

ning with the 29th week of gestation to treat gestational hypertension. At 40 weeks and 3 days, she spontaneously delivered a healthy female newborn (3,680 g, length 52 cm, cranial circumference [CC] 33 cm, and Apgar score 9/10) who developed jaundice, needing phototherapy for 1 day.

N.G. submitted to a cesarean section at her 39th gestational week and had a male newborn (2,650 g, length 45 cm, CC 33.5 cm, and Apgar score 9/10).

Both birth weights were adequate for the gestational ages, and no congenital malformations were observed. Six weeks later, they did not report neonatal or maternal morbidity.

Our experience regarding the use of repaglinide in pregnancy is limited to these two subjects, whose unplanned conception was with a good HbA<sub>1c</sub> (L.M. preconception 6.8%, conception 7%, and 3rd trimester 5.6%; N.G. conception 6.4% and 3rd trimester 5.1%; normalized variance 3–6%) obtained with the use of repaglinide from several months before conception until early pregnancy.

Repaglinide did not affect embryo development; no minor or major malformations were observed. Because of its early discontinuation, we have no data about its influence on fetal growth.

These observations do not allow us to draw any conclusions about the effects and risks of repaglinide in pregnancy.

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## Decreased High-Molecular Weight Adiponectin-to-Total Adiponectin Ratio in Sera Is Associated With Insulin Resistance in Japanese Metabolically Obese, Normal-Weight Men With Normal Glucose Tolerance

Adiponectin is a key regulator of insulin resistance. Recent studies on multimer formation in human blood have demonstrated that high-molecular weight (HMW) adiponectin is the active form of the protein (1–3). Recently, Hara et al. (3) demonstrated that the ratio of HMW adiponectin to total adiponectin (HMWR) in systemic circulation is useful for the prediction of insulin resistance and metabolic syndrome.

Metabolically obese, normal-weight (MONW) subjects (BMI <25 kg/m<sup>2</sup>) are characterized by excess visceral fat area (VFA; ≥100 cm<sup>2</sup> by abdominal computed tomography scanning) and insulin resistance (4–6). In addition, we previously demonstrated that the plasma level of total adiponectin is significantly associated with insulin resistance and hyperinsulinemia in Japanese MONW men with normal glucose tolerance (NGT) (6). However, the relationship of HMWR with insulin resistance has not yet been evaluated in Japanese MONW men with NGT.

The present study comprised 24 Japanese MONW (mean [±SE] age 35.7 ± 1.5 years, BMI 23.5 ± 0.2 kg/m<sup>2</sup>, and VFA 130.1 ± 4.3 cm<sup>2</sup>) and 28 age-matched normal (BMI <25 kg/m<sup>2</sup> and VFA <100 cm<sup>2</sup>) men (aged 31.6 ± 1.5 years, BMI 21.2 ± 0.3 kg/m<sup>2</sup>, and VFA 61.5 ± 4.2 cm<sup>2</sup>) with NGT.

The serum levels of HMW and total adiponectin were measured using a commercially available enzyme-linked immu-

nosorbent assay kit (Daiichi Pure Chemicals, Ibaraki, Japan) (7).

The serum levels of HMW (1.260 ± 0.152 vs. 1.791 ± 0.172 μg/ml, *P* < 0.05) and total (4.593 ± 0.307 vs. 5.680 ± 0.395 μg/ml, *P* < 0.05) in MONW men were significantly decreased compared with normal men. HMWR was significantly decreased in MONW subjects (0.261 ± 0.018, *P* < 0.05) compared with normal subjects (0.321 ± 0.023). The glucose infusion rate (GIR; index of insulin resistance during the euglycemic-hyperinsulinemic clamp study) in MONW subjects (50.2 ± 2.1 μmol · kg<sup>-1</sup> · min<sup>-1</sup>, *P* < 0.01) was significantly decreased compared with normal subjects (62.8 ± 0.3 μmol · kg<sup>-1</sup> · min<sup>-1</sup>). The serum levels of HMW (*r* = 0.491, *P* < 0.05) and total (*r* = 0.414, *P* < 0.05) adiponectin were significantly correlated with GIR in MONW subjects. Significant correlation was observed between HMWR and GIR (*r* = 0.454, *P* < 0.05) in MONW men.

This is the first report that demonstrates the relationship of HMWR with insulin resistance in Japanese MONW men with NGT. In our present study, three of the MONW subjects had hypertriglyceridemia (≥1.7 mmol/l) and nine men had arterial hypertension (blood pressure ≥130/85 mmHg), but the remaining subjects showed no low HDL cholesterol (<1.0 mmol/l). Based on these findings, these subjects are considered to have premetabolic syndrome (8). This clinical condition should be diagnosed at early stages to prevent the progression of oxidative stress and the occurrence of obesity-related complications (9). The results of this study showed that in addition to total serum levels of adiponectin, HMWR should also be evaluated for screening and early diagnosis of insulin resistance in Japanese MONW subjects with NGT.

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## A Patient With Extreme Insulin Resistance Syndrome Treated With Pioglitazone

Genetic types of extreme insulin resistance include type A insulin resistance syndrome, leprechaunism, congenital generalized lipodystrophy, and Rabson-Mendelhall syndrome (1). Acanthosis nigricans and ovarian masculinization are frequently associated with these syndromes. Genetic defects in insulin action at the receptor or postreceptor levels are responsible for insulin resistance. Since thiazolidinediones enhance insulin sensitivity in patients with insulin resistance, we administered pioglitazone to an insulin-resistant patient with a mutation of the insulin receptor.

A 15-year-old Japanese female was referred to the hospital for an evaluation of hirsutism. Acanthosis nigricans was present in the axillary area and on the neck. She had been amenorrheic since menarche at the age of 12 years. She had two elder sisters, one of whom had the same phenotype. The other sister and the mother of this individual appeared to be unaffected. The father died from laryngocarcinoma at the age of 45 years after being on hemodialysis due to diabetic renal failure. The patient was normoglycemic (glucose 69 mg/dl) and hyperinsulinemic (immunoreactive insulin [IRI] 148  $\mu$ U/ml) under fasting conditions. The homeostasis model assessment of insulin resistance was 25.21, and the serum testosterone level was elevated (1.23 ng/ml). A 75-g oral glucose tolerance test generated the following values: glucose 59, 161, 195, and 184 mg/dl and IRI 109, 300, 450, and 695  $\mu$ U/ml at 0, 30, 60, and 120 min, respectively. Thus, insulin resistance was marked, and hyperandrogenemia was evident. We determined partial DNA sequences of the insulin receptor gene of this patient and found heterogeneous triplet basic deletion from exon 17 of the human insulin receptor gene that resulted in a leucine deletion at amino acid 1,026.

We administered 15 mg/day of pioglitazone. Although fasting glucose levels were not changed, fasting IRI decreased from 148 to 104  $\mu$ U/ml and HbA<sub>1c</sub> (A1C) decreased from 6.0 to 4.5% after 5 months. We continued pioglitazone (15

mg/day), and after another 5 months, fasting IRI decreased to 73  $\mu$ U/ml and A1C to 4.4%. The serum testosterone level decreased from 1.23 to 0.97 ng/ml after 5 months and normalized to 0.68 ng/ml after 10 months. Menstruation recovered after pioglitazone for 2 months. Before treatment, plasma leptin and adiponectin levels were elevated to 15.9 ng/ml and 19.8  $\mu$ g/ml, respectively. Serum adiponectin increased to 30.5  $\mu$ g/ml after pioglitazone for 5 months, while the leptin level remained similar.

A number of studies suggest an important link between adiponectin and insulin resistance (2). Although its physiological and pathophysiological role has not been fully elucidated, its low levels in insulin-resistant states suggest that therapeutic modulation of adiponectin may provide a novel treatment modality for insulin resistance (2). Interestingly, the level of adiponectin in this case was not low, but pioglitazone further increased the serum adiponectin level. Thus, pioglitazone might have been beneficial to this patient via both adiponectin-dependent and -independent pathways (3).

The mutation in this patient was situated in the ATP binding site of the insulin receptor  $\beta$  subunit (4). This might disturb the intrinsic tyrosine kinase activity that is essential for signal transduction. However, the means by which the heterogeneous mutation caused insulin resistance remains to be elucidated. Pioglitazone attenuated insulin resistance and ameliorated masculinization. Thus, thiazolidinediones should be considered for treating patients with extreme insulin resistance syndrome. Coadministration of pioglitazone with IGF-1 (5) might be a more optimal treatment strategy for patients with such extreme syndromes.

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