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Association of Serum Fetuin-A With Insulin Resistance in Type 2 Diabetic and Nondiabetic Subjects

Fetuin-A (α2-Heremans Schmid glycoprotein) is a circulating glycoprotein that can inhibit insulin receptor autophosphorylation and subsequent downstream signaling in vitro (1,2). Recently, it has been reported (3) that fetuin-A–deficient mice demonstrate enhanced insulin sensitivity. These data indicate that fetuin-A might be a negative regulator of insulin signaling. However, the physiological significance of fetuin-A in insulin resistance in humans remains unclear.

To address this, we investigated the relationship of serum fetuin-A levels and insulin resistance in nondiabetic (n = 160) and type 2 diabetic (n = 161) subjects. Serum fetuin-A was measured by an enzyme-linked immunosorbent assay kit (BioVender Laboratory Medicine, Brno, Czech Republic) in nondiabetic subjects (54 men and 106 women, aged 57.0 ± 10.7 years [mean ± SD], BMI 25.3 ± 2.9 kg/m^2, fasting plasma glucose 5.5 ± 0.5 mmol/l, and HbA_{1c} 5.0 ± 0.3%) and type 2 diabetic subjects (96 men and 65 women, aged 53.5 ± 12.0 years, BMI 25.2 ± 4.8 kg/m^2, fasting plasma glucose 8.2 ± 2.2 mmol/l, and HbA_{1c} 8.6 ± 1.9%). Insulin resistance was evaluated by homeostasis model assessment (HOMA) of insulin resistance in both groups of subjects and by the M/I value assessed using the hyperinsulinemic-euglycemic clamp in type 2 diabetic subjects.

There were no differences of fetuin-A levels between the nondiabetic and type 2 diabetic groups (260.0 ± 45.0 vs. 260.1 ± 44.1 μg/ml, respectively). In simple regression analyses, serum fetuin-A levels were significantly correlated with log(HOMA) in nondiabetic subjects (r = 0.197, P = 0.014). To explore the impact of serum fetuin-A levels on insulin resistance in nondiabetic subjects, multiple regression analyses were performed in which log(HOMA) was included as a dependent variable and BMI, sex, age, triglycerides, and fetuin-A as independent variables. Fetuin-A (β = 0.197, P = 0.004) showed a strong independent contribution to log(HOMA) as well as BMI (β = 0.369, $P < 0.0001$) and triglyceride level (β = 0.298, $P < 0.0001$) in this model (R^2 = 0.345, $P < 0.0001$). However, no significant relationships were observed between fetuin-A levels and log(HOMA) in type 2 diabetic subjects (r = 0.010, P = 0.909), nor were fetuin-A levels correlated with M/I values (r = −0.068, P = 0.410).

The present study first demonstrates the independent impact of fetuin-A on insulin resistance in nondiabetic subjects. On the other hand, we found a lack of significant association of fetuin-A with insulin resistance in type 2 diabetic subjects. Under diabetic conditions, it might be due to the existence of stronger determinants such as glucose toxicity and/or protein modifications such as nonenzymatic glycation that overcome and veil the effect of fetuin-A on insulin resistance. Or, pharmacological treatment for diabetic subjects may affect fetuin-A levels, although the precise mechanism to regulate them is not yet clear. Since an in vitro study has shown that phosphorylated fetuin has stronger inhibitory effects in insulin receptor autophosphorylation (1), further studies will be needed to investigate the association of phosphorylated fetuin-A levels with insulin resistance. In conclusion, fetuin-A could be a modulator of insulin resistance in humans.

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