triglyceride degradation due to insulin resistance leads to an increase in remnant particles and a decrease in HDL. A recent study using LPL-overexpressed animals demonstrated that reducing hypertriglyceridemia, i.e., decreasing remnant particles, markedly inhibited the progression of atherosclerosis (3). This means that active therapeutic intervention is desirable when dealing with conditions characterized by hypertriglyceridemia or high blood remnant particle levels, especially cases of syndrome X in whom diabetes mellitus and insulin resistance are also seen.

Hypertriglyceridemia is often accompanied by low blood HDL levels. This is because HDL is formed as a result of degrading VLDL which includes triglyceride. Therefore, an increase in blood triglyceride promotes atherosclerosis by hampering the extravascular elimination of cholesterol accumulated within the vascular wall. In cases of hypertriglyceridemia, the production of remnant particles (lipoprotein which is likely to accumulate in the vascular wall) and small dense LDL increases, leading to accelerated vascular wall cholesterol accumulation and atherogenic changes in the blood vessel.

Hyperlipidemia has important effects because, not only are vascular endothelial cells injured, they actually supply cholesterol which is then deposited in the vascular wall. Treatment of hyperlipidemia reduces the cholesterol level in plaques and normalizes the function of vascular endothelial cells, leading to plaque stabilization and inhibiting the onset of cardiovascular events.

### Insulin resistance and pathophysiology

Insulin resistance synergistically augments the potency of individual risk factors and thus accelerates atherosclerosis. The Japanese population is characterized by a low prevalence of obesity. Even in such a population, the metabolic abnormalities constituting syndrome X are recognizable. It is expected that improvement of insulin resistance and glucose tolerance will inhibit the onset of atherosclerosis by stabilizing plaques. It is now desirable to clarify how insulin acts on the vascular wall and how insulin resistance is involved in atherosclerosis, plaque formation, and cardiovascular events.

### References


### 4. Life-Style Related Disease and Adipocytes

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**Key words:** obesity, visceral fat, aquaporin, adiponectin, adipocytokine and multiple risk factors

Recently, the number of obese people has rapidly increased due to the changes in life-style in Japan. Obesity is defined as the over-accumulation of adipocytes, leading to various disorders such as hypertension, hyperlipidemia, glucose intolerance, and atherosclerotic vascular diseases. Several studies including ours have demonstrated that the excess accumulation of abdominal fat, especially intra-abdominal visceral fat easily leads to these disorders. Accordingly, we proposed the term ‘visceral fat syndrome’ defined as a highly atherogenic state associated with multiple risk factors based on visceral fat accumulation (1).

We investigated 586 middle-aged men who underwent a health examination and computed tomographic scan for estimating abdominal fat distribution. One half of the subjects had excess visceral fat and frequently showed multiple risks and abnormalities on electrocardiogram both at rest and on exercise. The subjects with visceral fat accumulation had some life-style characteristics, which were unbalanced dietary habits, the lack of physical activity, and smoking habit.

We have demonstrated several mechanisms by which visceral adipocytes may be involved in the occurrence of life-style related disorders. The lipolytic substances such as free fatty acid (FFA) and glycerol derived from visceral fat adipocytes

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play an important role in the mechanisms. In the study using Otsuka Long Evans Tokushima fatty (OLETF) rats, an animal model for visceral fat accumulation, increased visceral fat brings about high portal FFA and the increased FFA induces the expressions of hepatic acyl-CoA synthetase (ACS), an important enzyme for triglyceride synthesis, and microsomal triglyceride transfer protein (MTP), a critical factor for very low-density lipoprotein (VLDL) synthesis and secretion, resulting in the increased VLDL levels in plasma (Fig. 1) (2). Furthermore, aquaporin adipose (AQPap), which has recently been cloned by us, also may play a key role in a mechanism through glycerol metabolism (3). Glycerol released from adipocytes may be utilized as a substance for gluconeogenesis in liver. This membrane molecule is considered as a glycerol channel expressed in visceral adipose tissue and AQP9 is considered as a glycerol channel specifically expressed in liver (4). In the study using obese diabetic db/db mice, portal glycerol and systemic glucose levels were significantly higher and both expressions of AQPap in visceral fat and AQP9 in liver were significantly increased compared to those in control lean mice. These re-

![Figure 1. Molecular mechanism of hyperlipidemia and diabetes mellitus in visceral fat accumulation.](image)

![Figure 2. Anti-atherogenic effect of a novel adipose-specific protein, adiponectin.](image)
results suggest that the increased expressions of visceral fat AQPap and hepatic AQP9 may be involved in the development of diabetes mellitus through the increased glycerol release and uptake (Fig. 1).

We also analyzed the expressed genes in adipose tissue by large scale random sequencing. Unexpectedly, adipocytes, especially visceral adipocytes, expressed a variety of genes for secretory proteins including various bioactive substances; we designated them ‘adipocytokines’. One of them, plasminogen activator inhibitor-1 (PAI-1) was overproduced in accumulated visceral fat and it might contribute to the development of vascular disease (5). We have also cloned a novel adipose-specific gene named adiponectin. Adiponectin is a collagen-like plasma protein and its plasma levels are paradoxically decreased in obesity especially in visceral obesity and diabetes mellitus with insulin resistance (6). Adiponectin has been suggested to have potent antiatherogenicity, since this molecule was shown to attenuate the TNF-α-induced expression of adhesion molecules in vascular endothelial cells, and moreover, we found that the plasma adiponectin levels were significantly lower in age- and BMI-matched control subjects (Fig. 2) (7). Based on these results, it is thought that adipocytokines may play important and direct roles in the development of atherosclerosis by changing the plasma levels in the subjects with visceral fat syndrome.

In summary, an over-accumulation of adipocytes, in particular, visceral adipocytes, causes the elevated portal FFA and glycerol to become hyperlipidemia or diabetes mellitus. Further, the elevated portal FFA brings about the insulin resistance, and through this, hyperlipidemia and diabetes mellitus get worse, and hypertension occurs. Then the cluster of these lifestyle related disorders leads to vascular disease. Furthermore, adipocytokines originating from visceral fat such as PAI-1, adiponectin and so on, directly or indirectly transmit numerous effects on the development of vascular disease. Thus, it is very important for us to pay attention to visceral fat accumulation and to prevent the development of lifestyle related disease.

References


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In accordance with the improvement of the environmental sanitation and the advancement in medical technology, Japan has achieved the longest lifespan in the world. On the other hand, along with the rapid aging, the proportion of life style-related diseases, (including cancer, heart disease, stroke, and diabetes) to overall morbidity has been increasing. As a result, an increased number of people who need special care have become a serious problem in our society. Therefore, we should not limit our effort only to early detection through routine medical examination, which is the basis of traditional disease control. It is important to promote health and emphasize “primary prevention” in order to prevent the occurrence of diseases in advance.

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