Pathophysiology and Molecular Mechanisms of Visceral Fat Syndrome: The Japanese Experience

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1. INTRODUCTION

Contemporary civilized countries provide an increasing number of opportunities for overeating and decreased muscular exercise, where common health problems are closely correlated to this over-nutritional state and its typical consequence, obesity. Therefore, obesity has become a main target for medical research in the field of 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.1-4 Several classifications of obesity concerning body fat distribution have been proposed in order to distinguish the possible mechanisms of morbidity of obesity. An ancient Japanese artist showed great insight into the morbidity of obesity 800 years ago when he painted a picture of an obese woman with the title of “A very obese woman who can hardly walk” (Figure 1) in the old Japanese picture scroll “Yamai-Zoshi”, which means a scroll for various morbid states.5 This artist had already noticed that this type of obesity was considered

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Figure 1. “A very obese woman who can hardly walk”, from Yamai-Zoshi, painted in Japan 800 years ago.
unhealthy and morbid. In 1947, Vague first reported that incidence of metabolic complications among equally obese subjects may differ depending on their physique. He differentiated between android obesity in which fat is likely to accumulate in the brachium, and gynoid obesity in which fat accumulation occurs in the femoral region. He showed that morbidity is higher in android type than in gynoid type. Kissebah et al. simplified the indicators for adipose tissue distribution by using waist-to-hip circumference ratio (W/H) and defined those with higher W/H as upper body segment obesity and those with low W/H as lower body segment obesity. They found abnormalities in glucose metabolism more frequently in upper body segment obesity than in lower body segment obesity and revealed that upper body segment obesity is a high-risk group for metabolic disorders. Björntorp gave the name abdominal obesity to high W/H and confirmed that the incidence of diabetes mellitus, hyperlipidaemia and ischaemic heart disease are higher in this group than in the peripheral obesity group.

High W/H as an expression of upper body or abdominal obesity has thus seemed to present a feasible index for predicting risks associated with fat accumulation. However, “waist” originality comprises both abdominal subcutaneous fat and intra-abdominal visceral fat, so discrimination of two types of adipose tissues is necessary for analysing the relationship between fat distribution and morbidity. At present computed tomography (CT) is the most useful method for measuring fat volume and fat distribution, which enables the analysis of intra-abdominal visceral fat. Using this method, we defined obese subjects as having visceral fat obesity when the ratio of visceral fat area to subcutaneous area at the level of the umbilical (V/S) was high (>0.4); when the ratio was lower than 0.4, the obese subjects were defined as having subcutaneous fat obesity. Metabolic disorders such as glucose intolerance or hyperlipidaemia were present 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 closely correlated with cardiovascular complications.

The entity of visceral fat obesity may basically correspond to that of upper body segment obesity or abdominal obesity because a positive correlation between W/H and V/S has been demonstrated by a study on white women. However, our investigations have revealed that approximately one-third of obese Japanese 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. Therefore the classification based on the content of intra-abdominal visceral fat might be most appropriate for predicting morbidity (Figure 2).

These clinical studies indicate the importance of characterizing visceral adipose tissue on a metabolic, cellular and molecular basis, which may contribute to the elucidation of molecular mechanism in multiple disorders related to obesity. This review article will describe the pathophysiology of visceral fat obesity in Japanese subjects, and discuss the mechanism of visceral fat accumulation as well as the pathogenesis of metabolic and cardiovascular complications in the light of recent studies, including ours.

2. PATHOPHYSIOLOGY OF VISCERAL FAT OBESITY

A. Metabolic and Cardiovascular Disorders in Visceral Fat Obesity

A number of clinical studies have demonstrated the contribution of visceral fat...
accumulation to the development of metabolic disorders including glucose intolerance and hyperlipidaemia. Our studies have demonstrated that V/S correlated more significantly to glucose area after oral glucose tolerance test (OGTT), plasma triglyceride and cholesterol in obese subjects. Visceral fat accumulation is associated not only with quantitative changes in serum lipid and lipoprotein but also with qualitative changes in lipoproteins such as small, dense lipoprotein (LDL) particles, which may be related to the high triglyceride–low high-density lipoprotein (HDL) dyslipidaemic state found in visceral fat obesity.23,24

Many people believe that insulin resistance or hyperinsulinaemic state in visceral fat obesity might be a key abnormality for these metabolic disorders. Previous reports have shown that hyperinsulinaemia, although not so predominant in Japanese subjects, is present in visceral type obesity.25 Studies on glucose uptake of muscle clone by Kisselah et al.26 and steady state plasma glucose method by us clearly demonstrated that visceral fat obesity has greater insulin resistance than subcutaneous fat obesity.27–29 Visceral fat accumulation has been shown to have causative effects on circulatory disorders in addition to metabolic disorders.30–32

We have demonstrated the close correlation between V/S ratio and the diastolic dimension index or stroke index in obese subjects which reflected the presence of a hypertensive state in visceral fat obesity.13 There is a close correlation between systolic blood pressure and V/S ratio in premenopausal female subjects.14,15 Recent studies of ours also suggest that sleep apnoea syndrome more frequently occurs in visceral fat obesity than in subcutaneous fat obesity.33 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 and sleep apnoea syndrome.

### B. Significance of Visceral Fat Accumulation in Subjects with Normal Body Weight

Obesity has been conventionally identified by the body weight for the height in each individual and body mass index (weight/m²) is an appropriate index for the judgement of obesity. Analysis of adipose tissue by CT scan, however, indicated that there was a substantial variation in visceral fat volume even among subjects with normal body weight.34 The correlation between topographic markers and metabolic markers in 52 subjects with normal body weight is shown in Table I. The visceral fat area correlated significantly with fasting plasma glucose, serum triglyceride and cholesterol. Visceral fat area was also correlated to blood pressure in subjects with normal body weight. In the subjects with normal body weight, the V/S ratio had no significant correlation with these markers, which is different from the case in obese subjects in which the ratio correlated with morbidity more significantly than the absolute visceral fat area. These data suggest that subcutaneous fat might have some protective role against the effect of visceral fat accumulation at least in obese subjects who are exposed to over-nutritional state. Therefore, influence of visceral adiposity can be more definitely demonstrated in subjects with normal body weight, since the effect of subcutaneous fat is small.

These results clearly demonstrate that visceral fat accumulation is related to the development of both metabolic disorders and circulatory disorders even in normal weight subjects. Thus, a disease entity, “visceral fat syndrome”, can be proposed as a disorder which is frequently accompanied by glucose intolerance, hyperlipidaemia and hypertension irrespective of absolute body weight.

| Table I. Correlation of Age, BMI and Fat Area to Metabolic Profile in Subjects with Normal Weight (n = 52) |
|----------------|----------------|--------|--------|--------|
| Age            | Correlation coefficient | BMI    | V. fat | S. fat | V/S    |
| FPG            | 0.08          | 0.20   | 0.43** | 0.22   | 0.21   |
| TG             | 0.06          | 0.27   | 0.45** | 0.21   | 0.27   |
| T-Chol         | 0.22          | 0.24   | 0.34*  | 0.27   | 0.13   |
| HDL-Chol       | 0.11          | −0.03  | −0.03  | 0.15   | −0.01  |

*p <0.05; **p <0.01.

V. fat, visceral fat area; S. fat, subcutaneous fat area; V/S, visceral fat area/subcutaneous fat area ratio; FPG, fasting plasma glucose; TG, triglycerides; T-Chol, total cholesterol; HDL-Chol, high-density lipoprotein cholesterol.
C. Visceral Fat Syndrome and Coronary Artery Disease

In recent years the clustering of multiple risk factors for coronary atherosclerosis has been recognized as a syndrome, defined by Reaven as “syndrome X” and by Kaplan as “the deadly quartet”.34–37 Visceral fat obesity or visceral fat syndrome including non-obese subjects corresponds to these syndromes. Previous epidemiological studies by the Gothenberg group have already suggested that W/H is a significant predictor for coronary artery disease independent of BMI.42–44 Previous studies have shown that there is a negative correlation between plasma level of sex hormone binding globulin (SHBG) and W/H ratio in females, indicating that the active form of testosterone is an important determinant of visceral adiposity in females.45

In contrast, low testosterone levels in males was reported to relate to visceral adiposity.46 Björntorp indicated that hyperreactivity of limbic–hypothalamo-pituitary–adrenal (LHPA) axis, probably followed by interference by corticotrophin-releasing hormone (CRH) of the gonadal–pituitary axis, might act as pathogenetic roles.47–49

Ageing is also an important factor in promoting visceral adiposity.50 A close linear correlation between age and visceral fat volume was obtained in male subjects by the cross-sectional study of 157 obese subjects of varying ages.41 Although this correlation was also present in female obese subjects the slope was gentle in premenopausal subjects, but suddenly steepened after menopause, which is comparable to that of males.

Among dietary factors, high sucrose intake is a candidate for promoting visceral fat accumulation. We have previously reported that high sucrose loading caused the increase of mesenteric fat both in ventromedial hypothalamus (VMH)-lesioned obese rats and control rats.51

Physical exercise has been suggested to reduce visceral adiposity. We analysed visceral fat and subcutaneous fat in Japanese Sumo wrestlers in order to investigate the effect of physical exercise on regional fat distribution in obesity. Sumo wrestlers eat a high energy diet (5000–7000 kcal/day) to gain weight but, at the same time, they are forced to perform strenuous physical training daily. Although they showed marked obesity, the average V/S ratio was 0.25, which was comparable to subcutaneous fat obesity, while their glucose and lipid levels were normal. A typical CT scan imaging of wrestlers at the level of the umbilicus demonstrated fat accumulation only in the subcutaneous regions and showed marked musculularity (Figure 3).52 The incidence of diabetes increases markedly among retired wrestlers who do not continue muscular exercise, but remain heavy eaters. Muscular exercise is not

3. FACTORS INDUCING VISCERAL FAT ACCUMULATION

Sex hormones might be a major factor determining fat distribution.41 Visceral fat accumulation is more predominant in male obesity than in female obesity when compared among age-matched subjects with similar BMI.42–44 Previous studies have shown that there is a negative correlation between plasma level of sex hormone binding globulin (SHBG) and W/H ratio in females, indicating that the active form of testosterone is an important determinant of visceral adiposity in females.45
only useful in preventing visceral adiposity, but also in diminishing it. Figure 4 shows a representative case in whom visceral fat area was selectively reduced within several months by regular daily exercise under moderately limited caloric intake. Genetic factors for the induction of visceral adiposity might be present, since it is not rare that the visceral type of obesity clusters in the same family. Very recently a non-conservative

**Figure 3.** A typical CT scan image from an average young Sumo wrestler (note high musculature and scanty visceral fat).

**Figure 4.** Changes in visceral adiposity after treatment with physical exercise in addition to diet therapy.
missense mutation in the $\beta_{2}$-adrenergic receptor gene at the junction between the first transmembrane domain and the first intracellular loop (Trp64 Arg) was suggested as a candidate for genetic factors of visceral adiposity.$^{53,54}$

4. CELL BIOLOGICAL AND METABOLIC CHARACTERISTICS OF VISCERAL ADIPOSE TISSUE

Observation of cellularity of regional fat tissues in Zucker fatty rats and VMH-lesioned rats suggested that the increase in mesenteric fat depots is attributed to adipose cell enlargement rather than an increase in cell numbers.$^{55}$ Mature adipocyte number is defined by both cell replication and differentiation from preadipocytes. Previous studies indicate that preadipocytes (vascular stromal cells) obtained from mesenteric adipose tissue are less active for replication as well as differentiation than those from subcutaneous tissue,$^{56}$ suggesting that mesenteric fat accumulation might be due to a predominant enlargement of mature adipocytes. Intra-abdominal visceral fat including mesenteric fat and omental fat has been shown to have greater lipolytic activity than other adipose tissues,$^{57-59}$ which might be partly attributed to the fact that larger adipocytes tend to be more sensitive to lipolytic stimulation than smaller adipocytes.$^{60}$ The response of mesenteric fat to the alternation of caloric balance or physical exercise has been suggested to be more predominant than that of subcutaneous fat, as mentioned earlier in clinical studies in Sumo wrestlers and obese patients.$^{33,52}$ To clarify the molecular mechanism of cellular response in adipose tissues to over-nutrition or physical exercise, we focused on LPL,$^{61}$ which functions as a gate for energy influx from serum lipids into adipocytes or muscles, glucose transporter (GLUT-4),$^{65,66}$ which is a channel protein of glucose transport, and acyl CoA synthetase (ACS), which is a key enzyme for fat accumulation by activating fatty acids to acyl CoA before their incorporation into triacylglycerol.$^{61}$ By observing the sequential change in the gene expression of ACS and LPL after VMH lesion in rats, we found that mesenteric fat showed greater increases in both ACS and LPL mRNA than subcutaneous fat at the early stage in obesity development, suggesting that visceral fat responds more quickly to calorie excess than subcutaneous fat.$^{62}$

The response of mesenteric fat to physical exercise is greater than that of subcutaneous fat. Our studies$^{63}$ on exercised rats (which were) loaded included 60 min running on a treadmill for 7 days demonstrated the selective reduction of fat cell volume of mesenteric fat. Both activity and mRNA expression of ACS showed marked reduction in mesenteric fat, while there were no changes in those of subcutaneous fat and only a slight increase in gastrocnemius muscle. The mRNAs of LPL and GLUT-4 of mesenteric fat were markedly decreased in exercised rats (Figure 5), while there were no significant changes in subcutaneous fat and the tendency of muscles to increase.$^{64}$ These results may suggest that mesenteric fat responds to physical exercise more sensitively at molecular levels than subcutaneous fat, reducing triglyceride formation as well as the uptake of energy source from plasma lipids and glucose. These characteristics of mesenteric fat may contribute to switching of the direction of energy flow from adipose tissue to muscle during muscular activity (Figure 6), which may partly explain our clinical observations that visceral fat may decrease more than subcutaneous fat in response to exercise therapy with calorie restriction in visceral fat type obesity and that Japanese Sumo wrestlers have scanty visceral fat.

Figure 5. Effect of physical exercise on mRNA expression of LPL, GLUT-4 and ACS in mesenteric and subcutaneous fat. Reproduced with kind permission from the American Journal of Physiology.$^{64}$
9 VISCERAL FAT SYNDROME

Interrelationships between FFA metabolism and insulin have been extensively studied with respect to insulin action in peripheral tissue and in the liver. Visceral fat is characterized by enhanced lipolysis and augmented plasma FFA flux, especially in the portal circulation. Kissebah et al. have proposed that an increase in the size of the visceral fat depot, which might precede the increased lipolysis and elevated FFA flux and metabolism, leads to overexposure of hepatic and extrahepatic tissues to FFA, which then promotes aberrations in insulin action and dynamics. In vitro studies from Kissebah's group have demonstrated that palmitate exposure caused dose-dependent reduction in cell surface insulin receptor binding of isolated hepatocytes and is associated with a proportionally diminished receptor-mediated internalization and decreased intracellular and total receptor-mediated insulin degradation. This phenomenon may contribute to the reduced hepatic insulin extraction and peripheral hyperinsulinaemia. Insulin resistance in muscle and the liver and peripheral hyperinsulinaemia induced by visceral fat accumulation may be related to glucose intolerance, hyperlipidaemia and hypertension.

It has also been speculated that visceral adiposity may contribute to metabolic and cardiovascular disorders independently of insulin resistance. For example, the inflow of FFA into the liver is thought to enhance lipid synthesis, lipoprotein formation and lipoprotein secretion. Recent genetic studies indicate that microsomal triglyceride transfer protein (MTP), a lipid transfer protein found in the lumen of microsomes, plays a key role in the process of lipoprotein assembly from lipids and apolipoprotein B to form very low-density lipoprotein (VLDL) in the liver. Since FFA is suggested to induce mRNA expression of MTP in the liver, increased influx of FFA to the liver may enhance VLDL formation and secretion, which results in the increase of VLDL particles in plasma.

5. MOLECULAR MECHANISM OF VISCERAL FAT SYNDROME

A. Contribution of Free Fatty Acid to Insulin Resistance and Hyperlipidaemia

As already mentioned, the multiple risk factor clustering syndrome which may be called syndrome X or the deadly quartet is considered to be an almost identical disease entity to visceral fat obesity or visceral fat syndrome. Previous reports have emphasized insulin resistance as a key factor for inducing multiple disorders in these syndromes. We agree with the concept, considering that insulin resistance has been shown to be much severer in visceral fat obesity than in subcutaneous fat obesity, although the precise molecular mechanism of insulin resistance in visceral fat obesity has not been elucidated. Several reports suggest that insulin resistance of visceral fat obesity is exacerbated by an increased supply of free fatty acid (FFA).
secrete biologically active molecules, such as complements or cytokines. Namely, adipose tissues act not only as an organ for the storage of excess energy, but also as an endocrine organ or an organ secreting cytokines. Overexpression of tumour necrosis factor α (TNF-α) in adipose tissue was reported in obese animals with insulin resistance and in obese human subjects. A new molecule is the ob gene product, leptin, which is produced only in adipose tissues. Our latest studies using random cloning of cDNA in adipocytes have revealed that genes for secretory proteins are relatively abundant in visceral fat compared with subcutaneous fat. Besides, some genes such as ob genes were found to increase more quickly during the development of obesity. We recently found that another important bioactive substance, plasminogen activator inhibitor-1 (PAI-1), is produced in adipose tissue. PAI-1 has been shown to have an important regulatory role in the fibrinolytic process and thrombus formation and its increase may be related to atherosclerosis. Recent studies revealed that plasma levels of PAI-1 were closely correlated with visceral adiposity but not with subcutaneous adiposity in human subjects. We found that PAI-1 mRNA was detected in both types of adipose tissues in obese rats, but increased only in visceral fat during the development of obesity, suggesting that an enhanced expression of the PAI-1 gene in visceral fat may increase plasma levels and may have a role in the development of vascular disease in visceral fat obesity.

These recent observations suggest that adipose tissues directly secrete multiple bioactive molecules (adipocytokines). Adipocytokines may have important roles in the development of vascular changes as well as metabolic diseases.

6. CONCLUSION

Visceral fat obesity or visceral fat syndrome coincides with syndrome X or the deadly quartet, which is susceptible to atherosclerosis by clustering of multiple risk factors. In these syndromes, insulin resistance may be involved in various disorders, but we have demonstrated the possibility that visceral fat accumulation might be present in the upstream of insulin resistance and contributes to the onset of morbidities independently of insulin resistance. For example, increased visceral adiposity may bring about the increase of FFA content in portal circulation, because visceral fat has a high activity of both lipogenesis and lipolysis. Increased inflow of FFA into the liver from portal circulation is thought to retard insulin clearance and to enhance lipid synthesis, which may result in peripheral hyperinsulinaemia, hypertension and hyperlipidaemia. Recent studies also suggest that FFA may enhance the expression of microsomal triglyceride transfer protein, which is a key protein for lipoprotein assembly and secretion into blood, leading to hyperlipidaemia, especially increase of low-density lipoprotein (LDL) particle number. According to the latest findings, visceral fat contains more genes for secretory protein than does subcutaneous fat. For example, in the accumulated state, PAI-1 may be synthesized and secreted in large quantities, and may be involved in vascular changes or thrombogenesis. In addition to PAI-1, recent studies revealed that adipose tissue acts as an organ secreting numbers of bioactive substances including leptin, TNF-α and many complements; some of them might induce insulin resistance, hypertension and direct vascular changes (Figure 7). The mechanism of visceral fat accumulation has not been fully elucidated, although imbalance of sex hormones, ageing, physical inactivities and sucrose diet has been shown to be inducing factors for visceral fat accumulations, while genetic factors might also be important.

References


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Figure 7. Molecular mechanism of visceral adiposity-induced multiple risk factors (contribution of FFA and adipocytokines).


VISCERAL FAT SYNDROME


