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REVIEW ARTICLE

# Metabolic syndrome: its history, mechanisms, and limitations

**Eiji Oda**

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**Abstract** In late twentieth century, Ruderman and Reaven showed that insulin resistance might be fundamental to metabolic syndrome (MetS) which means a constellation of obesity-related metabolic derangements predisposing to type 2 diabetes and cardiovascular disease. In 2001, user-friendly National Cholesterol Education Program (NCEP) criteria of MetS were proposed. In 2005, the International Diabetes Federation (IDF) and the Examination Committee for Criteria of Metabolic Syndrome in Japan issued different criteria of MetS where abdominal obesity is a necessary component. In 2009, IDF, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity jointly adopted the revised NCEP criteria, where abdominal obesity is not a necessary component, as worldwide criteria of MetS. In 2010, WHO Expert Consultation warned that MetS is a concept that focuses attention on complex multifactorial health problems but has limited practical utility as a management tool. In animal studies, adipose tissue inflammation characterized by an increased number of crown-like structures in adipose tissue, rather than obesity per se, was shown to be a fundamental mechanism of metabolic derangements.

**Keywords** Metabolic syndrome · Insulin resistance · Obesity · Inflammation

E. Oda (✉)
Medical Check-up Center, Tachikawa Medical Center, Nagachou 2-2-16, Nagaoka, Niigata 940-0053, Japan
e-mail: ijie@venus.sannet.ne.jp

## Introduction

Insulin resistance syndrome (IRS, syndrome X [1]) or metabolic syndrome (MetS) [2–6] is a constellation of interrelated metabolic risk factors that appear to directly promote the development of diabetes and cardiovascular disease. In 2005, the International Diabetes Federation (IDF) issued a new definition of MetS where abdominal obesity is a necessary component [4] and the Examination Committee for Criteria of Metabolic Syndrome in Japan proposed visceral fat syndrome [7] as the Japanese MetS [8]. In 2009, IDF, National Heart, Lung, and Blood Institute (NHLBI), American Heart Association (AHA), World Heart Federation (WHF), International Atherosclerosis Society (IAS), and International Association for the Study of Obesity (IASO) jointly adopted the revised National Cholesterol Education Program (NCEP) criteria (AHA/NHLBI criteria) [3], where abdominal obesity is not a necessary component, as the worldwide harmonizing definition of MetS. That is; IDF withdrawn its 2005 definition of MetS. However, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) jointly stated that no existing definition of MetS meets criteria as a syndrome [9], and WHO Expert Consultation reported that MetS is an educational concept that focuses attention on complex multifactorial health problems, is a pre-morbid condition rather than a clinical diagnosis, and has limited practical utility as a diagnostic or management tool and that there is limited utility in epidemiological studies in which different criteria of MetS are compared [10]. MetS may be the systemic manifestation of adipose tissue disease [11] defined as an increased aggregation of activated macrophages into adipose tissue from bone marrow induced by chronic energy overload and characterized by an increased number of crown-like

structures (CLSs) in adipose tissue [12]. However, MetS is related with many other complex pathophysiological mechanisms. Established components of MetS are increased waist circumference (WC), high blood pressure, increased serum triglyceride levels, decreased serum high-density lipoprotein (HDL) cholesterol levels, and impaired fasting glucose [5, 6]. In this review, the author summarized the history of MetS, animal studies showing that adipose tissue inflammation rather than obesity per se is fundamental to obesity-related metabolic derangements, other proposed mechanisms of MetS, and the limitations of MetS concept.

## Brief history of MetS

In 1956, Vague suggested that abdominal obesity may predispose to diabetes and cardiovascular disease [13]. In 1981, Ruderman et al. pointed out that there were metabolically obese, normal-weight (MONW) individuals who might be characterized by hyperinsulinemia and possibly increased fat cell size [14]. In 1982, Kissebah et al. reported that, in women, upper body obesity offered an important prognostic marker for glucose intolerance, hyperinsulinemia, and hypertriglyceridemia [15]. In 1987, Fujioka et al. proposed a novel classification of obesity (visceral fat obesity vs. subcutaneous fat obesity) based on the data from 15 obese men and 31 obese women [16]. In the same year, Ferrannini et al. demonstrated that essential hypertension is an insulin-resistant state [17]. In 1988, Reaven proposed syndrome X to describe the phenomenon in which individuals displaying a cluster of insulin resistance and compensatory hyperinsulinemia, high plasma triglycerides and low HDL cholesterol levels, and hypertension were at significantly increased risk of cardiovascular disease [1]. Several similar concepts were proposed [7, 18–20]. In 1999, WHO defined the criteria of IRS and introduced the name MetS [2]. But, the European Group for the Study of Insulin Resistance proposed a modified version of MetS to be used for nondiabetic subjects only and renamed it IRS [21]. In 2001, the Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults adopted the user-friendly definition of MetS proposed in the Third Report of the NCEP [3]. This definition and its modified versions were used worldwide. But, in 2003, the American Association of Clinical Endocrinologists modified this definition to refocus on insulin resistance as the primary cause of MetS and again excluded diabetic subjects from MetS and returned to the name IRS [22]. In 2004, Ridker et al. proposed the inclusion of high-sensitivity C-reactive protein (hs-CRP) as a component of MetS because hs-CRP is strongly related to obesity and insulin resistance, and was established as a strong risk factor of cardiovascular disease [23]. In 2005, the IDF issued a new definition of MetS in which abdominal obesity is a necessary component [4]. But, AHA and NHLBI jointly criticized the IDF definition of MetS and slightly revised the NCEP definition [5]. In the same year, ADA and EASD jointly stated that no existing definition of MetS meets the criteria of a syndrome and that one should not apply MetS to individuals [9]. Thereafter, there have been endless debates on the pros and cons of diagnosing MetS for individuals [24]. In 2007, the Association for Weight Management and Obesity Prevention, the Obesity Society, the American Society for Nutrition, and ADA issued a consensus statement concerning WC where they stated that there is not yet a compelling body of evidence demonstrating that WC provides clinically meaningful information that is independent of well-known cardio-metabolic risk factors [25]. In 2009, a harmonizing worldwide consensus statement [6] for the criteria of MetS was jointly issued by IDF Task Force on Epidemiology and Prevention, NHLBI, AHA, WHF, IAS, and IASO. In this statement, the revised NCEP criteria (AHA/NHLBI criteria) [5] where abdominal obesity is not a necessary component were adopted as the worldwide definition of MetS. However, the cutoff points of WC were not determined for any particular ethnic group [6].

In Japan, visceral fat syndrome [7] was adopted as the Japanese MetS by the Examination Committee for Criteria of Metabolic Syndrome in 2005 [8]. But, criteria that regard obesity as an inevitable component of MetS have a serious pit hole because there are a substantial number of MONW individuals [14] and only about one-third of the most insulin-resistant individuals are actually obese [24]. Although visceral adipose tissue is an important unique depot of fat, fat in the liver is also an important fat depot and subcutaneous adipose tissue is larger than any other fat depots in volume and an important adipose tissue compartment regarding MetS. In 2007, visceral adipose tissue volume and abdominal subcutaneous adipose tissue volume were compared in regard to the relationship with cardiometabolic risk factors, inflammatory markers, and markers of endothelial dysfunction, and oxidative stress from Framingham Heart Study [26, 27]. The conclusions of these studies showed that the risk contribution of the two fat compartments is not substantially different and subcutaneous adipose tissue cannot be ignored as a risk contributor [26, 27]. The correlation between visceral adipose tissue volume and hs-CRP was weaker than the correlation between body mass index (BMI) and hs-CRP [27]. The correlation between visceral adipose tissue area and insulin resistance is not statistically different from the correlation between BMI and insulin resistance [24]. Fox et al. examined the relation of visceral and subcutaneous adipose tissue to coronary artery calcification (CAT), which

predicts coronary heart disease, among 3,103 men and women from Framingham Heart Study [28]. The age- and gender-adjusted odds ratios [95% confidence interval] for CAT was not statistically different among visceral adipose tissue volume (1.23 [1.11–1.37]), subcutaneous adipose tissue volume (1.18 [1.06–1.31]), WC (1.26 [1.14–1.39]), and BMI (1.21 [1.05–1.39]) [28]. Importantly, none of these four indices of obesity was significantly associated with CAT after further adjusting for systolic blood pressure, antihypertensive therapy, diabetes, total cholesterol, HDL cholesterol, and antihyperlipidemic therapy [28]. Abdominal visceral fat may contribute to the clustering of risk factors beyond obesity. To test this hypothesis, Herrera et al. assessed the additional effect of sudden visceral fat reduction by omentectomy on MetS, acute-phase reactants, and inflammatory mediators in patients with grade III obesity undergoing laparoscopic Roux-en-Y gastric bypass (LRYGB) [29]. They concluded that omentectomy does not have an ancillary short-term significant impact on the components of MetS and does not induce important changes in the inflammatory mediators in patients undergoing LRYGB [29]. Thus, the concept of visceral fat syndrome which considers visceral adipose tissue as an only morbid fat compartment and considers abdominal subcutaneous adipose tissue as a protective or neutral fat depot was completely disproved. However, there is an opinion in Japan that clinicians should discriminate the clustering of multiple risk factors based upon abdominal obesity from other types of the cardiovascular risk clustering. Therefore, I tested the legitimacy of this opinion and reported the results which did not support the legitimacy of this opinion [30]. Although some investigators believe that physical activity preferentially reduces visceral fat, the correlations between physical activity index and visceral adipose tissue volume were weaker than those between physical activity index and subcutaneous adipose tissue volume [26]. In 2007, it was shown by NIPPON DATA90 that the definition of MetS where obesity is a necessary component is dangerous because non-obese individuals have a high mortality risk and are more prevalent than obese or overweight subjects [31]. In 2009, it was clarified that the MetS definition requiring obesity is dangerous because normal-weight individuals have a high mortality risk and are more prevalent than overweight or obese subjects, and that IDF MetS is inferior to revised NCEP MetS as a predictor of cardiovascular disease by studies using Japan Public Health Center-based (JPHC) data [32, 33]. Therefore, the harmonizing worldwide criteria of MetS (revised NCEP criteria) should also be adopted in Japan.

In 2010, WHO Expert Consultation reported that MetS is an educational concept that focuses attention on complex multifactorial health problems, is a pre-morbid condition rather than a clinical diagnosis, and has limited practical utility as a diagnostic or management tool and that there is limited utility in epidemiological studies in which different criteria of MetS are compared [10]. This report summarized six inherent limitations of criteria of MetS: Dichotomization of the diagnosis of MetS and of risk factors used to define MetS; Omission of established risk factors; MetS describes relative risk as opposed to absolute risk; Heterogeneity among individuals diagnosed with MetS, Cardiovascular risk varies according to the risk factor combination used to diagnose MetS in an individual; Problems defining obesity within MetS criteria [10].

A concise chronological table of MetS is presented in Table 1.

**Table 1** A concise chronological table of metabolic syndrome (MetS)

| | |
|---|---|
| 1956 | Vague et al.: Abdominal obesity may predispose to diabetes and cardiovascular disease |
| 1981 | Rudermann et al.: Metabolically obese normal-weight (MONW) individuals with hyperinsulinemia |
| 1987 | Matsuzawa et al.: Visceral fat obesity: visceral fat area/subcutaneous fat area >0.4 |
| | Ferrannini E, et al.: Insulin resistance in essential hypertension |
| 1988 | Reaven: Syndrome X: clustering around insulin resistance |
| 1989 | Kaplan: Deadly qualtet: abdominal obesity, diabetes, hypertension, and hypertriglyceridemia |
| 1994 | Nakamura, Matsuzawa et al.: Visceral fat syndrome: visceral fat area $\geq$127 $cm^2$ among Japanese men |
| 1999 | WHO: The first criteria of MetS based on insulin resistance |
| 2001 | National Cholesterol Education Program (NCEP) Criteria of MetS: The clustering of 3 or more of the following 5 components: abdominal obesity, high blood pressure, impaired fasting glucose, hypertriglyceridemia, and hypo-HDL cholesterolemia |
| 2005 | International Diabetes Federation (IDF) Criteria of MetS: Abdominal obesity is necessary among the 5 components |
| | Japanese Criteria of MetS: Visceral fat syndrome as Japanese MetS coordinating with the IDF Criteria |
| | American Heart Association (AHA)/National Heart, Lung, and Blood Institution (NHLBI): Revised NCEP Criteria |
| | American Diabetes Association (ADA)/European Association for the Study of Diabetes: Do not label individuals with MetS |
| 2007 | ADA/Obesity Society/American Society for Nutrition: The clinical usefulness of waist circumference is limited |
| 2009 | IDF/AHA/NHLBI/World Heart Federation/International Atherosclerosis Society/International Association for the Study of Obesity: Revised NCEP Criteria were adopted as harmonizing worldwide criteria of MetS although cutoff points of waist circumference could not be determined for any particular ethnic group |
| 2010 | WHO Expert Consultation report: MetS has limited utility as a tool for clinical management or epidemiological study |

## Mechanisms of MetS

High energy fast-food environment, sedentary life style, and other obesogenic socioeconomic environment have brought an obesity pandemic in developed and developing countries. Genetic predisposition to obesity and proinflammatory reactions may contribute to develop MetS in individuals. Adipose tissue secretes many humoral substances, such as tumor necrosis factor-α (TNF-α), leptin, adiponectin, resistin, visfatin, monocyte chemoattractant protein-1, retinol binding protein-4, and adipocyte-type fatty acid binding protein, and obesity has been considered as an endocrine and inflammatory disorder intimately related with insulin resistance rather than merely an anthropometric fatness. Hotamisligil et al. reported that adipose expression of TNF-α plays a direct role in obesity-linked insulin resistance [34]. Folli et al. demonstrated cross-talks between insulin and angiotensin signaling systems [35, 36]. Federici et al. reported that tissue metaloproteinase 3 deficiency in insulin receptor-haploinsufficient mice promotes diabetes and vascular inflammation via increased TNF-α [37]. Monroy et al. demonstrated impaired regulation of the TNF-α converting enzyme/tissue inhibitor of metalloproteinase 3 proteolytic system in skeletal muscle of obese type 2 diabetic patients [38]. Although adiponectin or its high molecular weight oligomer was considered a hopeful inflammatory marker regarding MetS, its superiority to hs-CRP is controversial [39]. Semenkovich reviewed insulin resistance and atherosclerosis, emphasizing mitochondrial, nuclear, and endoplasmic reticular stress caused by the excess delivery of fuel [40]. Cinti et al. clarified a histological feature of adipose tissue disease as an increased number of CLSs characterized by accumulation of activated macrophages surrounding enlarged dead adipocytes [12]. They found CLSs not only in mice adipose tissue but also human visceral and subcutaneous adipose tissue [12]. Kolak reported an increased number of CLSs in human subcutaneous adipose tissue in a high liver fat group compared with a low liver fat group independently of obesity [41]. Katagiri et al. emphasized dysfunction of autonomic nervous system and leptin resistance as underlying mechanisms of MetS [42] and Dandona et al. emphasized the reciprocal relationship between insulin resistance and inflammation as a core mechanism of MetS [43]. Kim et al. reviewed molecular mechanisms of reciprocal relationships between insulin resistance and endothelial dysfunction [44]. Many animal studies using transgenic and diet-induced obesity models indicate that the infiltration of macrophages into adipose tissue characterized by an increased number of CLSs and inflammation, but not an increased adipocyte size, an increased adipose tissue mass, or an increased visceral fat mass per se, are crucial for the metabolic consequences of obesity [45–49].

**Table 2** Mechanisms of metabolic syndrome

| | |
|---|---|
| 1 | High energy fast-food environment, sedentary life style, and other obesogenic socioeconomic stress |
| 2 | Genetic predisposition to obesity and proinflammatory reactions |
| 3 | Obesity and fatty liver |
| 4 | Cell stress due to energy overload |
| 5 | Adipose tissue inflammation |
| 6 | Disregulation of adipokines such as leptin and adiponectin |
| 7 | Insulin resistance or selective insulin resistance |
| 8 | Cross-talks between insulin and angiotensin signaling systems |
| 9 | Leptin resistance or selective leptin resistance |
| 10 | Neurohormonal disregulation in hypophyseal-pituitary-adrenal axis |
| 11 | Dysfunction in autonomic nervous system |
| 12 | Endothelial dysfunction and oxidative stress |
| 13 | Low-grade systemic inflammation with hypercoagulability |

Pathophysiological mechanisms of MetS are summarized in Table 2.

## Limitations and prospects of MetS concept

ADA and EASD summarized concerns regarding MetS as followings. (1) Criteria of MetS are ambiguous or incomplete and rationale for thresholds of MetS components are ill-defined. (2) Value of including diabetes in MetS definition is questionable. (3) Insulin resistance as the unifying etiology is uncertain. (4) No clear basis for including/excluding other cardiovascular risk factors. (5) A risk value of cardiovascular disease is variable and dependent on the specific risk factors present. (6) The cardiovascular disease risk associated with MetS appears to be no greater than the sum of its parts. (7) Treatment of MetS is no different than the treatment for each of its component. (8) The medical value of diagnosing MetS is unclear [9]. As WHO Expert Consultation reported, MetS is an educational concept that focuses attention on complex multifactorial health problems and is a pre-morbid condition rather than a clinical diagnosis [10]. This report summarized six inherent limitations of criteria of MetS: (1) Dichotomization of the diagnosis of MetS and of risk factors used to define MetS; (2) Omission of established risk factors; (3) MetS describes relative risk as opposed to absolute risk; (4) Heterogeneity among individuals diagnosed with MetS; (5) Cardiovascular risk varies according to the risk factor combination used to diagnose MetS in an individual; (6) Problems defining obesity within MetS criteria [10]. In the harmonizing worldwide consensus criteria of MetS issued by IDF, NHLBI, AHA, WHF, IAS, and IASO, the cutoff points of WC were not determined for any particular ethnic group [6]. We demonstrated that BMI and WC are not

**Table 3** Limitations of metabolic syndrome (MetS)

| | |
|---|---|
| 1 | Criteria of MetS and rationale for thresholds of MetS components are not scientific enough |
| 2 | Dichotomization for diagnosing MetS and its risk factors is inherently inferior to scoring used in other risk evaluation systems |
| 3 | Predicting diabetes and predicting cardiovascular disease are different issues which MetS seeks simultaneously |
| 4 | There is no clear basis for including/excluding other cardiovascular risk factors such as high-sensitivity CRP, fatty liver, and adiponectin |
| 5 | Value of including diabetes in MetS definition is questionable |
| 6 | A risk value of cardiovascular disease is variable and dependent on the specific risk factors present |
| 7 | The cardiovascular disease risk associated with MetS appears to be no greater than the sum of its parts |
| 8 | Treatment of MetS is no different than the treatment for each of its component |
| 9 | Superiority of waist circumference to body mass index is not scientifically established for defining obesity within MetS criteria |
| 10 | MetS has limited utility in epidemiological studies in which different ethnic-specific cutoff points of waist circumference are used |

significantly different as obesity indices for the clustering of cardiovascular risk factors in a Japanese population [50] and that BMI is more strongly associated with hypertension than waist circumference in apparently healthy Japanese men and women [51]. In developed countries, BMI, WC, and waist-to-hip ratio, whether assessed singly or in combination, do not importantly improve cardiovascular disease risk prediction in people when additional information is available for systolic blood pressure, history of diabetes, and total and HDL cholesterols [52]. These limitations of MetS are summarized in Table 3.

MetS is a risk factor of diabetes and cardiovascular disease [53–56]. However, recent studies suggested that MetS is a systemic pre-disease state beyond type 2 diabetes and cardiovascular disease. Inflammation, which is linked to many overtly noninflammatory chronic systemic diseases including atherosclerosis, is regarded as one of the major underlying mechanisms of MetS and hs-CRP is shown to be superior to white blood cell count as an inflammatory marker of MetS [11, 23, 43, 57]. Kotronen and Yki-Järvinen showed that liver fat storage is highly significantly correlated with all components of MetS independent of obesity, and proposed fatty liver as a novel component of MetS [58]. Hanley et al. reported that alanine aminotransferase predicts MetS independent of insulin sensitivity [59]. Lee et al. reported that gamma glutamyltransferase predicts onset of MetS, incidence of cardiovascular disease, and mortality adjusting for established cardiovascular risk factors and hs-CRP [60]. Urinary excretion of albumin was an independent predictor of diabetes after controlling for components of MetS [61, 62]. However, elevated estimated glomerular filtration rate is not associated with the diagnosis of MetS, and does not predict diabetes [63]. MetS is independently associated with an increased risk for incident chronic kidney disease in subjects with [64] and without diabetes [65, 66]. Esteghamati et al. reported that MetS is independently associated with microalbuminuria in type 2 diabetes [67]. Lower vital capacity is reported to be an independent predictor of diabetes and subjects with lower vital capacity had many features of MetS at baseline [68]. In our study, decreased vital capacity is significantly associated with MetS and diabetes also in Japanese [69]. Resting heart rate, which is a marker of autonomic dysfunction, is reported to be associated with MetS. We showed that the prevalence of MetS increased linearly through the increase in heart rate in Japanese [70]. Large epidemiologic studies have confirmed that heart rate is a predictor of cardiovascular and all-cause mortality independent of currently accepted risk factors in men and women with and without diagnosed cardiovascular disease in Western societies [71]. The risk of malignancies is increased in the presence of MetS or diabetes, with a linear relationship between cancer risk and plasma insulin levels [72]. Thus, MetS suggests a more extended systemic pre-disease state beyond type 2 diabetes and cardiovascular disease.

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