3. Insulin Resistance and Atherosclerosis

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The pathogenesis of various diseases has changed markedly in parallel with changes in the social environment. The clinical and epidemiological importance of atherosclerotic disorders, which primarily involve vascular lesions, has increased rapidly in recent years. Atherosclerotic diseases develop with aging. Needless to say, genetic predisposition and environmental factors play important roles in the onset of these diseases. Diabetes mellitus, hyperlipidemia, hypertension, and obesity, which serve as a basis for the development of atherosclerosis, are induced by a genetic predisposition coupled with environmental factors. Hypernutrition and insufficient exercise lead to diabetes mellitus, hyperlipidemia, obesity, and hypertension in individuals genetically predisposed to these disorders, which eventually produce ischemic heart disease and cerebrovascular disease. It is therefore essential to actively control risk factors when dealing with diabetic patients. This approach requires patient counseling of individual patients to alter the lifestyle factors leading to obesity i.e., overeating and insufficient exercise.

Process of atherosclerosis

Individual foci of atherosclerosis are composed of various cell groups. These cell groups actively secrete various biologically active substances in response to the underlying condition, that precipitated the onset of atherosclerosis. If endothelial cells are activated by factors such as diabetes mellitus (including IGT), hypertension smoking, and genetic predisposition, the cells begin to secrete various biologically active substances, accompanied by the expression of adhesion molecules. As a result, peripheral monocytes adhere to the surfaces of endothelial cells. Peripheral monocytes invade, via the intercellular spaces between endothelial cells, entering the subendothelial layers where they mature and differentiate to become macrophages. In the presence of excessive low density lipoprotein (LDL), denaturated LDL, modified by oxidation or glycosylation of the vascular wall, is taken up by macrophages, leading to the formation of foam cells.

Foam cells accumulate, forming plaques. If the plaques undergo dissolution, thrombi form, resulting in obstruction of blood vessels and the onset of cardiovascular events. More than half (reportedly 75%) of acute events of ischemic cardiac diseases, such as angina pectoris and myocardial infarction, have

been attributed to stenosis or obstruction of the vascular lumen secondary to thrombus formation caused by platelet adhesion or aggregation following the rupture of plaques. It has also been demonstrated that these acute events are more likely to be caused by the dissolution of fresh, unstable plaques in moderate or mild stenotic lesions rather than by the break-up of plaques in old severely stenosed lesions.

The processes between plaque rupture and thrombus formation are closely related to the instability of lipid-rich plaques and their structural fragility. Macrophages secrete proteinases which can digest extracellular matrices and fibrous components and thus make plaques more fragile.

Coexistence of multiple risk factors

The terms "syndrome X" and "deadly quartet" have been proposed to indicate individuals in whom the coexistence of two or more factors precipitates ischemic cardiac disease, although each individual risk factor is not severe when taken into consideration separately. Reaven used the term "syndrome X" to indicate cases in whom hyperinsulinemia, IGT, low blood HDL (high-density lipoprotein)-cholesterol level, high blood VLDL (very low density lipoprotein)-triglyceride level, and hypertension are all present (1). Visceral fat syndrome caused by accumulation of visceral fat has also been proposed. These conditions are accompanied by certain concomitant risk factors such as obesity, hypernutrition, insufficient exercise, and genetic predisposition, and are related to insulin resistance. Those with syndrome X or deadly quartet secrete an excessive amount of insulin to compensate for insufficient insulin effect (insulin resistance), which results in hyperinsulinemia. The Helsinki, Busselton, and Paris studies all demonstrated that blood insulin levels correlate significantly with the onset of coronary artery disease.

The author and his co-workers analyzed the blood pressure, plasma lipid level, and body mass index (BMI) of 2,113 individuals who received a 100 g oral glucose tolerance test at the Toranomon Hospital Health Science Center and compared these parameters to blood glucose curves and insulin reactivity (2). As the insulin level rose, the severity of each factor became higher, indicating that insulin resistance is closely related to the coexistence of risk factors for coronary atherosclerosis.

Involvement of abnormal lipid metabolism

Lipoprotein lipase (LPL) is an enzyme catalyzing the degradation of triglyceride. It is activated by insulin. A decrease in

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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.

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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