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The –8503 G/A Polymorphism of the Adiponectin Receptor 1 Gene Is Associated With Insulin Sensitivity Dependent on Adiposity

Adiponectin has beneficial effects on insulin sensitivity. Unexpectedly, adiponectin knockout mice exhibit no or only mild insulin resistance. Nevertheless, under a high-fat/high-carbohydrate diet, severe insulin resistance was induced in those animals (1). Consistent with this, recent evidence (2) suggests that the relationship of adiponectin with insulin sensitivity is stronger with increasing adiposity. In addition, a haplotype in the adiponectin gene was associated with type 2 diabetes only in obese and morbidly obese subjects but not in lean subjects (3).

Single nucleotide polymorphisms (SNPs) of the genes encoding adiponectin receptor (ADIPOR) 1 and 2 were associated with type 2 diabetes (4) or prediabetes phenotypes (5) in some but not in all (6) studies. We found that the –8503 G/A SNP of the *ADIPOR1* gene was associated with insulin sensitivity (7). In a very recent study (6) in rather lean subjects with a mean BMI of 21 kg/m², no associations with insulin sensitivity were found. In our study (7), subjects were more obese (BMI 26 kg/m²). This new information lead us to investigate whether the association of the –8503 G/A SNP of *ADIPOR1* with insulin sensitivity is modulated by adiposity. If this was the case, then this may partly explain the inconsistent results regarding SNPs of *ADIPOR1* and 2.

Recently reported data (7) from 502 nondiabetic Caucasians were analyzed. Insulin sensitivity was estimated from an oral glucose tolerance test and determined during a euglycemic-hyperinsulinemic clamp ($n = 299$). Subjects were divided into two groups by the median percentage of body fat (PFAT). In the more obese group ($n = 250$, PFAT 27–55%), carriers of the –8503 A allele had lower insulin sensitivity estimated from

the oral glucose tolerance test using the formula proposed by Matsuda and DeFronzo (8) (G/G, G/A, and A/A: 14.4 ± 0.8 , 11.9 ± 0.9 , and 9.2 ± 1.7 arbitrary units, respectively, $P = 0.003$, ANOVA) and determined during the clamp (0.07 ± 0.005 , 0.06 ± 0.005 , and $0.04 \pm 0.01 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot \text{pmol/l}^{-1}$, respectively, $P = 0.007$) compared with homozygous carriers of the G allele, independent of age, sex, and PFAT. In contrast, in the lean group ($n = 252$, PFAT 7–26%), no significant relationships were found (oral glucose tolerance test: 24.6 ± 1.0 , 27.2 ± 1.1 , and 23.0 ± 2.4 , respectively, $P = 0.60$; clamp: 0.13 ± 0.006 , 0.13 ± 0.007 , and 0.12 ± 0.016 , respectively, $P = 0.84$).

In summary, we show that the A allele of the –8503 G/A SNP of the *ADIPOR1* gene is associated with less insulin sensitivity only in more obese but not in lean individuals. This finding may be important for further studies on the relationships of genetic variants of *ADIPOR1* and possibly of *ADIPOR2* with metabolism.

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Evaluation of a Diagnostic Algorithm for Hereditary Hemochromatosis in 3,500 Patients With Diabetes

Hereditary hemochromatosis may lead to hepatic cirrhosis, cardiomyopathy, diabetes, arthritis, and impotence (1,2). In the Caucasian population, *HFE* gene mutations (C282Y and H63D) are present in the majority of patients demonstrating phenotypic expression (3–6). Conversely, the clinical penetrance in mutation carriers is low (7).

In the precirrhotic stage, ~20% of hemochromatotic patients demonstrate hyperglycemia, with the prevalence increasing to >70% in the presence of liver cirrhosis (8). Two mechanisms contribute to the development of hyperglycemia and diabetes. Liver iron overload leads to insulin resistance, and the pancreatic β -cell iron accumulation results in cell damage and diminished insulin secretion (1). The