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DIABETES + INSULIN RESISTANCE (M RUTTER, SECTION EDITOR)

Fat Distribution and Cardiovascular Disease Risk

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Abstract The increase in obesity and cardiovascular disease (CVD) is a major problem in developed countries. As a consequence, metabolic syndrome, a disorder that links obesity and CVD, is becoming an important health concern. The underlying mechanisms of metabolic syndrome are considered to be excess visceral fat accumulation and insulin resistance. Visceral adipose tissue essentially takes up and stores excess energy and buffers against hyperglycemia and hyperlipidemia. However, excess visceral fat accumulation causes dysregulation of various adipocyte-derived bioactive molecules (adipocytokines), which leads to chronic systemic low-grade inflammation and CVD. The reduction of visceral fat through lifestyle modification is a potentially useful strategy for the prevention of CVD. Waist circumference is a good surrogate marker of visceral fat accumulation and is useful for monitoring the results of lifestyle changes. Moreover, adipocytokines are useful biomarkers and therapeutic targets for obesity-induced CVD.

Keywords Obesity · Cardiovascular disease · Metabolic syndrome · Visceral fat · Waist circumference · Lifestyle modification · Adiponectin · Inflammation

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Introduction

According to the World Health Organization (2010) Global Status Report on noncommunicable diseases, an estimated 17.3 million people died from cardiovascular disease (CVD) in 2008, representing 30 % of all global deaths [1]. The most important lifestyle-related risk factors for CVD are unhealthy diet, physical inactivity, and tobacco use, and the worldwide prevalence of obesity, diabetes, hypertension, and dyslipidemia has increased as a result of these same lifestyle-related factors. Therefore, CVD risk factors are closely correlated with unfavorable lifestyle, and addressing these risk factors can reduce the risk of CVD. However, the clustering of risk factors is not only correlated with the morbidity of obesity but also with the distribution of body fat.

It is difficult to overemphasize the negative impacts of obesity and the risks of metabolic syndrome. As obesity becomes more common, it is almost becoming accepted, and the metabolic syndrome-associated abnormalities of high blood pressure and elevated lipid and glucose levels are relatively mild in the early stages. Most people enjoy food, and many do not want to diet or take up exercise if they are not convinced of the need for lifestyle changes. Therefore, it is important to establish a biomarker for the detection of asymptomatic CVD. In this paper, we will review the relationship between fat distribution and the risk of CVD.

CVD and Body Fat Distribution

Vague was the first to report a link between fat distribution and metabolic complications and proposed the classification of android- and gynoid-type obesity [2]. In the mid-1980s, Kissebah [3], Bijorntrop [4], and our group [5] proposed the classification of upper body obesity, central obesity, and visceral fat obesity, respectively. Android-type, upper body,

central, and visceral obesity are all associated with an increased risk of CVD. The measurement of body fat distribution by computed tomography (CT) in obese Japanese subjects revealed that the ratio of visceral to subcutaneous fat area at the umbilical level was correlated with abnormal glucose and lipid metabolism and high blood pressure [6–8]. Furthermore, in subjects with the same degree of obesity, a larger accumulation of visceral fat was associated with a clustering of cardiovascular risk factors. In a weight reduction study, we found a close correlation between the reduction in visceral fat and the reduction in glucose, lipids, and blood pressure [9, 10]. Taken together, these findings suggest that the accumulation of visceral fat is associated not only with the clustering of CVD risk factors but also with the development of CVD.

In addition, we hypothesized that subcutaneous fat may have a defensive action against the clustering of cardiovascular risk factors. In fact, we have studied several individuals with massive subcutaneous fat type obesity but with normal blood pressure, glucose levels, and lipid metabolism. These people were physically active and eating very well and included a sumo wrestler. Barry et al. performed a meta-analysis of the combined effect of obesity and cardiorespiratory fitness on all-cause mortality. They compared six groups (normal weight-unfit and normal weight-fit, overweight-unfit and overweight-fit, and obese-unfit and obese-fit) and found that overweight and obese-fit individuals had similar mortality risks as normal weight-fit individuals [11•]. Obese-fit subjects might have decreased visceral fat and increased subcutaneous fat compared with obese-unfit subjects. In an animal fat transplantation study, mice with subcutaneous fat transplanted into the visceral cavity exhibited decreased body weight, total fat mass, and glucose and insulin levels, suggesting that subcutaneous fat is intrinsically different from visceral fat and might produce bioactive substances that can act systemically to improve glucose metabolism [12]. However, in humans, abdominal subcutaneous liposuction did not significantly change obesity-associated metabolic abnormalities [13], indicating that subcutaneous fat tissue has no effects on insulin sensitivity and inflammation. Although subcutaneous fat may not have a defensive action against the development of cardiovascular risk factors, the role of subcutaneous fat in the pathophysiology of CVD is quite different to the role of visceral fat. Therefore, it is important to assess visceral fat accumulation, by precisely measuring visceral fat area (VFA) on CT, as a useful clinical parameter for CVD risk estimation.

A larger waist circumference is associated with a greater risk of CVD and type 2 diabetes, and higher all-cause mortality. Both VFA and waist circumference increase with age, especially after menopause and with declining levels of physical fitness. However, VFA may be a better predictor of CVD than waist circumference. Wormser et al. reported that BMI, waist circumference, and waist-to-hip ratio, whether assessed singly or in combination, did not markedly improve CVD risk prediction when additional information was available for systolic blood pressure, history of diabetes, and lipid profiles [14]. However, waist circumference is an important screening tool for excess visceral fat accumulation.

Metabolic Syndrome

Joint Scientific Statement on metabolic syndrome for "harmonizing metabolic syndrome" in 2009 proposed that the presence of three of the five risk factors, abdominal obesity, hypertriglyceridemia, hypo-HDL cholesterolemia, high blood pressure, and high blood glucose, should lead to a diagnosis of metabolic syndrome [15]. In the Japanese diagnostic criteria for metabolic syndrome established in 2005, waist circumference is used as an index of visceral fat accumulation. Metabolic syndrome is diagnosed in individuals with visceral fat accumulation indicated by increased waist circumference and two or more risk factors including elevated blood pressure, dyslipidemia, and hyperglycemia. In 2005, the IDF also published diagnostic criteria for metabolic syndrome on the basis of the same concept, with abdominal obesity as an essential factor [16].

However, the clinical significance of waist circumference has been controversial. Increased waist circumference is not a cause of CVD like high blood pressure but is a surrogate marker of visceral fat accumulation. In Japan, metabolic syndrome is diagnosed on the basis of the clustering of cardiovascular risk factors caused by visceral fat accumulation. Although the 2009 Joint Scientific Statement supported the importance of abdominal obesity, the criteria for metabolic syndrome included visceral fat-independent clustering of risk factors. There are two types of metabolic syndrome, the type in which visceral fat accumulation plays a key role (the narrow sense) and the type in which risk factors cluster coincidentally (the wide sense). In Japan, the advantage of diagnosing metabolic syndrome in the narrow sense is to select subjects with risk factors for whom lifestyle intervention to reduce visceral fat has priority over drug intervention.

A large-scale cross-sectional study was performed in Japan to investigate the association between VFA and obesity-related cardiovascular risk factors [17••]. The investigated risk factors were hyperglycemia, dyslipidemia, and elevated blood pressure. The study found that the VFA of all males and elderly females followed an almost symmetric distribution. The mean number of risk factors exceeded 1.0 for a VFA of around 100 cm^2 in all groups, irrespective of gender, age, and body mass index (BMI).

The Japanese Committee of the Metabolic Syndrome adopted the VFA cutoff point of 100 cm^2 because the number of risk factors increases above this area in both men and women. The cutoff points for waist circumference were set at 85 cm for men and 90 cm for women, on the basis of the waist

circumference corresponding to a VFA of 100 cm^2. Although different cutoff points for waist circumference have been adopted in different ethnic groups, the Japanese cutoff points were selected to reflect the VFA thresholds for the morbidity of cardiovascular risk factors. Moreover, visceral fat reduction was correlated with a decrease in the number of risk factors for CVD in subjects with a VFA ≥100 cm^2, but not in those with a VFA <100 cm^2. The mean waist circumference of middle-aged women is less than 90 cm. Therefore, the cutoff of 90 cm is acceptable to identify women who can reduce cardiovascular risk factors through lifestyle changes. Conversely, the mean waist circumference of middle-aged men is larger than 85 cm. Therefore, the cutoff length of 85 cm is unsatisfactory for men, even in Japan. Higher cutoff points are arbitrarily adopted in different ethnic groups. Because cardiovascular risk is part of a continuum, a reduction in waist circumference from 105 to 95 cm would be expected to be associated with an improvement in accumulated risk factors.

Characteristics of Visceral Fat

Although the characteristics of visceral fat differ from those of subcutaneous fat, there is no conclusive evidence that visceral adipocytes differ from subcutaneous adipocytes. Visceral adipocytes are more prone to hypertrophy than subcutaneous adipocytes. Laviola et al. investigated the insulin signaling system in visceral and subcutaneous fat deposits in nonobese, nondiabetic humans [18]. The total protein levels of multiple insulin signaling intermediates were found to be higher in visceral fat than in subcutaneous fat, suggesting that visceral fat may display increased metabolic activity with regard to insulin action. Visceral fat is characterized by higher expression levels of specific signaling proteins and more pronounced and/or earlier activation of the signaling pathways in response to insulin administration.

Another important feature of visceral adipose tissue is that it is anatomically located upstream of the liver and downstream of the intestinal tract. Intra-abdominal visceral fat shows high activity of both lipogenesis and lipolysis, and visceral fat accumulation results in high levels of portal free fatty acids, a product of lipolysis, which flow into the liver. Excess free fatty acids may enhance lipid synthesis and gluconeogenesis as well as insulin resistance, resulting in hyperlipidemia, glucose intolerance, hypertension, and finally atherosclerosis (Fig. 1).

In addition, visceral adipose tissue provides an important defense against bacteria derived from the intestinal tract. Toll-like receptors (TLRs) are involved in the activation of macrophages in obese adipose tissue. In addition to bacteria-derived lipopolysaccharide (LPS), Lee et al. reported that saturated fatty acids (SFAs) activated the TLR4-mediated inflammatory signaling pathway [19]. They proposed that increased SFAs

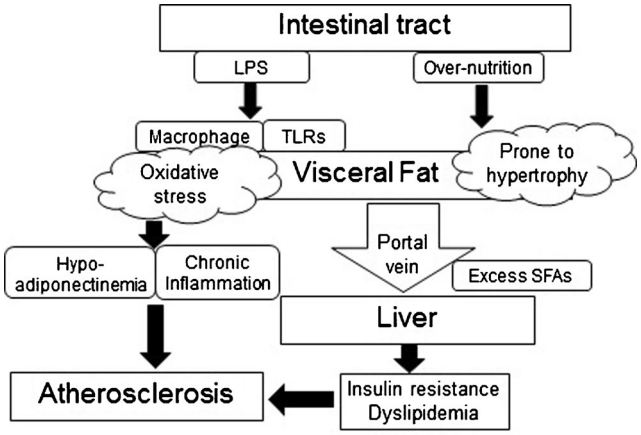

Fig. 1 Visceral fat and atherosclerosis

might influence the macrophage inflammatory response in obese adipose tissue. Conversely, Errdge et al. reported that SFAs did not activate TLR4-mediated signals and suggested that the contamination of LPS in bovine serum albumin for solubilizing SFAs might affect the signals [20]. Although the effect of SFAs on TLR4 is controversial, postprandial elevation of plasma LPS might contribute to the development of obesity and insulin resistance [21]. Moreover, TLR5-deficient mice exhibit the phenotype of metabolic syndrome [22]. These findings strongly suggest that abnormalities of the innate immune system in visceral fat might be involved in the pathophysiology of metabolic syndrome.

Molecular Link Between Visceral Fat and CVD

To elucidate the molecular mechanisms of visceral fat-induced disorders, our group investigated the gene expression profiles of human visceral and subcutaneous fat tissues and found that the majority of expressed genes encoded secretory proteins. We classified these adipose tissue-derived bioactive molecules as adipocytokines [23]. Among them, plasminogen activator inhibitor type 1 (PAI-1), tumor necrosis factor (TNF)-alpha, and monocyte chemoattractant protein (MCP)-1 are representative proinflammatory adipocytokines, and plasma levels of these molecules were positively correlated with VFA in humans [24–26]. Moreover, adipocyte fatty acid-binding protein (A-FABP) was suggested to be pro-atherogenic, because plasma A-FABP levels were positively correlated with the number of stenotic vessels in coronary artery disease [27]. Resistin was also found to be a risk factor for acute coronary syndrome in different clinical studies [28]. In contrast to these proinflammatory adipocytokines, we found that plasma adiponectin levels were negatively correlated with VFA [29]. Omentin, another adipocytokine expressed in

visceral fat, may also play a protective role in atherosclerosis by activating endothelial nitric oxide (NO) synthase [30, 31]. Adiponectin paralogs, C1q/TNF-related proteins (CTRPs), have recently been reported to modulate inflammation and metabolism [32–34]. Some CTRPs are expressed in adipose tissue and have protective properties against CVD [35–39], although it remains unknown if they can complement adiponectin function.

Among the adipocytokines, adiponectin is the key molecule for the development of metabolic syndrome and associated CVD. Hypoadiponectinemia was observed in patients with type 2 diabetes mellitus, hypertension, and coronary artery disease, and was an independent risk factor for these conditions [40–42]. In vitro experiments have revealed that adiponectin suppresses all the key steps for atherosclerosis, including monocyte adhesion to vascular endothelial cells [43], apoptosis of vascular endothelial cells [44], macrophage foam cell transformation [45], and vascular smooth muscle cell proliferation [46]. It is of importance that humans with genetic hypoadiponectinemia had a high prevalence of metabolic syndrome and coronary artery disease, independent of obesity [47]. Accordingly, we generated adiponectin-deficient (KO) mice to elucidate the causal relationship between hypoadiponectinemia and metabolic syndrome. The KO mice developed diabetes mellitus or hypertension while being maintained on a high-fat/high-sucrose or high-salt diet, respectively [48, 49]. After ischemia-reperfusion injury of the myocardium, KO mice exhibited a larger myocardial infarct size and elevated TNF-alpha production compared with wild-type (WT) mice [50]. The administration of adiponectin to KO mice reduced all the metabolic and cardiovascular abnormalities. These results suggest that hypoadiponectinemia is not only necessary for the development of metabolic syndrome but also an important factor in the development of atherosclerotic CVD. Therefore, measurement of plasma adiponectin levels would be useful for CVD risk estimation.

Conclusion

Overnutrition causes visceral fat accumulation along with activation of the innate immune system, resulting in the dysregulated production of adipocytokines. The downregulation of adiponectin and upregulation of PAI-1, TNF-alpha, and MCP-1 accelerate the vascular inflammatory response. Therefore, visceral fat accumulation is closely associated with vascular inflammation as well as diabetes, dyslipidemia, and hypertension, all of which lead to the development of CVD.

Waist circumference is a useful surrogate marker for visceral fat accumulation and adipocytokine dysregulation and can be easily measured by individuals to monitor the progress of lifestyle changes.

Compliance with Ethics Guidelines

Conflict of Interest Shinji Kihara and Yuji Matsuzawa declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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