REVIEW

Diabetes Management

Obesity and metabolic syndrome: the contribution of visceral fat and adiponectin

Yuji Matsuzawa*

Practice points

- Visceral fat accumulation is one of the key factors for obesity-related diseases including Type 2 diabetes.
- Dysregulation of adipocytokines, bioactive substances secreted from adipose tissue by visceral fat accumulation, might be a key mechanism for the development of Type 2 diabetes, metabolic syndrome and cardiovascular disease.
- Adiponectin has antidiabetic, antiatherogenic and anti-inflammatory functions, and its plasma levels decrease in subjects with visceral fat accumulation.
- In the metabolic syndrome, reduction of visceral fat to normalize the production and secretion of adipocytokines, especially adiponectin, is an effective strategy for prevention of Type 2 diabetes and cardiovascular disease.

SUMMARY Multiple risk factor syndrome in which hyperglycemia, dyslipidemia and hypertension cluster simultaneously has been noted as a highly atherosclerotic status with the name of metabolic syndrome, but there has not been consensus about the definition and diagnostic criteria for this syndrome. In this review, I showed that visceral fat accumulation has a crucial role in the development of multiple risk factors and discussed its mechanism, focusing on adipocytokines, especially adiponectin. The concept of metabolic syndrome as multiple risk factor syndrome based on visceral fat accumulation should be emphasized because lifestyle modification for the reduction of visceral fat may be very effective for the reduction of risks and also cardiovascular disease.

KEYWORDS
• adipocytokines • adiponectin • metabolic syndrome • multiple risk factor clustering syndrome • visceral fat

Present day lifestyles provide an increasing number of opportunities for overeating and for a decrease in physical exercise in Asian as well as western countries. As a consequence, many common health problems, worldwide, are closely associated with an excessive intake of calories with its typical consequences, obesity and Type 2 diabetes.

However, recent studies on the morbidity of obesity have indicated that the severity of obesity-related diseases such as diabetes mellitus, lipid disorders and cardiovascular disease do not necessarily correlate with the accumulation of body fat [1]. This is particularly illustrated in Asian countries, including Japan, where the prevalence of Type 2 diabetes is not much different from that in western countries [2], although the prevalence of obesity is much lower according to a WHO report [3]. Many studies on the morbidity of obesity have revealed that fat distribution rather than the extent of fat accumulation is more important for the development of obesity-related diseases such as Type 2 diabetes [4]. Several classifications of obesity concerning body fat distribution have been proposed to determine the possible mechanisms of obesity-related diseases.

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In 1947, Professor Jean Vague proposed a classification of obesity into android and gynoid types [5]. He noted that excess fat is dangerous because of metabolic complications. He also noted that women normally have twice the fat mass as men, and although they are often as obese or fatter than men, they live longer and are less likely to suffer metabolic complications of obesity. Björntorp, in the early 1980s, proposed a distinction between central and peripheral obesity [6] and Kissebah *et al.* suggested one between upper and lower body segment obesity based on waist/hip ratio [7]. They showed by epidemiological and clinical studies that patients with central and upper body segment obesity have more obesity-related disorders than those with peripheral and lower body obesity.

In a previous study in 1983, our group developed a method for fat analysis using CT scan that enabled us to analyze adipose tissues in body cavity, and it was noticed that there was marked variation in fat distribution between subcutaneous and intra-abdominal visceral fat **(Figure 1)** [8]. As shown later, the subjects with visceral fat accumulation have been demonstrated to have more obesity-related diseases than the subjects with subcutaneous fat [9]. Therefore, the obese subjects with visceral fat accumulation, namely visceral fat obesity, correspond to the previous categories for morbid obesity such as android obesity, central obesity and upper body segment obesity. In this review, I would like to show that visceral fat accumulation caused by over nutrition with physical inactivity play a key role in the development of cardiometabolic risks including Type 2 diabetes and discuss its mechanism, focusing on adipocytokines and adipose tissue-derived bioactive substances, especially adiponectin.

Visceral fat accumulation & obesity-related diseases

Using a CT scan analysis, we demonstrated the contribution of visceral fat accumulation to the development of a variety of metabolic disorders [9,10]. The visceral fat area has a significant correlation with the glucose area after an oral glucose tolerance test and also with plasma levels of cholesterol and triglyceride [10]. Visceral adiposity has been shown to be associated not only with quantitative changes in serum lipids and lipoproteins, but also with qualitative changes in lipoproteins, such as the increase of small-dense low-density lipoprotein [11]. The steady-state plasma glucose method demonstrated the subjects with visceral fat obesity have greater insulin resistance than the subjects with subcutaneous obesity [12].

Visceral fat accumulation correlates closely with systolic blood pressure [13]. In addition, there is a close correlation between the extent of visceral, but not subcutaneous, fat reduction and a lowering of blood pressure after weight reduction in the hypertensive obese subjects who underwent diet and physical exercise at Obesity Clinic in Osaka University [14]. Visceral fat accumulation relates not only to cardiovascular risks, but also directly to the development of cardiovascular disease [15]. Several studies, including ours, have demonstrated that visceral adiposity, as determined by CT scanning, is related to the development of cardiovascular risks and also coronary artery disease even in mildly obese subjects [16,17] and Fox *et al.* reported also the contribution of abdominal visceral adiposity to metabolic risk factors in the subjects who were drawn from the Framingham Heart Study [18]. More recently, Britton *et al.* reported that visceral adiposity is associated with incident cardiovascular disease and also cancer after adjustment for clinical risk factors and generalized adiposity in the subjects from the Framingham Heart Study [19]. These results suggest that visceral fat accumulation may become a key factor for multiple risk factor syndrome and also cardiovascular disease.

Multiple risk factor syndrome as a strong coronary risk status

The Framingham Heart Study is a well-known epidemiological study that clearly demonstrated the significance of hypercholesterolemia as a major risk factor in the occurrence of coronary heart disease [20]. The study also suggested that the clustering of multiple risk factors appeared to raise the risk of coronary heart disease [21]. Several clinical concepts of multiple risk factor clustering syndrome were proposed around 1990 after Reaven suggested the concept of syndrome X in which insulin resistance is considered to play the leading role in the clustering of cardiovascular risks such as hyperglycemia, hypertriglyceridemia, low levels of HDL, high cholesterol, hypertension and cardiovascular disease [22]. DeFronzo proposed a similar concept, which he called insulin resistance syndrome [23]. In 1989, Kaplan posited a multiple risk factor clustering syndrome, termed the deadly quartet, in which upper body obesity is one of four

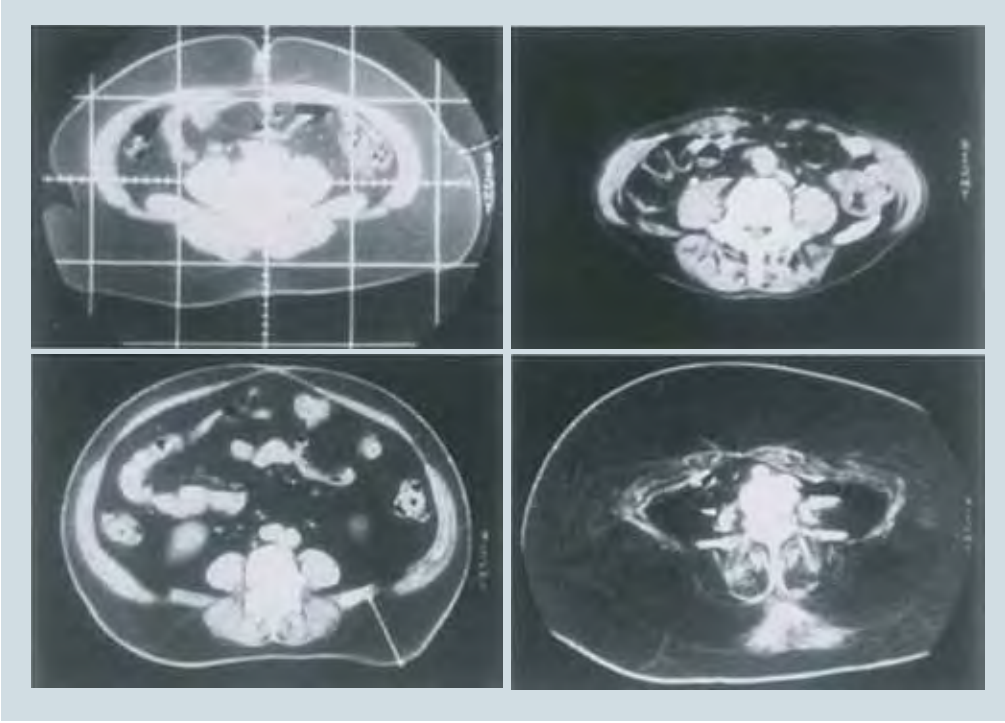

Figure 1. Marked variation of fat distribution in obese subjects. A novel technique for the determination of body fat by computed tomography.
Adapted from [8].

components including hypertriglyceridemia, hypertension and hyperglycemia [24].

In Japan, the study group, Association between Host Origin and Atherosclerotic Diseases, surveyed ten years of medical records of 122,051 employees from 31 industries [25]. Of this population, 94 cases of acute myocardial infarction, which occurred between 1991 and 1992, were compared with 191 age-matched controls in the same industries but without coronary artery disease. The study demonstrated that subjects with a combination of three or more risk factors of obesity, hyperglycemia, hyperlipidemia and hypertension increased the relative risk of acute myocardial infarction by almost ten-times. These findings suggest that multiple risk factor clustering may become a strong cardiovascular risk in Asian as well as western countries.

The question then arises as to whether these common disorders occur coincidently in one individual or whether some key factors play a role in the development of a variety of disorders. Insulin resistance has been considered a key indicator of multiple risk factor clustering syndrome as proposed in the concept of syndrome X or insulin resistance syndrome [22,23]. There is no doubt that insulin resistance is one of the main causes of Type 2 diabetes in multiple risk factor clustering syndrome [26]. In addition, there are epidemiological studies showing the association of insulin resistance to dyslipidemia or hypertension. Therefore, insulin resistance might play an important role in multiple risk factor clustering syndrome.

However, the etiology of insulin resistance has not been fully explicated in syndrome X or in the insulin resistance syndrome. It may be natural that visceral fat accumulation could be present upstream of insulin resistance, as well as hyperglycemia, dyslipidemia and hypertension in multiple risk factor clustering syndrome [27]. Thus, a key factor for multiple risk factor clustering syndrome could be visceral fat accumulation, and thus, multiple risk factor syndrome caused by visceral fat accumulation could be called visceral fat syndrome, although there may be some cases in which the symptoms from each genetic and environmental factor may cluster coincidently in one individual.

Visceral fat syndrome & metabolic syndrome

As described above, visceral fat accumulation might be present upstream in a variety of disorders including cardiovascular disease. Therefore,

on the basis of our clinical research, we have proposed the concept of a visceral fat syndrome, a similar concept to metabolic syndrome [28].

The term metabolic syndrome has been proposed by several investigators, although there has been considerable disagreement over the terminology and diagnostic criteria related to this multiple risk factor clustering syndrome. Metabolic syndrome was first formalized by a consultation group on the definition of diabetes for WHO, which accorded it high-risk status with multiple risk factors for cardiovascular disease [29]. This group emphasized insulin resistance as the major underlying factor along with the requirement for evidence of insulin resistance. In 2001, the National Cholesterol Education Program Adult Treatment Panel III (ATP III) proposed other criteria that included abdominal obesity estimated by waist circumference instead of BMI, elevated triglycerides, reduced HDL-cholesterol, elevated blood pressure and fasting glucose as the basis for establishing the diagnosis, although it did not require abdominal obesity as an essential component [30]. In 2005, the International Diabetes Federation (IDF) attempted to reconcile the different clinical definitions and made abdominal obesity an essential factor in the diagnosis with particular emphasis on waist measurement as a single screening tool [31]. The remaining four risk factors were identical to those proposed by ATP III [30].

Since then, a general agreement seems to have been reached that metabolic syndrome be defined as a multiple risk factor clustering syndrome that is induced by abdominal or visceral obesity. However, in recent years, there has been some disagreement about the waist circumference measurement site and the cutoff points [26]. As a result, representatives from the IDF, the American Heart Association and National Heart, Lung and Blood Institute (AHA/NHLBI) held discussions in an attempt to resolve the remaining differences between definitions of metabolic syndrome [32]. It was agreed that abdominal obesity should not be a prerequisite for diagnosis, but it is one of five factors and the presence of any three of the five risk factors will determine diagnosis. This recent definition is identical to the previously recognized ATP III criteria for multiple risk factor clustering syndrome [30].

The controversy may have come about by a misunderstanding of the significance of waist circumference and its relationship to visceral obesity in the pathophysiology of the multiple risk factor clustering syndrome. Waist circumference is not a medical biomarker and does not equate to other risks such as fasting blood glucose, triglycerides, HDL-cholesterol and blood pressure, but it is only a surrogate marker of visceral fat accumulation. Although waist circumference has been shown to correlate to visceral adiposity more strongly than BMI, it only estimates the total abdominal fat, which includes subcutaneous as well as visceral fat [33].

In Japan, metabolic syndrome has been designated a multiple risk factor clustering syndrome, and is evidenced by visceral fat accumulation. It is held that lifestyle intervention to reduce visceral adiposity should take priority over drug treatment. Diagnosis of metabolic syndrome in subjects with multiple risk factor clustering syndrome is made of visceral fat areas as determined by CT scan exceed 100 cm^2. Treatment for these patients is primarily by lifestyle modification. The Japanese committee convened to evaluate diagnostic standards for metabolic syndrome adopted a cutoff point of 100 cm^2 visceral fat area for both men and women because the number of risks over this point increases equally in men and women. A recent epidemiological study called the Vacation-J study confirmed the validity of this cutoff point for visceral adiposity in a large-scale Japanese general population [33]. In the study, fat distribution was measured using CT scans in 12,443 subjects who underwent medical check-ups. This study clearly demonstrated that the visceral fat area correlated to the number of cardiovascular risk factors. The mean number of risks exceeded 1.0 at around 100 cm^2 for visceral fat area irrespective of gender, age or BMI. By contrast, there was no correlation to the number of risks from the subcutaneous fat area **(Figure 2)**. This study also confirmed that the waist circumference corresponding to the cutoff point for visceral fat of 100 cm^2 is 85 cm in men and 90 cm in women. Although there are many different cutoff points adopted by different organizations and countries, the Japanese waist circumference threshold is the only one that is estimated from visceral fat area thresholds for morbidity [29]. Women have physiologically more subcutaneous fat than men, which makes their waist circumference larger in subjects with equal visceral fat [34].

A Joint Interim Statement on metabolic syndrome published in *Circulation* in 2009 concluded that in the interim, national cutoff points

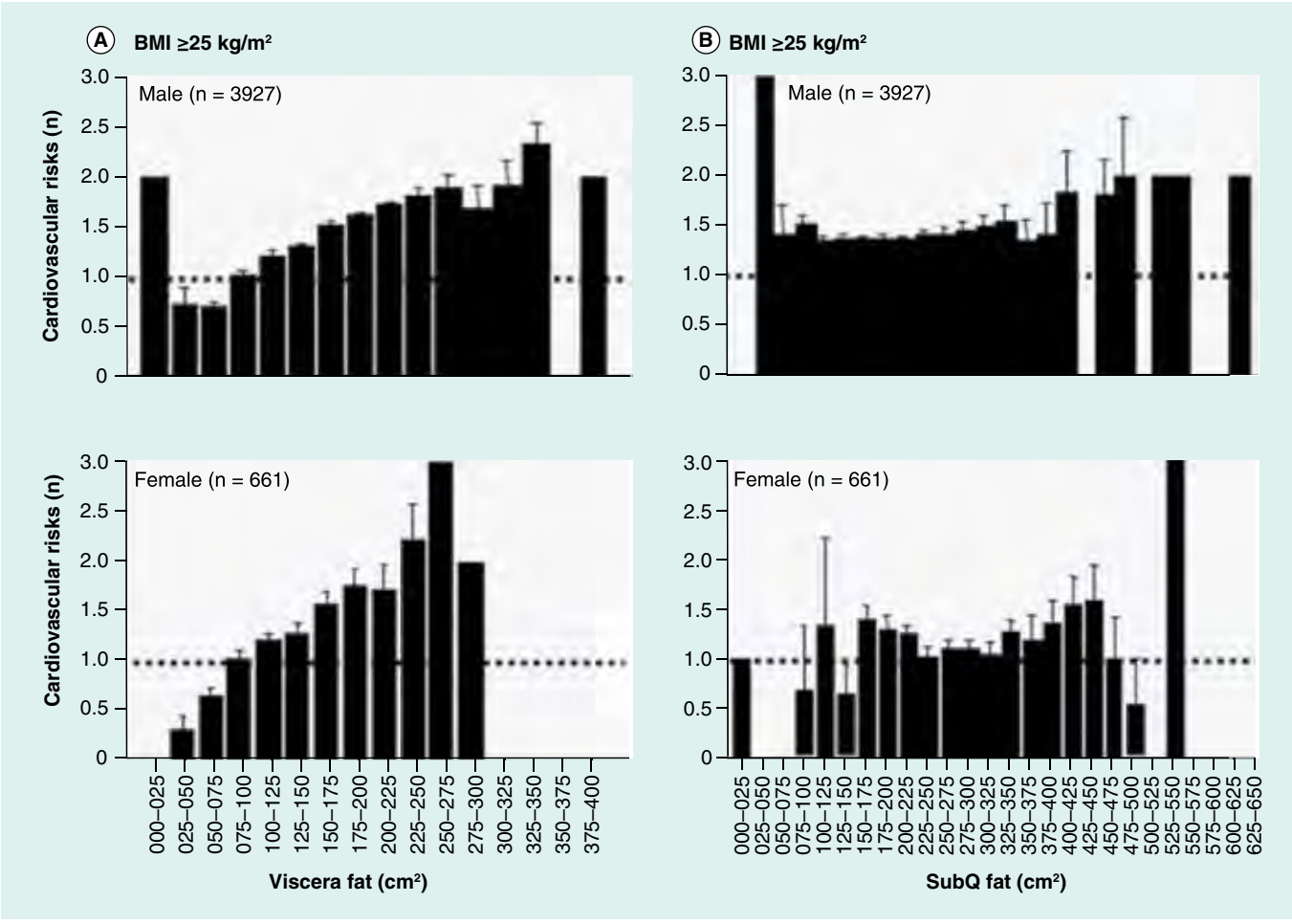

Figure 2. Correlation between number of cardiovascular risks and visceral fat area or subcutaneous fat area.

can be used [35]. According to ATP III criteria and the joint statement, abdominal obesity is not an obligatory component because only three abnormal findings out of the five components would qualify a person for a diagnosis of metabolic syndrome [30,35]. Thus, this concept of metabolic syndrome may include the multiple risk factor clustering syndrome in which visceral fat and other independent risks coincidently cluster in one individual. In such cases lifestyle intervention has limited effectiveness, so drug treatment may be necessary for each risk. Therefore, multiple risk factor clustering syndrome should be divided into two types, one in which visceral fat accumulation plays a key role in the development of multiple risks and cardiovascular disease (metabolic syndrome in the narrow sense), and the other in which multiple risks may occur coincidently. The purpose of diagnosing metabolic syndrome caused by visceral fat accumulation is to select subjects with multiple risk factors in which lifestyle modification to reduce visceral adiposity has priority over drug treatment **(Figure 3)**. The Japanese Committee for the definition and diagnosis of metabolic syndrome adopted the criteria for metabolic syndrome in the narrow sense, namely caused by visceral fat accumulation.

From 2008, the Japanese government started a new health program of providing a system of targeted health checkups followed by personalized counseling for subjects diagnosed with metabolic syndrome according to the Japanese criteria. Health insurers were made responsible for conducting the checkups and counseling, and approximately 56 million people aged 40–74 years and covered by the public health insurance scheme were involved. Through this nationwide project, not only is there expected to be a reduction of lifestyle-related diseases, including cardiovascular disease and Type 2 diabetes, but the government also expects to control the

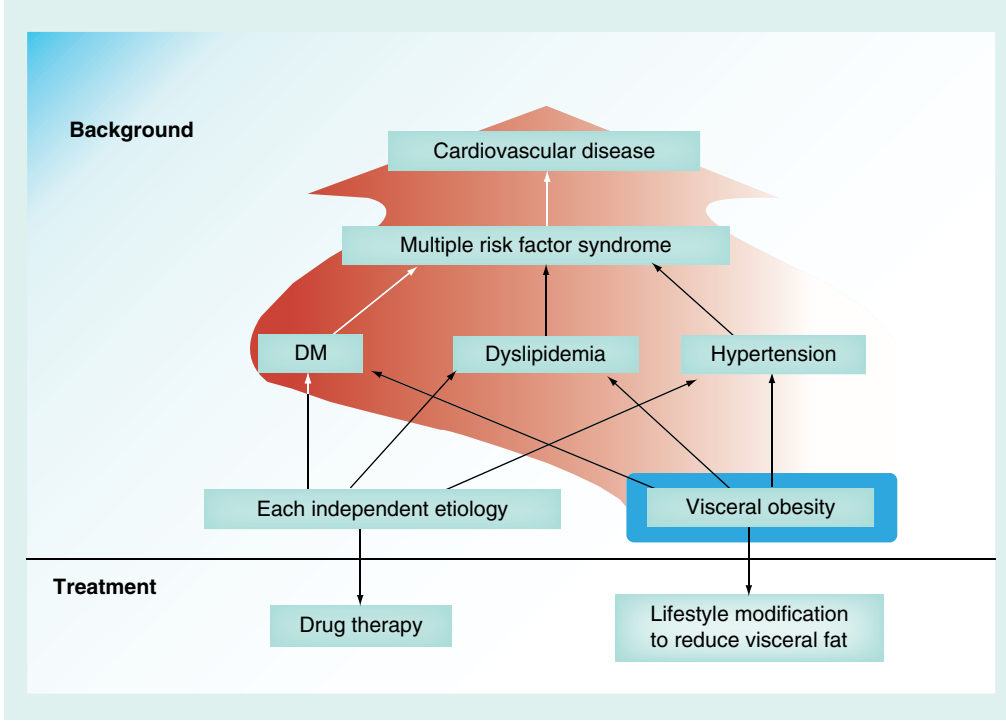

Figure 3. Background and strategy of treatment of mutiple risk factor syndrome and metabolic syndrome.
DM: Diabetes mellitus.
Adapted from [36].

increase in medical costs for lifestyle-related diseases. The results of a pilot study performed in an urban area demonstrated that the extent of a reduction in visceral adiposity was clearly associated with a lessening of risk factors [37]. Namely intensive consultation to those with metabolic syndrome for lifestyle modification to reduce visceral adiposity has demonstrated to be effective for the reduction of risk factors [38].

Metabolic syndrome & adipocytokines

To clarify the mechanism by which visceral fat accumulation causes the development of Type 2 diabetes and other cardiovascular risks, we investigated the functions of adipose tissue, which has been traditionally regarded as a tissue passively storing excess energy in the form of triglycerides. We analyzed and compared the gene expression profile of human adipose tissue in collaboration with the 'human gene map project team' to determine the biological characteristics of visceral and subcutaneous adipose tissue. The most important finding was that adipose tissue, especially visceral adipose tissue, abundantly expresses the genes encoding secretory proteins, most of which are important bioactive substances. In visceral adipose tissue, genes encoding secretory protein comprised approximately 30% of all genes. **(Figure 4)**. We classified these adipose-tissue-derived bioactive substances as adipocytokines or adipokines [39].

The genes encoding PAI-1 and heparin binding epidermal growth factor-like growth factor were highly expressed in adipose tissue [40,41]. Using ventromedial hypothalamic-lesioned rats as an experimental animal model of obesity, PAI-1 mRNA expression increased up to tenfold in visceral adipose tissue during fat accumulation. In subcutaneous adipose tissue, its expression remained unchanged in contrast with the case of visceral adipose tissue. In human cases, plasma levels of PAI-1 were significantly correlated with visceral adiposity assessed by CT scanning [40]. Since it is well known that circulating PAI-1 is a strong risk factor for thrombotic diseases, including acute myocardial infarction, increased PAI-1 secretion from accumulated visceral adipose tissue might be attributable to the occurrence of cardiovascular disease in the metabolic syndrome. Heparin binding epidermal growth factor-like growth factor, a potent factor for smooth muscle cell proliferation, which

is secreted from accumulated adipose tissue, could also have some significance for vascular remodeling in visceral obesity [41].

Adiponectin as a defence adipocytokine against metabolic syndrome

The gene encoding adiponectin was discovered as a novel gene that expresses most abundantly in adipose tissue and was named to be *apM-1* [42]. The molecule encoded by *apM-1* possesses a signal peptide, collagen-like motif and globular domain, and has notable homology with collagen X, VIII and the complement factor C1q. This collagen-like protein was named adiponectin and we established a method for the measurement of plasma levels using ELISA. The mouse homolog of adiponectin has been cloned as *ACRP30* [43]. The average levels of adiponectin in human plasma are 5–10 μg/ml, which are extremely high compared with other cytokines and hormones [44]. Surprisingly the plasma concentrations of adiponectin are negatively correlated with visceral adiposity, nevertheless this protein is secreted only from adipose tissue.

The mechanism of the reduction of adiponectin plasma levels by visceral fat accumulation has not been yet clarified. Some inhibiting factors for adiponectin synthesis was suggested to be secreted from visceral adipose tissue, since co-culture with visceral fat inhibits adiponectin secretion from subcutaneous adipocytes [45]. TNF-α is a strong inhibitor of adiponectin promoter activity [46]. The negative correlation between visceral adiposity and adiponectin levels might be explained by the increased secretion of this cytokine from accumulated visceral fat and may be one of the mechanisms involved.

Hypoadiponectinemia & metabolic syndrome

The subjects with Type 2 diabetes have been shown to have lower adiponectin levels than in control [47]. There is a close correlation between plasma concentrations and insulin sensitivity determined by glucose cramp test, which suggests that low plasma concentrations are related to insulin resistance and Type 2 diabetes [48]. In a study of Pima Indians, individuals with high levels of adiponectin were less likely than those with low concentrations to develop Type 2 diabetes [49].

Studies on adiponectin knockout (KO) mice support observations in humans in that the KO mice showed no specific phenotype when they were fed a normal diet, but with a high-sucrose

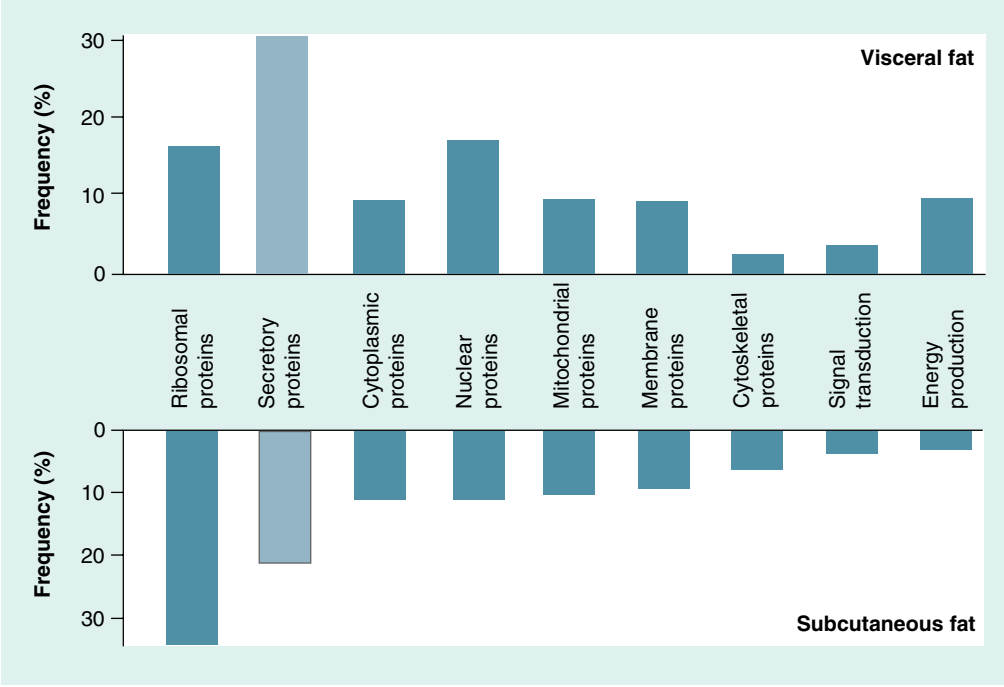

Figure 4. Distribution of expressed gene profile in adipose tissue classified by gene function and subcellular localization.

and high-fat diet a marked elevation of plasma glucose and insulin levels were observed in the KO mouse [50]. Notable insulin resistance, estimated by an insulin tolerance test during a high-sucrose and high-fat diet, also developed in the KO mice. Supplementing adiponectin by adenovirus transfection has been found to clearly reduce this insulin resistance [50]. These results show that hypoadiponectinemia induced by visceral fat accumulation might be an important factor for Type 2 diabetes and insulin resistance.

Hypertensive humans were reported to have lower levels of adiponectin irrespective of the presence of insulin resistance [51]. Endothelium-dependent vasoreactivity is impaired in people with hypoadiponectinemia, which might be one mechanism of hypertension in visceral obesity [52]. Plasma adiponectin negatively correlated with serum triglycerides and positively correlated with serum HDL cholesterol in subjects who received annual health examinations [53].

These reports are suggesting hypoadiponectinemia induced by visceral fat accumulation might have a central role in the development of multiple risk factors which are the components of metabolic syndrome.

In addition to the contribution to these cardiovascular risks, hypoadiponectinemia is related to cardiovascular disease directly. Many studies reported that the subjects with coronary heart disease have lower levels of adiponectin even BMI and age matched [54]. A case–control study demonstrated that the group with hypoadiponectinemia with plasma levels less than 4 μg/ml was shown to have increased risk of CAD and multiple metabolic risk factors, which indicates that hypoadiponectinemia is a key factor in metabolic syndrome [55]. A prospective study also confirmed that high adiponectin concentrations are associated with reduced risk of acute myocardial infarction in men [56]. More recently in the Framingham offspring study, we showed that high plasma adiponectin levels are a significant predictor of a lower risk of future cardiovascular events [57]. This clinical evidence shows that hypoadiponectinemia is a strong risk factor for cardiovascular disease [58,59].

Cardiovascular disease is caused by multiple pathogenic conditions. While visceral fat accumulation is a common background, it does not explain all causes of cardiovascular disease.

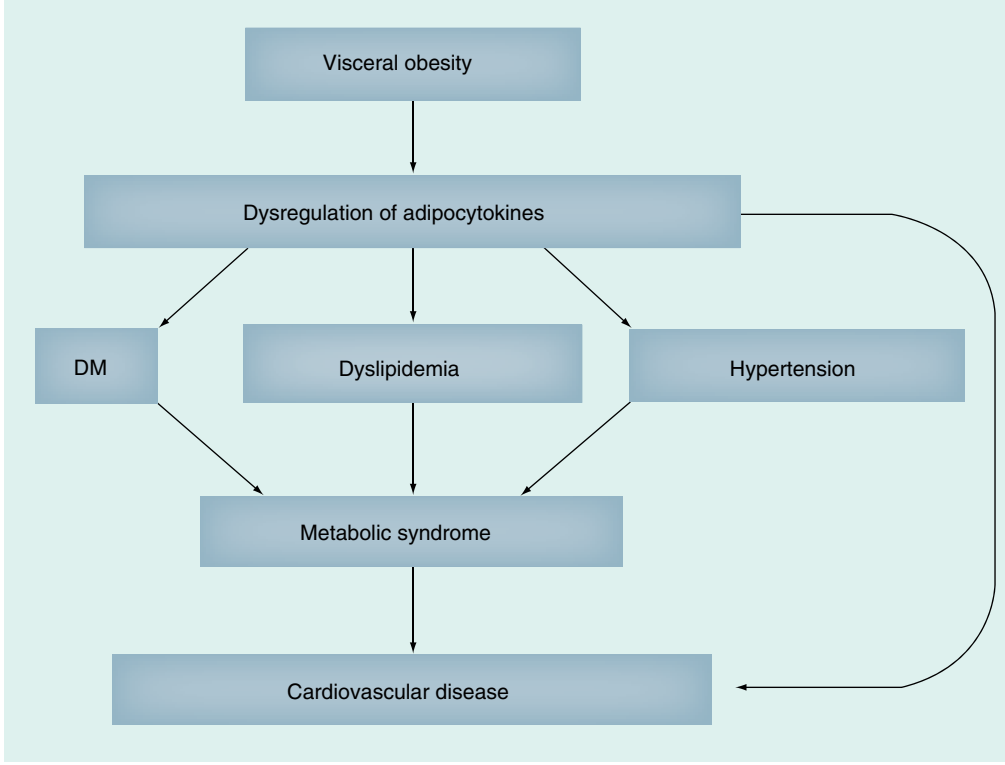

Figure 5. Concept and pathogenesis of metabolic syndrome.
DM: Diabetes mellitus.

Adiponectin is a protective protein related to various components of metabolic syndrome. Adiponectin-deficient mice show no apparent phenotype without exposure to metabolic and vascular stress. However, once they are exposed to various nutritional or chemical stress such as high-fat/high-sucrose diet or mechanical stress to vascular walls, they exhibit severe phenotype, suggesting that adiponectin has a protective properties against lifestyle related disease [50,60]

Conclusion

This article shows the important role of visceral fat accumulation in the development of obesity-related diseases and also metabolic syndrome. Because visceral fat accumulation causes Type 2 diabetes, hypertension and dyslipidemia, one can clearly understand why plural disorders cluster in one individual and have a central role in the development of metabolic syndrome.

The mechanism was also discussed focusing on the important contribution of dysregulation of adipocytokine secretion induced by visceral fat accumulation. Adiponectin, an adipose tissue-specific collagen-like protein, in particular, has plural functions for antidiabetes, antiatherogenicity and hypoadiponectinemia in subjects with visceral fat accumulation. They may play a key role in Type 2 diabetes and multiple risk factor clustering syndrome, so-called metabolic syndrome. Therefore, it is natural that lifestyle modification to reduce visceral fat should become a primary measure for the prevention of the development of cardiovascular diseases as well as its risks including Type 2 diabetes in metabolic syndrome with visceral fat accumulation (metabolic syndrome in the narrow sense) **(Figure 5)** through the improvement of adiponectin production [36].

Future perspective

Metabolic syndrome has become a major target for the prevention of cardiovascular disease. As mentioned in this review, visceral fat accumulation and dysregulation of adipocytokines, especially hypoadiponectinemia associated with visceral fat accumulation play a key role in the development of a variety of cardiometabolic risks, including Type 2 diabetes and cardiovascular disease. Therefore, in addition to the reduction of visceral adiposity, the development of novel procedures, including novel drugs for the enhancement of adiponectin production in adipocytes, may become emerging therapeutic strategies for metabolic syndrome.

Basic studies on molecular nature of adiponectin, a new category of endocrine proteins and studies on visceral obesity should enhance the understanding of visceral fat syndrome or metabolic syndrome and help the development of prevention of cardiovascular disease.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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