OBSERVATIONS

Elevated Plasma Adiponectin and Leptin Levels in Sisters With Genetically Defective Insulin Receptors

Circulating levels of adiponectin have been shown to inversely correlate with insulin sensitivity. Interestingly, elevated adiponectin levels have been observed following treatment with thiazolidinediones. It has recently been reported (1) that paradoxical hyperadiponectinemia is observed in patients with mutations, leading to a loss of insulin receptor function. Here, we evaluated circulating levels of adiponectin and leptin following treatment with pioglitazone in two sisters referred for evaluation of hirsutism who were found to have insulin resistance secondary to an insulin receptor mutation.

A 15-year-old Japanese female patient, the younger of the two sisters, has been amenorrheic since menarche at age 12 years. She was normoglycemic (glucose 69 mg/dl) and hyperinsulinemic (immunoreactive insulin [IRI] 148 μU/ml) under fasting conditions. The homeostasis model assessment of insulin resistance (HOMA-IR) was 25.21, and she had an elevated serum testosterone level (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 μU/ml at 0, 30, 60, and 120 min, respectively. Her 19-year-old sister showed the same phenotype, data as follows: glucose 98 mg/dl, IRI 95 μU/ml, HOMA-IR 22.98, testosterone 1.26, and for a 75-g oral glucose tolerance test: glucose 98, 225, 270, and 210 mg/dl and IRI 95, 338, 440, and 770 μU/ml at 0, 30, 60, and 120 min, respectively. We determined partial DNA sequences of the insulin receptor gene of these patients and found a heterogeneous triplet basic deletion (TTC) from exon 17, resulting in a leucine deletion at amino acid 1,026. Marked insulin resistance and hyperandrogenemia were evident in both sisters. Interestingly, circulating adiponectin levels were elevated: 19.8 μg/ml in the younger sister and 20.3 μg/ml in the older sister. Circulating leptin levels were also elevated: 15.9 ng/ml in the younger sister and 13.3 ng/ml in the older sister.

We treated both patients with 15 mg/day pioglitazone. Although fasting glucose levels did not change, fasting IRI and A1C levels decreased from 148 to 104 mg/dl and 6.0 to 4.5%, respectively, in the younger patient, whereas fasting IRI and A1C levels decreased from 95 to 56 mg/dl and 6.8 to 5.5%, respectively, in the older patient after 5 months. The serum adiponectin level increased to 30.5 μg/ml in the younger sister and to 58.1 μg/ml in the older sister after treatment with pioglitazone for 5 months, whereas the leptin level remained consistent at 14.2 μg/ml in the younger and 13.0 μg/ml in the older sister.

Fat-specific disruption of the insulin receptor gene in mice (FIRKO mice) has provided a model to investigate the role of insulin in regulating the secretion of adiponectin and leptin from adipocytes in vivo. Elevated adiponectin expression in adipocytes and elevated adiponectin serum concentrations, while normal or only slightly elevated plasma leptin levels, are observed in FILKO mice (2). A recent in vitro study (3) has suggested that insulin is a negative regulator of adiponectin expression within adipocytes. This may explain the finding of increased adiponectin levels in FILKO mice as well as in the two sisters.

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