin resistance. However, not only are the effects of insulin on sodium reabsorption and sympathetic nervous system activation maintained despite insulin resistance, but increases in angiotensinogen, resistin, and leptin secretion from adipose tissue have also been implicated in the pathophysiology of hypertension in the syndrome[91]. Moreover, insulin resistance is closely associated with abnormalities in nitric oxide (NO) bioavailability and reduced phosphatidylinositol 3-kinase/protein kinase B signalling in the vascular wall, both of which have a crucial role in mobilisation of endothelial progenitor cells from bone marrow[91]. Not only do higher levels of free fatty acids directly reduce NO-dependent vasodilatation, but insulin resistance itself also results in structural or functional damage to the endothelium and apoptosis[91]. Reparative processes that regenerate injured endothelium might be increased by agents such as peroxisome proliferator-activated receptor γ agonists that enhance insulin sensitivity, an effect mediated by endothelial progenitor cells[92].

Genetic predisposition also relates to the MetS. A recent study found that a polymorphism in the multi-PDZ domain-containing adaptor protein, a protein that regulates the high-density lipoprotein-receptor scavenger-receptor type B class 1, was associated with the MetS[93]. Shift work, sleep deprivation, and bright-light exposure at night also relate to increased adiposity and prevalence of the MetS; clock genes are expressed in adipose tissue, and both their levels of expression and their genetic variants correlate with different components of the syndrome[94].

Another area of recent interest is vitamin D. Increasing evidence indicates that vitamin D deficiency is associated with the risk of CVD. Particularly relevant is a study that examined the association of serum vitamin D concentrations with risk factors for CVD in US adolescents[95].

The hypothesis that the MetS is an outgrowth of insulin resistance provides a strategy for management. Weight loss often reduces insulin resistance; and caloric restriction, weight-loss drugs, and bariatric surgery have been proved to be effective.

Although long-term weight reduction through dietary and pharmacological means is theoretically possible, most dietary and weight-loss drug studies have only continued for a few years. In contrast, in one 10-year follow-up after bariatric surgery[96], weight loss of 25% and improvement in the MetS were achieved; total mortality was also reduced. Even in the absence of weight loss, long-term physical activity, as measured by cardiorespiratory fitness, prevents the MetS[97], reduces cancer incidence and related mortality, and all-cause mortality[98].

Finally, one class of drugs that reduces insulin resistance and many of the components of the syndrome is the thiazolidinediones. These drugs act mainly in adipose tissue to favourably modify secretions of products that contribute to the pathophysiology of the MetS, including free fatty acids and adipocytokines. The major effect of thiazolidinediones is on dysglycaemia, which accounts for their use in the treatment of diabetes, yet the class as a whole has anti-inflammatory effects. At present, however, drug therapy for the MetS largely requires separate agents for the treatment of dysglycaemia, dyslipidaemia, and hypertension[99].

The MetS is a widely accepted concept that identifies the centrally obese patient with increased risk for CVD and diabetes. A global definition has now been proposed, insights into aetiology and mechanisms have been furthered, and, despite the controversies, lifestyle interventions remain the primary therapy. After lifestyle, residual risk for CVD needs to be treated with appropriate drugs.

US AND NAFLD

US is currently the most common method for screening asymptomatic patients with elevated liver enzymes and suspected NAFLD[100]. US findings of fatty liver include hepatomegaly, diffuse increases in the echogenicity of the liver parenchyma, and vascular blunting.

Nonsteatotic hepatic parenchyma exhibits an echotexture similar to that of renal parenchyma, but becomes "brighter" when infiltrated with fat[101]. This hepatorenal contrast can be used to detect hepatosteatosis[102,103]. However, bright liver contrast associated with fibrosis is discussed in the literature[103]. US is easily performed and has a low cost, however, it also has limitations. It is operator dependent and subject to significant intra- and interobserver variability[104]. It is impossible for US to provide quantitative information about the degree of fat accumulation. The sensitivity of US to detect steatosis decreases with a degree of fat infiltration less than 30%[105]. In obese patients, sensitivity lower than 40% has been reported in the detection of hepatosteatosis[106]. Finally, US has failed to prove efficacious in the detection of inflammation and fibrosis, therefore, it cannot be utilized to diagnose NASH and hepatic fibrosis[107]. However, in a recent study, Iijima *et al*[108] used an ultrasound contrast agent (Levovist; Sherling, Berlin, Germany) to distinguish between simple steatosis and NASH. Levovist contains galactose and palmitic acid and is taken up by hepatocytes[109]. These moieties participate in sugar and fat metabolism[110]. The uptake of Levovist was observed to significantly decrease in NASH patients, thus correlating with fibrosis rather than steatosis[108]. Larger studies are needed to evaluate the use of contrast US in the diagnosis of NASH characterised by inflammation and fibrosis, although there is a no absolute consensus in separating NASH from simple fatty liver as two distinct entities.

FUTURE REMARKS

The MetS is associated with abdominal obesity and its criteria include waist circumference[30,31]. In addition, NAFLD has been reported to be associated with abdominal obesity[110].

The presence of multiple metabolic disorders such as diabetes mellitus, obesity, dyslipidaemia and hypertension is associated with a potentially progressive, severe liver disease[14,111-115]. Previous reports demonstrated that the prevalence of NAFLD increased to 10%-80% in individuals with obesity, 35%-90% in individuals with type 2 diabetes mellitus, 30%-56% in individuals with hypertension, and 26%-58% in individuals with dyslipidaemia[116-119].

It is clinically critical that a large number of patients with NAFLD were not diagnosed with the MetS, when we used today's definition of the MetS[120]. Why not change the approach and use the presence of NAFLD as a new criterion for detecting the MetS?

Recently, it was shown that ultrasonographically-detected NAFLD (US-NAFLD) is an independent predictor for identifying patients with insulin resistance in non-obese, non-diabetic middle-aged Asian adults[121]. Therefore, US-NAFLD may identify individuals with insulin resistance that cannot be identified by MetS in this population[121].

On this basis, we believe that this suggestion, *i.e.*, the inclusion of NAFLD could help initiate weight control at the "earliest possible time" in the progression of disease, *i.e.*, obesity/MetS, which means diagnosing NAFLD earlier rather than later, using the simplest method possible, *i.e.*, at US[110].

CONCLUSION

NAFLD is highly prevalent and is considered the hepatic component of the MetS. The WHO, the NCEP-ATP Ⅲ and the IDF have different criteria to define MetS. The MetS is associated with NAFLD, with the WHO definition being the best to determine its presence, probably due to the inclusion of insulin resistance as a main component. Unification of criteria is needed to adequately compare the prevalence of MetS and its relationship with NAFLD in different population, however, this is very hard task.

Further study will be needed to verify whether the inclusion of steatosis in the panel of MetS indicators will improve the predictive power of cardiovascular risk bet-

ter than the current MetS criteria.

To define MetS, the presence of at least three of the proposed criteria is required, however, sometimes it is sufficient to have only one laboratory value, modified by diet or drugs, for the classification. US-NAFLD detection is more stable, and changes in the middle-to-long term. Although the controversy surrounding the utility of the MetS continue, considering that abdominal US in the diagnosis of NAFLD has a sensitivity of 91.7% and a specificity of 100%[122] and guidelines to modify the natural course of NAFLD by diet composition or lifestyle have not been established[123], why should we not introduce US-NAFLD as a new criterion to define MetS?

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