INTERNAL MEDICINE

□ SYMPOSIUM I □

Clinical Diagnosis of Metabolic Syndrome
1. Metabolic Syndrome and Insulin Resistance

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Insulin resistance and compensatory hyperinsulinemia are seen not only in type 2 diabetes mellitus (DM) but also in essential hypertension (EHT), dyslipidemia and obesity; these are known as the components of metabolic syndrome. To evaluate the significance of insulin resistance, we examined the relations between insulin resistance and accumulation of components of metabolic syndrome in residents of rural communities in Japan (Tanno and Sobetsu-Town Study). To assess the existence of insulin resistance, we used a practical index based on the euglycemic-hyperinsulinemic glucose clamp method. Subjects with a value of HOMA>1.73 were considered to have insulin resistance. HOMA showed significant correlations with body mass index (BMI), systolic blood pressure, diastolic blood pressure, triglyceride and HDL cholesterol. It was found that the higher the HOMA value, the higher the number of components of metabolic syndrome. The number of components of metabolic syndrome was particularly high in subjects with HOMA>1.70. Results of stepwise regression analysis for accumulation of risk factors showed that age, BMI and insulin sensitivity evaluated by immuno-reactive insulin levels 120 min after a 75 g oral glucose tolerance test or HOMA were independently correlated with metabolic syndrome (Table 1) (1). When coronary angiographic findings were evaluated in patients with coronary artery disease, the severity was higher in coronary artery disease with DM than in that without DM. Even in coronary artery disease without DM, the severity of coronary angiographic findings was higher in coronary artery disease with insulin resistance than in that without insulin resistance (2). When residents in Tanno Town and Sobetsu Town were followed 8 years, the incidence of cardiovascular diseases was much higher in subjects with insulin resistance than in subjects without insulin resistance. These findings suggest that insulin resistance is a significant background of metabolic syndrome, and insulin resistance is one of the major factors facilitating genesis and progression of cardiovascular diseases.

Table 1. Stepwide Regression Analysis for Metabolic Syndrome (from Ref. 1).

	β	t	P
AGE	0.117	3.003	<0.01
BMI	0.342	8.522	<0.01
120-IRI	0.213	5.323	<0.01

R^2=0.203

	β	t	P
AGE	0.100	2.650	<0.01
BMI	0.352	9.279	<0.01
HOMA-R	0.249	6.545	<0.01

R^2=0.222

Diagnostic guidelines for metabolic syndrome in Japan were issued in April 2005 by a committee that consisted mainly of members of the Japan Atherosclerosis Society. The guidelines indicate that both abdominal obesity (AO, waist circumference of ≧85 cm for males and ≧90 cm for females) as a required component and two out of three factors, high blood pressure (BP≧130/85 mmHg), dyslipidemia (high triglyceride: TG≧150 mg/dl and/or low HDL-cholesterol: HDL-C<40 mg/dl), and high fasting plasma glucose (FPG≧110 mg/dl), are necessary for the diagnosis. We modified the NCEP-ATP III guideline (2001) based on the standard Japanese build (AO, waist circumference of ≧85 cm for males and ≧90 cm for females) and used it in the Tanno and Sobetsu-Town Study for evaluating the prevalence and prognosis of metabolic syndrome in Japan. We re-evaluated the subjects by using the new Japanese definition. Based on the modified NCEP-ATP III guideline, the prevalence of metabolic syndrome in people over 40 years of age excluding patients with hypertension or diabetes mellitus re-

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ceiving treatment is 23.2% in males and 7.3% in females; however, the prevalences are 17.6% in males and 5.5% in females by the new Japanese definition. The rates of high BP in untreated males (56.2%) and untreated females (45%) are the highest among these risk factors. Concerning the prognosis, based on the modified NCEP-ATP III, the rate of cardiovascular events in the male population over 40 years of age is 2.23-times higher in males with metabolic syndrome than in males without metabolic syndrome. On the other hand, we found that this rate is 1.78-times higher using the new Japanese definition.

Recent studies have shown that adiponectin, a novel adipocyte-derived hormone, is one of the candidates for insulin resistance and the development of atherosclerosis in diabetes patients. As shown in Fig. 1, adiponectin levels in subjects with metabolic syndrome were significantly lower than those in subjects without metabolic syndrome in the Tanno and Sobetsu-Town Study (3). We therefore investigated the relationships of adiponectin levels with insulin resistance and atherosclerosis estimated by measurement of pulse wave velocity (PWV). Adiponectin showed significant negative correlations with BMI, HOMA and PWV. The results of multiple regression analysis indicated that adiponectin and age were independently correlated with PWV. When HOMA was added to this analysis, HOMA was found to be independently correlated with PWV, but the adiponectin level showed a tendency toward correlation with PWV (4). These results indicated that adiponectin may correlate with atherosclerosis either directly or indirectly through improvement of insulin resistance.

The roles of adipocytokine interleukin-6 (IL-6) in the modulation of glucose metabolism and in the pathogenesis of atherosclerosis have recently received considerable attention partly in connection with the adipocytokine adiponectin. As mechanisms of these roles of IL-6, it has been postulated that an increased IL-6 can inhibit insulin signal transduction directly and/or induce a decrease in production and secretion of adiponectin, resulting in induction of insulin resistance

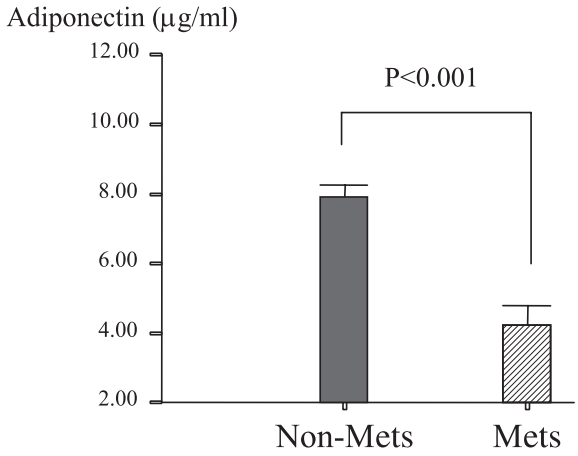

Figure 1. **Age-adjusted plasma adiponectin in subjects with or without metabolic syndrome (from Ref. 3).**

and atherosclerosis. We therefore re-evaluated the Tanno and Sobetsu-Town Study including IL-6 and high sensitivity CRP (hCRP). When adjusted by age, BMI, adiponectin and HOMA, IL-6 was associated with hCRP. After adjustment for systolic blood pressure, BMI, HOMA and adiponectin, IL-6 was significantly associated with PWV. After adjustment for age, BMI, systolic blood pressure, IL-6 was significantly associated with HOMA. When adiponectin was added to this analysis, adiponectin was significantly associated with HOMA, but IL-6 showed a tendency of association with HOMA. Thus, IL-6 may contribute to insulin resistance and atherosclerosis. Although the possibility of a direct association could not be eliminated, these associations might be modulated by adiponectin.

The findings suggest that insulin resistance is a significant background factor of metabolic syndrome, and insulin resistance itself is one of the major factors facilitating genesis and progression of cardiovascular diseases in connection with various adipocyte-derived hormones, adipocytokines.

References

1. Takeuchi H, Saitoh S, Takagi S, et al. Relation of metabolic syndrome and insulin resistance in Japanese male population: Tanno Sobetsu-Town Study. J Japanese Diabetes Society **46**: 739-744, 2003 (in Japanese).
2. Tsuchihashi K, Hikita N, Hase M, et al. Role of hyperinsulinemia in atherosclerotic coronary arterial disease: studies of semi-quantitative coronary angiography. Intern Med **38**: 691-697, 1999.
3. Isobe T, Saitoh S, Takagi S, et al. Relation of metabolic syndrome and plasma adiponectin levels—Tanno Sobetsu-Town Study—. J Japanese Diabetes Society **49**: 119-126, 2006 (in Japanese).
4. Higashiura K, Ura N, Ohata J, et al. Correlations of adiponectin level with insulin resistance and atherosclerosis in Japanese male populations. Clin Endocrinol **61**: 753-758, 2004.