Role of Body Weight Reduction in Obesity-Associated Co-Morbidities

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Abstract: Obesity is associated with various health problems such as impaired glucose tolerance, hypertension, and hyperlipidemia. The Japan Society for the Study of Obesity (JASSO) has issued new guidelines for the evaluation of obesity and diagnostic criteria of obesity as a disease in the Japanese population and cited 10 obesity-related health problems that require weight loss or are improved by weight loss. Among these health problems, atherosclerotic diseases including ischemic heart disease and cerebrovascular disorder are of particular importance. The Third Report of the US National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP III) emphasizes the high risk of people who have a constellation of risk factors for atherosclerosis, categorized as the metabolic syndrome. The pathologic features of metabolic syndrome include insulin resistance, which is related to visceral fat accumulation. Metabolic disorders associated with visceral fat accumulation are closely related to the amount of accumulated visceral fat, and reduction of visceral fat causes improvement in such complications. In designing treatment targeted at adipose cells, it is useful to consider the goals and benefits of obesity therapy by evaluating variations in visceral fat.

Key words: Complications; Visceral fat; Insulin resistance; Metabolic syndrome

Introduction

The pathologic condition of obesity consists of various factors, including genetics, metabolic disorders, lifestyle, and personality. Therefore, comprehensive action based on a clear understanding of the relative contributions of individual factors is necessary in the treatment of obesity.

In 2000, the Japan Society for the Study of Obesity (JASSO) issued new guidelines for the evaluation of obesity and diagnostic criteria of obesity as a disease in the Japanese population, to provide clear guidance for evaluating and
diagnosing obesity in daily clinical practice. Recent years have seen progress in elucidating the mechanisms by which obesity and its accompanying metabolic disorders develop, and hence the target of therapy for obesity as a disease has become more obvious. It became apparent that the accumulation of visceral fat around the abdominal organs is associated with a number of metabolic disorders, and that such visceral fat-type obesity is closely related to insulin resistance, an important factor in the development and progression of metabolic syndrome. As this pathologic condition continued to be better defined, investigation of the responsible adipose cells increased, with attention focused on their morphologic role as lipid-accumulating cells and their function in inducing metabolic disorders accompanying obesity, and the importance of weight loss therapy, particularly of the accumulated visceral fat, was demonstrated.

Obesity-Associated Co-Morbidities

Obesity is associated with various health problems including impaired glucose tolerance, hypertension, and hyperlipidemia. JASSO’s new guidelines for the evaluation of obesity and diagnostic criteria of obesity cites 10 health problems associated with obesity. Although many other conditions in addition to these 10 problems are related to obesity, those that are unlikely to be much improved by weight loss are mentioned separately only for reference.

Much recent attention has focused on the importance of obesity in cases of liver diseases such as non-alcoholic steatohepatitis (NASH), insulin resistance, and metabolic syndrome. Among these health problems associated with obesity, atherosclerotic diseases including ischemic heart disease and cerebrovascular disorders are of particular importance. Although obesity is an independent risk factor for coronary artery disease, its direct contribution is slight (about 1.3-fold), and it becomes less independent with aging. Namely, when an increase in whole body fat in terms of degree of obesity is present, the degree of contribution of obesity to atherosclerotic disease is low, and the concomitant presence of other risk factors, rather than obesity itself, is more important. In fact, obese people are about 5-fold and about 3.5-fold more likely to develop diabetes and hypertension, respectively, than those of normal weight. For atherosclerosis, obesity itself is an independent risk factor. However, it is of greater importance that obesity is likely to be accompanied with other risk factors, particularly a constellation of risk factors.

The concept of metabolic syndrome as a new disease has been proposed in recent years. Together with this concept, the importance of visceral fat accumulation, rather than the absolute amount of obesity as expressed by degree of obesity, has been stressed.

Metabolic Syndrome

The US National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) emphasizes that a constellation of athero-

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
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<tbody>
<tr>
<td>Abdominal Obesity</td>
<td></td>
</tr>
<tr>
<td>(Waist Circumference)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥102 cm (&gt;40 in)</td>
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<tr>
<td></td>
<td>&gt;88 cm (&gt;35 in)</td>
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<tr>
<td>Triglycerides</td>
<td>≥150 mg/dl</td>
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<tr>
<td>HDL-cholesterol</td>
<td></td>
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<tr>
<td>Men</td>
<td>&lt;40 mg/dl</td>
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<tr>
<td></td>
<td>&lt;50 mg/dl</td>
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<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mmHg</td>
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<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dl</td>
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</tbody>
</table>

Metabolic syndrome is identified by the presence of three or more of the risk factors. [Adapted from Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285: 2486–2497]
sclerotic risk factors should be diagnosed as metabolic syndrome and be treated to reduce the risk of coronary artery disease, considering it the secondary target of therapy following the primary target of low-density lipoprotein cholesterol (Table 1).3) This disease concept is pathologically similar to previously described conditions: multiple-risk-factor syndrome, visceral-fat syndrome, the deadly quartet, syndrome X, and insulin-resistance syndrome.

The mechanism by which the visceral fat accumulation involved in the pathology of these syndromes is closely related to the obesity-associated co-morbidities is suggested by the difference in function between visceral fat and subcutaneous fat. In recent years, it has become apparent that the genes of various adipocytokines, such as plasminogen activator inhibitor-1 (PAI-1), tumor necrosis factor-α (TNF-α), and adiponectin, are expressed in adipose tissue, leading to the view that adipose tissue is a kind of endocrine organ. In particular, it has been reported that the expression of PAI-1 increases with the accumulation of visceral fat, whereas there is no change in PAI-1 expression in subcutaneous fat.4)

Impaired glucose tolerance in cases of visceral fat accumulation resulting from these pathologic conditions is characterized by insulin resistance and compensatory hyperinsulinemia.5) Even if the fasting blood glucose level is normal in the glucose tolerance test, obese people often show impaired glucose tolerance or diabetic response after loading, with insulin levels being high both during fasting and after loading. An index of insulin resistance, the homeostasis model assessment of insulin resistance (HOMA-IR), shows a significant positive correlation with visceral fat area (Fig. 1).

The characteristic features of lipid metabolism disorder include increased serum triglyceride (TG) and decreased high-density lipoprotein (HDL) cholesterol. The mechanisms involved in this metabolic disorder are increased synthesis of very low-density lipoprotein (VLDL) in the liver and disturbed catabolism of the TG-rich lipoprotein associated with insulin resistance. In addition, the incidence of hypertension has a positive correlation with body mass index (BMI). In particular, visceral fat accumulation is involved in the concomitant development of hypertension. In people with visceral fat-type obesity, blood pressure values are higher than in those with subcutaneous-type obesity, and reduction in visceral fat by weight loss contributes to improvement in blood pressure. Thus, insulin resistance plays an important role in metabolic syndrome, which is characterized by various pathologic conditions derived from obesity.

**Obesity-Associated Co-Morbidities and Body Weight Reduction**

The therapeutic goal in treating obesity is to improve health problems resulting from exces-
sive fat accumulation. Therefore, in treating the obesity-associated co-morbidities, it is important to determine the relationship between variations in visceral fat accumulation and improvement in complications during the course of treatment. A diagnosis of visceral fat accumulation is established by CT scan performed at the umbilical level. Ultrasonography, which causes minimal stress to the patient, is useful for determining variations in visceral fat and subcutaneous fat during treatment. By this technique, the degree of visceral fat accumulation can be expressed as anterior abdominal fat thickness, and subcutaneous fat accumulation as subcutaneous fat thickness. When fat thickness is measured every day during the hospitalization of obese patients, anterior abdominal fat thickness is found to decrease markedly in the early stage of therapeutic weight loss, whereas the concurrent decrease in subcutaneous fat thickness is minimal (Fig. 2). As anterior abdominal fat thickness decreases, hypertriglyceridemia improves. Blood insulin, PAI-1 and TNF-α levels also decrease, suggesting that reduction in anterior abdominal fat thickness causes improvement in insulin resistance.

Thus, metabolic disorders associated with visceral fat accumulation are closely related to the amount of accumulated visceral fat, and the obesity-associated co-morbidities can be ameliorated by reducing the accumulation of visceral fat. From this point of view, it is useful when designing treatment targeted at adipose cells to consider the goals and benefits of obesity therapy by the simple evaluation of variations in visceral fat.

**Conclusion**

Obesity-associated co-morbidities, particularly pathologic conditions related to insulin resistance, have been outlined, and the effects of weight loss on such conditions have been described. A variety of approaches have been used to study the obesity-associated co-morbidities and the effects of weight loss on these complications. The results of such investigations may lead to rapid progress in the treatment of obesity. It is expected that the treatment system used to accurately assess and selectively decrease multifunctional adipose cells, particularly those of visceral fat, will be established on the basis of JASSO’s new guidelines for the evaluation of obesity and diagnostic criteria of obesity as a disease in the Japanese population.
REFERENCES


