Review

The Metabolic Syndrome as a Concept of Adipose Tissue Disease

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The metabolic syndrome is a constellation of interrelated metabolic risk factors that appear to directly promote the development of diabetes and cardiovascular disease. However, in 2005, the American Diabetes Association and the European Association for the Study of Diabetes jointly stated that no existing definition of the metabolic syndrome meets the criteria of a syndrome, and there have been endless debates on the pros and cons of using the concept of this syndrome. The controversy may stem from confusion between the syndrome and obesity. Obesity is an epidemic, essentially contagious disease caused by an environment of excess nutritional energy and reinforced by deeply rooted social norms. The epidemic of obesity should be prevented or controlled by social and political means, similar to the approaches now being taken to combat global warming. The diagnosis of metabolic syndrome is useless for this public purpose. The purpose of establishing criteria for diagnosing metabolic syndrome is to find individuals who are at increased risk of diabetes and cardiovascular disease and who require specific therapy including diet and exercise. The syndrome may be an adipose tissue disease different from obesity; in that case, it would be characterized by inflammation clinically detected through systemic inflammatory markers such as high-sensitivity C-reactive protein and insulin resistance reflecting histological changes in adipose tissue. However, many problems in defining the optimal diagnostic criteria remain unresolved. (*Hypertens Res* 2008; 31: 1283–1291)

***Key Words*: metabolic syndrome, obesity, diabetes, cardiovascular disease, inflammation**

Introduction

For the past several decades, cardiovascular disease and diabetes have been major causes of morbidity and mortality in the Western developed world, where obesity prevails. Considerable effort has been spent on understanding the underlying biology of cardiovascular disease and on identifying its risk factors. As these factors have been identified, it has become apparent that they tend to cluster within individuals. The metabolic syndrome is a constellation of interrelated metabolic risk factors that appear to directly promote the development of diabetes and cardiovascular disease. The predominant underlying mechanisms for the syndrome appear to be insulin resistance (*1*, *2*), abdominal obesity (*3*, *4*), and inflammation (*5*, *6*). Other associated conditions may be diet (*7–9*), smoking (*10*), physical inactivity (*11*), aging (*12*), socioeconomic status (*9*), hormonal imbalance (*13*), and xenobiotics (*14*).

Clinical Aspects of the Metabolic Syndrome

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 (*15*). In 1988, Reaven proposed the label syndrome X to describe the phenomenon in which individuals displaying a cluster of insulin resistance and compensatory hyperinsulinemia, high plasma triglyceride and low high-density lipoprotein (HDL) cholesterol concentrations, and hypertension were at significantly increased risk of cardiovascular disease (*1*). The following year, Kaplan added abdominal obesity to this syndrome, subtracted hypo-HDL-cholesterol-

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emia, and renamed it the "deadly quartet" (*3*). In 1991, DeFronzo and Ferrannini renamed syndrome X the insulin resistance syndrome (IRS) *(2)*. In 1994, Nakamura *et al*. proposed the name "visceral fat syndrome," considering subcutaneous fat as a rather protective factor against the morbid effects of visceral fat (*16*), and in 1998, Lamarche *et al*. reported a combination of hyperinsulinemia, elevated apolipoprotein B, and small dense low-density lipoprotein (LDL) cholesterol as the "atherogenic metabolic triad" (*17*). In 1999, the World Health Organization (WHO) defined the criteria of IRS and introduced the name metabolic syndrome (*18*). The European Group for the Study of Insulin Resistance (EGIR) proposed a modified version of the metabolic syndrome to be used for nondiabetic subjects only and renamed it IRS (*19*). In 2000, Lemieux *et al*. proposed the "hypertriglyceridemic waist" as a marker of the atherogenic metabolic triad in men (*4*). In 2001, the Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) reported adoption of the user-friendly definition of the metabolic syndrome put forth by the Third Report of the National Cholesterol Education Program (NCEP) (*20*), and this definition and its modified versions were used worldwide. The NCEP definition did not require demonstration of insulin resistance *per se*. It was noted that exact measures of insulin resistance were laborious and not well standardized, and that surrogate measures, such as glucose tolerance tests, were not routinely used in clinical practice. Although the ATP III recognized the clustering phenomenon of metabolic risk factors, it was not convinced that insulin resistance was the only mechanistic pathogenesis. Thus, the NCEP definition required no single factor for diagnosis, instead requiring the presence of 3 out of 5 risk factors as a diagnostic requirement; these were abdominal obesity defined as waist circumference (WC) $\geq$102 cm in men and $\geq$88 cm in women, elevated triglycerides defined as $\geq$150 mg/dL, reduced HDL cholesterol defined as $<$40 mg/dL in men and $<$50 mg/dL in women, elevated blood pressure defined as systolic pressure $\geq$130 mmHg and/or diastolic pressure $\geq$85 mmHg, and elevated fasting glucose defined as $\geq$110 mg/dL. In 2003, the American Association of Clinical Endocrinologists (AACE) modified this definition to refocus on insulin resistance as the primary cause of the metabolic syndrome and again returned to the name IRS (*21*). The major criteria in the AACE definition were impaired glucose tolerance, elevated triglycerides, reduced HDL cholesterol, elevated blood pressure, and obesity. No specified number of factors was required for diagnosis, which was left to clinical judgment. Once a person develops diabetes, the term IRS no longer applies. In 2004, Ridker *et al*. proposed the inclusion of high-sensitivity C-reactive protein (hs-CRP) as a component of the metabolic syndrome because hs-CRP is strongly related to obesity and insulin resistance, and was established as a risk factor of cardiovascular disease (*5*).

In 2005, the International Diabetes Federation (IDF) issued a new definition of the metabolic syndrome, in which the presence of abdominal obesity is necessary and the presence of 2 additional factors originally listed in the NCEP definition is sufficient for diagnosis (*22*). But, impaired fasting glucose was modified as $\geq$100 mg/dL and the criteria for abdominal obesity were specified by race: that is, for people of European origin, the cut points of WC were 94 cm in men and 80 cm in women; for Asian populations, the WC points were 90 cm in men and 80 cm in women. In the same year, the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) jointly criticized the IDF definition of the metabolic syndrome and slightly revised the NCEP definition. Consequently, the cut point of impaired fasting glucose became 100 mg/dL and the criteria of abdominal obesity became race-specific (*23*). Also in 2005, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) jointly stated that no existing definition of the metabolic syndrome meets the criteria of a syndrome and that one should not apply the "metabolic syndrome" to individuals (*24*). The joint statement named eight concerns regarding the metabolic syndrome, summarized as follows.

1) The criteria are ambiguous or incomplete. The rationale for the thresholds are ill defined. 2) The value of including diabetes in the definition is questionable. 3) Insulin resistance as the unifying etiology is uncertain. 4) There is no clear basis for including or excluding other risk factors of cardiovascular disease. 5) The risk value of cardiovascular disease is variable and dependent on the specific risk factors present. 6) The risk of cardiovascular disease associated with the "syndrome" appears to be no greater than the accumulated risk of the sum of the syndrome's parts. 7) Treatment for the syndrome is no different than the treatment for its components. 8) The medical value of diagnosing the syndrome is unclear.

After the publication of this statement and continuing to the present, there have been endless debates regarding the pros and cons of the concept of the metabolic syndrome (*25–32*). In these debates, Reaven endorsed the ADA/EASD joint statement and noted that it is possible to create an almost infinite number of scenarios in which persons who do not meet the diagnostic criteria for the metabolic syndrome would be at greater risk of cardiovascular disease than those who do (*27*). Grundy asserted that the metabolic syndrome is not meant to be a risk-assessment tool for short-term ($<$10-year) risk, but rather is meant to identify people at higher long-term risk for cardiovascular disease and diabetes, since the metabolic syndrome is a progressive disorder (*25*). However, Sundstrom *et al*. reported that the metabolic syndrome did not provide risk information above and beyond that of its individual components in their community-based long-term cohort study with 30 years of follow-up (*33*). Amid these debates, the AHA and ADA jointly issued a scientific statement titled "Preventing cardiovascular disease and diabetes. A call to action from the American Diabetes Association and the American Heart Association," in which they stated that despite the many unresolved scientific issues concerning the metabolic syndrome, a

Table 1. The Two Pedigrees of Concepts for Metabolic Syndrome

A: Concepts which consider obesity as the essential feature of metabolic syndrome	1951	Jouve *et al*.	Android obesity as a risk factor of cardiovascular disease
	1982	Kissebah *et al*.	Upper-body obesity
	1985	Bjorntorp	Abdominal obesity
	1987	Matsuzawa *et al*.	Visceral fat obesity (regarding subcutaneous fat as a protective factor from the morbid effect of visceral fat)
	1989	Kaplan	Deadly quartet
	1994	Nakamura *et al*.	Visceral fat syndrome based on visceral fat obesity
	2000	Lemieux	Hypertriglyceridemic waist
	2005	IDF	Abdominal obesity as the essential component of metabolic syndrome
	2005	Japanese definition of metabolic syndrome based on visceral fat syndrome	
B: Concepts which regard obesity as a non-essential feature of metabolic syndrome	1981	Rudermann *et al*.	MONW individuals with hyperinsulinemia
	1988	Reaven	Syndrome X with insulin resistance
	1991	DeFronzo and Ferrannini	Insulin resistance syndrome
	1993	Hotamisligil *et al*.	Inflammation (TNF-α) as a linker between obesity and insulin resistance
	1999	WHO	The first definition of metabolic syndrome
	1999	EGIR	Insulin resistance syndrome excluding diabetes
	2001	NCEP	Metabolic syndrome defined by 3 out of 5 components
	2003	AACE	Subjective criteria of insulin resistance syndrome excluding diabetes
	2004	Ridker	hs-CRP as a component of metabolic syndrome
	2006	Oda	Replacing waist circumference by hs-CRP among 5 components of metabolic syndrome

IDF, International Diabetes Federation; MONW, metabolically-obese, normal-weight; TNF-α, tumor necrosis factor-α; WHO, World Health Organization; EGIR, European Group for the Study of Insulin Resistance; NCEP, National Cholesterol Education Program; AACE, American Association of Clinical Endocrinologists; hs-CRP, high-sensitivity C-reactive protein.

number of cardiometabolic risk factors, such as hyperglycemia, overweight/obesity, elevated blood pressure, and dyslipidemia, are clearly related to diabetes and cardiovascular disease. The report recommended lifestyle modification with attention to weight loss and physical activity regardless of a diagnosis of metabolic syndrome because obesity, a prevailing threat in the Western world, is often a visible marker of other underlying risk factors (*34*). Since 2004, many epidemiological studies and meta-analyses of the metabolic syndrome have been reported (*35–41*), most of which have shown that the presence of the metabolic syndrome indicated a relative risk of a cardiovascular incident and mortality of around 1.5 to 2.5. After the issue of IDF definition, most of the studies comparing different definitions of the metabolic syndrome have suggested that the IDF definition was not superior to the NCEP definition, and pointed out that the former failed to identify metabolically abnormal but non-obese individuals known to be predisposed to diabetes and cardiovascular disease (*42–48*).

In 2007, the Association for Weight Management and Obesity Prevention, the Obesity Society, the American Society for Nutrition, and the ADA issued a consensus statement concerning WC (*49*). Their opinion held that no standard method provides the best correlation with disease risk for measuring WC, and that different anatomical landmarks have been used to measure WC in different studies. The current WC cut points were derived by regression from body mass index (BMI), and there is not yet a compelling body of evidence demonstrating that WC provides clinically meaningful information that is independent of well-known cardiometabolic risk factors. Therefore, the clinical usefulness of measuring WC is limited and unlikely to affect clinical management when BMI and other obesity-related risk factors are already being determined. Further studies are needed to establish the most appropriate WC cut points; this effort will be complex because the cut points are likely influenced by sex, race/ethnicity, age, BMI, and other factors. Previously, I proposed replacing WC with hs-CRP among the 5 components of metabolic syndrome because hs-CRP is the most widely used marker of low-grade inflammation, is strongly related to obesity and insulin resistance, and is an established risk factor for diabetes and cardiovascular disease (*50*). Of course, this proposal should be tested by longitudinal studies.

In summary, there have been two evolving lines of thought regarding the metabolic syndrome, as shown in Table 1. One considers the macroscopic anatomy of adipose tissue—that is, fat mass and distribution—as the essential feature of the syndrome (Table 1A). The other stands on the endocrine, inflam-

Table 2. Multi-Faceted View Points of Obesity and Adipose Tissue Disease

View points	Markers
General obesity	BMI, total fat mass, *etc*.
Abdominal obesity	waist circumference, waist-to-hip ratio, *etc*.
Visceral obesity	visceral fat area, visceral fat volume, *etc*.
Ectopic fat deposits	fatty liver, intra-muscular lipid, *etc*.
Endocrine disorders	leptin, adiponectin, RBP4, aFABP, *etc*.
Low-grade inflammation	hs-CRP, MCP-1, PAI-1, TNF-α, *etc*.
Histological changes	crown-like structure (enlarged adipocytes, adipocyte death, and accumulation of macrophages)

BMI, body mass index; RBP4, retinol binding protein 4; aFABP, adipocyte-type fatty acid binding protein; hs-CRP, high-sensitivity C-reactive protein; MCP1, monocyte chemoattractant protein-1; PAI-1, prasminogen activator inhibiter-1; TNF-α, tumor necrosis factor-α.

matory, and metabolic features of adipose tissue (Table 1B).

Obesity *vs.* Adipose Tissue Disease

Obesity as a Concept of Excess Body Fat Mass

Many methods have been developed to measure body fat mass and to define obesity as a state of excess body fat mass. However, no method or definition is clinically superior to BMI at present. A BMI cut point of 30 is generally used to define obesity, and that of 25 kg/m^2 is used to discriminate pre-obese or overweight persons from normal-weight persons. The prevalence of obesity was reported to be 32.2% in 2003–2004 in the United States (*51*) and 2.9% in 2004 in Japan (*52*). In a large prospective cohort study in the United States, the risk of death was 20 to 40% higher in overweight persons and two to at least three times higher in obese persons among those who had never smoked, compared to normal-weight, nonsmoking individuals (*53*). In Japan, compared with persons with BMI 23.0–24.9 kg/m^2, obese persons had a higher risk of coronary heart disease (relative risk: 1.8 with a 95% confidence interval: 1.1–3.0) in men not in women, but no significant increase in risk was detected for overweight persons (*54*).

Types of Obesity According to the Topology of Fat Deposition

In 1982, Kissebah *et al*. reported that body fat distribution and fat cell size were important markers of metabolic complications of obesity in women (*55*). Despres *et al*. later emphasized the role of visceral fat in the association between regional adipose tissue distribution and glucose tolerance in premenopausal obese women (*56*). Later, WC was proposed as a marker of abdominal (central, upper body, apple type, or android) or visceral obesity and obesity-related metabolic disorders (*57*). However, there is a report that WC is not superior to BMI as a predictive marker of diabetes (*58*), and the Association for Weight Management and Obesity Prevention, the Obesity Society, the American Society for Nutrition, and the ADA jointly criticized the clinical usefulness of WC (*49*). In 1997, a review by Matsuzawa found that insulin resistance was much more severe in visceral fat obesity than in subcutaneous fat obesity, based on limited data, and he proposed that subcutaneous fat might have some protective role against the morbid effect of visceral fat (*59*). However, in 2006, Reaven showed that among 19 qualified studies, there were only 2 where the relation between insulin-mediated glucose uptake (IMGU) and visceral fat was quite different from that between IMGU and abdominal subcutaneous fat, whereas in the other 17 studies the correlation coefficients between IMGU and visceral fat or subcutaneous fat did not vary a great deal (*27*). In 8 of those studies, they were somewhat higher with visceral fat; in 7, they were higher with subcutaneous fat; and in the remaining 2, they were identical. In 2007, Fox *et al*. examined the association of abdominal subcutaneous adipose tissue (SAT) volume and visceral adipose tissue (VAT) volume, assessed by multi-detector CT, with metabolic risk factors in the Framingham Heart Study and reported that, although VAT was more highly correlated with metabolic risk factors, it was possible that SAT volume actually contributes to a more absolute risk because SAT volume was greater than VAT volume (*60*). Later, Pou *et al*. examined the relations of SAT volume and VAT volume to circulating inflammatory and oxidative stress biomarkers in 1,250 Framingham Heart Study participants; they concluded that SAT and VAT were similarly associated with elevated concentrations of multiple inflammatory biomarkers (*61*). These results clearly show that SAT has no protective role against the morbid effect of VAT. Kelley and Goodpaster analyzed the linkage between excess fat storage within skeletal muscle and insulin resistance, and showed the effect of weight loss on skeletal muscle substrate metabolism (*62*). Montani *et al*. discussed the role of ectopic fat storage in the heart, blood vessels, and kidneys in the pathogenesis of cardiovascular disease (*63*), and Rasouli *et al*. also emphasized the role of ectopic lipid accumulation in the pathogenesis of the metabolic syndrome (*64*). Kotronen and Yki-Jarvinen showed that liver fat storage is highly significantly and linearly correlated with all components of the metabolic syndrome independent of obesity, and proposed fatty liver as a novel component of the syndrome (*65*).

Table 3. Up-to-Date Concept of Metabolic Syndrome

Chronic continued excess-energy environment surrounding cells
↓
Stress upon endoplasmic reticulum, nucleus, and mitochondria
↓
Enlargement and death of adipocytes with accumulation of macrophages (crown-like structure)
↓
Inflammation and insulin resistance
↓
Clustering of metabolic risk factors
↓
Diabetes and cardiovascular disease

Adipose Tissue Disease as a Metabolic Syndrome Concept

Adipose tissue secretes many hormone-like substances, such as tumor necrosis factor-α (TNF-α) (*66*), leptin (*67*), adiponectin (*68*), resistin (*69*), visfatin (*70*), monocyte chemoattractant protein-1 (MCP-1) (*71*), retinol binding protein 4 (*72*), and adipocyte-type fatty acid binding protein (*73*); and obesity has been considered an endocrine and inflammatory disorder intimately related with insulin resistance rather than merely an anthropometric fatness, a topologically altered fat distribution, or an ectopic fat deposition. Multi-faceted viewpoints and markers of obesity and adipose tissue disease are summarized in Table 2. Hotamisligil *et al*. reported the adipose expression of TNF-α and a direct role of this inflammatory cytokine in obesity-linked insulin resistance (*66*). Dandona *et al*. reported that insulin inhibits nuclear factor-κB and inhibits inflammation (*74*). Later, Hotamisligil reviewed the link between cell stress, inflammation, and metabolic disease, focusing on the c-Jun NH_2-terminal kinase, on an inhibitor of nuclear factor-κB kinase, and on obesity-induced endoplasmic reticulum (ER) stress (*75*). Semenkovich also reviewed insulin resistance and atherosclerosis, emphasizing mitochondrial, nuclear, and ER stress caused by the excess delivery of fuel, and recommended eating less and exercising more (*76*). A proposed up-to-date concept of metabolic syndrome is summarized in Table 3. Kim *et al*. reported a transgenic model of extreme obesity associated with an improved metabolic profile compared with the original obese mouse (*77*). In this transgenic model, adiponectin acts as a peripheral starvation signal promoting the storage of triglycerides preferentially in adipose tissue and reduces the macrophage infiltration into adipose tissue, thus preventing systemic inflammation and insulin resistance. Bains *et al*. reported a transgenic model of severe visceral obesity without insulin resistance, in which the adipocyte size is not increased and the plasma level of adiponectin is increased (*78*). Cinti *et al*. described the necrotic-like death of enlarged adipocytes having a crown-like structure consisting of activated macrophages, not only in the adipose tissue of obese mice and in both visceral and subcutaneous adipose tissue of obese humans, but also in the adipose tissue of hormone-sensitive lipase-deficient mice, which is a model of adipocyte hypertrophy without obesity but with insulin resistance (*79*). Kanda *et al*. reported a transgenic model of mice with normal body and adipose tissue weight, normal adipocyte size, and normal plasma adiponectin level, that manifests macrophage infiltration into adipose tissue, insulin resistance, and glucose intolerance (*80*). Kamei *et al*. reported a similar transgenic model and similar results emphasizing the role of circulating MCP-1 (*81*). Wellen *et al*. reported a transgenic model of mice that exhibit macrophage infiltration and overt inflammation only in visceral adipose tissue and not in subcutaneous adipose tissue, and that develop spontaneous metabolic disease, manifesting insulin resistance, glucose intolerance, mild hyperglycemia, dyslipidemia, and fatty liver (*82*). However, in this model of metabolic or visceral fat "syndrome," visceral fat weight was not increased but subcutaneous fat weight and liver weight were increased compared with wild-type mice. Strissel *et al*. reported adipocyte death and adipose tissue remodeling in mice in which obesity was induced by a high-fat diet (*83*). In this model, adipocyte death and macrophage infiltration in epididymal (visceral) adipose tissue were critical, but the weight of epididymal adipose tissue at a certain stage (12 weeks) of obesity was decreased and liver weight was increased at the same stage. These transgenic and diet-induced obesity animal models indicate that the infiltration of macrophages into adipose tissue and inflammation, rather than increased adipocyte size, adipose tissue mass, or visceral fat mass *per se*, are crucial for the metabolic consequences of obesity.

In humans, Kolak *et al*. demonstrated increased macrophage infiltration into subcutaneous adipose tissue and crown-like structures surrounding dead adipocytes in subcutaneous adipose tissue in a high liver fat group compared with a low liver fat group, independent of obesity and fat cell size (*84*). Although there are few histological studies involving humans (*79*, *84*), studies on a marker of systemic inflammation, hs-CRP, as a risk factor for diabetes and cardiovascular disease are abundant (*85–93*), and Ridker *et al*. proposed hs-CRP as a component of metabolic syndrome because hs-CRP is strongly related to obesity and insulin resistance, and was established as a risk factor for diabetes and cardiovascular disease (*5*). Though only about one-third of the most insulin-resistant individuals are actually obese according to Reaven (*27*), hs-CRP is significantly positively correlated with plasma leptin levels (*94*) and significantly negatively related with plasma adiponectin levels (*95*) even in persons with normal BMI. Nakamura *et al*. reported that WC has the strongest correlation with hs-CRP among the 5 components of the metabolic syndrome (*96*). Komatsu *et al*. reported that adiponectin was significantly correlated with hs-CRP but not with WC or BMI in a multivariate study among apparently

healthy Japanese men (*97*), and Yoneda *et al*. reported that hs-CRP differentiated nonalcoholic steatohepatitis (NASH) from simple steatosis of the liver, but BMI or visceral fat area did not (*98*). I and co-workers proposed hs-CRP ≥0.65 mg/L as a component of metabolic syndrome in Japanese (*99*), and this cut point may also be appropriate not only as a component of metabolic syndrome (*100*) but also as a risk factor for cardiovascular disease (*101*), coronary spasm (*102*), and NASH (*98*). I proposed replacing WC with hs-CRP as a marker of adipose tissue disease among the 5 NCEP components of the metabolic syndrome, not for diagnosing individuals with metabolic syndrome at present but rather for studying the syndrome; in that report, I also recommended the use of WC, BMI, or other anthropometric markers of obesity as convenient tools for the screening of more proximal risk factors for diabetes and cardiovascular disease (*50*). However, whether or not this new definition is useful for predicting the risk of diabetes and cardiovascular disease should be evaluated by longitudinal epidemiological studies and histological studies on human visceral adipose tissue in relation to systemic inflammatory markers, including hs-CRP, anthropometric parameters, and visceral fat volume, may clarify the concept of adipose tissue disease.

Conclusions

Not all obese persons eventually develop diabetes or suffer from cardiovascular disease, and conversely a substantial number of non-obese individuals do suffer from these diseases. Adipose tissue disease, which results from cell stress due to an environment of incessant excess energy and defined by histological features and systemic inflammatory, endocrine, and metabolic parameters, may be different from obesity defined by anthropometric parameters. On the other hand, hs-CRP may be a clinically useful marker of adipose tissue disease. However, obesity is an epidemic disease and a major cause of diabetes and cardiovascular disease in Western developed countries; through social norms, it spreads like an contagious disease (*103*). Even though the prevalence of obesity is low in Japan, the prevention of obesity is mandated by the national government. It is already proved, in obesity-prevailing countries such as the United States, that threatening people with the term "metabolic syndrome" is useless for the prevention of obesity. The most important preventive strategy in Japan may be stopping the spread of certain aspects of the Western lifestyle, especially of the still-prevalent fast-food diet in American society, by political and economical regulations. Obesity, like global warming, is an "inconvenient truth" in some Western countries, and the therapy for it may be inconvenient political and economic regulations on food culture and lifestyle.

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