Molecular mechanism of visceral obesity

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Summary: Visceral fat obesity or visceral fat syndrome coincides with syndrome X or deadly quartet, which is susceptible to atherosclerosis with the clustering of multiple risk factors. Visceral fat is located upstream of the liver via the portal vein. Numerous free fatty acids released from visceral fat are drained into the liver and enhance expression of the genes for lipoprotein synthesis, leading to hyperlipidemia. Visceral fat expresses numerous genes for secretory proteins including various bioactive substances. We proposed naming these adipocyte-derived bioactive substances 'adipocytokines'. One of the examples, plasminogen activator inhibitor-1 gene, is overexpressed in accumulated visceral fat, which may be involved in thrombotic disorders in visceral obesity. A newly found adipose-specific secretory protein, adiponectin, having a collagen-like motif may be related to vascular disorders. Adipocytokines may be a causative factor in the development of atherosclerotic disease in visceral obesity.

Key words: visceral fat, adipocytokines

Introduction

Obesity has become one of the main targets for medical research with respect to preventive medicine. Previous studies on the morbidity of obesity have indicated that the severity of complications, such as glucose intolerance or lipid disorders, does not necessarily correlate to the extent of body fat accumulation, but is closely related to body fat distribution [1]. Several classifications of obesity relating to body fat distribution have been proposed in order to explain the possible mechanism of morbidity of obesity. A Japanese ancient artist showed great insight into the morbidity of obesity 800 years ago by painting a picture of an obese woman with the title of "a very obese woman who can hardly walk (Fig. 1.) in the Japanese old picture scroll "Yamai-Zoshi", which means a scroll of various morbid states [2]. This artist already noticed that this type of obesity was considered unhealthy and morbid. In 1947, Vague first reported that the incidence of metabolic complications among equally obese subjects may differ depending on their physique [3]. He differentiated between android obesity, in which fat is likely to accumulate in the brachium, and gynoid obesity in which fat accumulation occur in the femoral region. He showed that morbidity is higher in the android type than in the gynoid type. Kissebah [4] et al. simplified the indicators of adipose tissue distribution by using the waist-to-hip circumference ratio (W/H) and defined those with higher W/H as upper-body-segment obesity and those with a low W/H as lower-body-segment obesity. He found abnormalities in glucose metabolism more frequently in cases with upper-body-segment obesity than lower-body-segment obesity and revealed that upper-body-segment obesity was a high risk group for metabolic disorders.

High waist-hip ratio as an expression of upper-body or abdominal obesity has thus appeared to present a feasible index for predicting risks associated with fat accumulation. However, 'waist' originally comprises both abdominal subcutaneous fat and intra-abdominal visceral fat, thus the discrimination of two types of adipose tissue is necessary for analyzing the relationship between fat distribution and morbidity. At present, computed tomography (CT), is the most useful method for measuring fat volume and fat distribution as we reported in 1983 [5], which enabled us to conduct an analysis of intra-abdominal visceral fat. Using this method, we defined obese subjects having a ratio of visceral fat area to subcutaneous area at the level of the umbilicus (V/S) equal to or greater than 0.4 as 'visceral fat obesity' and those having a ratio of less than 0.4 as 'subcutaneous fat obesity' [6, 7]. Metabolic disorders including glucose intolerance and hyperlipidemia were found more frequently in visceral fat obesity than in subcutaneous fat obesity. In addition to the metabolic disorders, visceral fat accumulation has been shown to be associated with the occurrence of cardiovascular complications [8, 9, 10]. The entity of visceral fat obesity may correspond basically to that of upper-body-segment obesity or abdominal obesity because a positive correlation between W/H and V/S was demonstrated by a study on white women. However our investigations have revealed, that approximately one-third of Japanese obese women belong to the subcutaneous type and the frequency of metabolic disorders was relatively low even in the upper-body obesity group with W/H above 1.0 [11]. Therefore, the
classification based on the amount of intra-abdominal visceral fat might be most appropriate for predicting morbidity. The above mentioned clinical studies suggested the importance of characterization of visceral adipose tissue at the metabolic, cellular and molecular level, which may facilitate the understanding of molecular mechanism in plural disorders related to obesity. In this review article, the pathophysiology of visceral fat obesity will be shown, and the mechanism of visceral fat accumulation will be discussed and finally, the pathogenesis of metabolic and cardiovascular complication will be also discussed from recent studies, including ours.

Pathophysiology of visceral fat obesity

Metabolic and cardiovascular disorders in visceral fat obesity

A number of clinical studies [6, 7] have demonstrated the contribution of visceral fat accumulation to the development of metabolic disorders, including glucose intolerance and hyperlipidemia. Our studies demonstrated that the V/S ratio significantly correlated to the glucose area after oral glucose tolerance test (OGTT), plasma triglyceride or cholesterol level in obese subjects. Visceral fat accumulation is associated with not only quantitative change in serum lipid and lipoprotein, but also qualitative changes in lipoproteins such as the appearance of small, dense LDL particles, which may be related to the high triglyceride-low HDL dyslipidemic state found in visceral fat obesity [12]. Many people believe that insulin resistance or hyperinsulinemic state which is often found in visceral fat obesity plays a key role in the development of metabolic disorders. Previous reports have shown that hyperinsulinemia, although not so predominant in Japanese subjects, is present in visceral type obesity. Studies using glucose clamp technique by Kissebah et al [13] and our steady state plasma glucose method [14] clearly demonstrated that visceral fat obesity have greater insulin resistance than those with subcutaneous fat obesity. Visceral fat accumulation has been shown to have causative effects in circulatory disorders in addition to metabolic disorders. We demonstrated a close correlation between the V/S ratio and the diastolic dimension index or stroke index in obese subjects which reflected the presence of a hypervolemic state in visceral fat obesity [8]. There was a close correlation between systolic blood pressure and V/S ratio in premenopausal female subjects [9, 10]. As stated above, visceral fat obesity is characterized by high risk obesity with multiple complications including insulin resistance, the disorders of glucose and lipid metabolism, hypertension, cardiac enlargement. We also demonstrated that the accumulation of visceral fat was related to the development of both metabolic disorders and circulatory disorders even in normal-weight subjects [15]. Thus, a disease entity, 'visceral fat syndrome' can be proposed as a state which is accompanied frequently with glucose intolerance, hyperlipidemia and hypertension irrespective of absolute body weight.