OBSERVATIONS

Associations of Total Testosterone and Sex Hormone–Binding Globulin Levels With Insulin Sensitivity in Middle-Aged Finnish Men

While sex hormone–binding globulin (SHBG) production in the liver is mainly regulated by sex steroids and thyroxine, insulin is suggested to be another important regulator, and a low SHBG level is a marker of insulin resistance (1) and, consequently, a predictor of type 2 diabetes (2). The role of testosterone, another risk marker of type 2 diabetes, has been insufficiently clarified (2). Further, only one earlier study (3) has found evidence suggesting that, compared with total testosterone, high SHBG may be a more powerful correlate of insulin sensitivity, mediating the link between total testosterone and insulin sensitivity. We investigated the contribution of SHBG to the association between total testosterone and insulin sensitivity in a population of 438 out of 614 men born in 1945 and living in the City of Oulu (Finland) on 1 January 2001. Oral glucose tolerance tests were performed, and men with diabetes ($n = 50$) and those using any medication with a possible effect on insulin sensitivity (oral glucocorticoids, thiazides, β-blockers, ACE inhibitors, or angiotension II receptor antagonists) ($n = 42$) were excluded, leaving 346 men to be analyzed. Quantitative insulin sensitivity check index (QUICKI) was used to measure insulin sensitivity (4), and serum concentrations of total testosterone and SHBG were also measured. Possible multicollinear relations between independent variables were tested, but none were found (variance inflation factor <2.5) (5).

In our study population, the median (interquartile range) fasting insulin level was 8.4 mU/l (6.0–11.7), and the means ± SD of fasting plasma glucose and QUICKI were 4.9 ± 0.5 and 0.350 ± 0.029 mmol/l, respectively. The corresponding means ± SD for total testosterone and SHBG were 19.4 ± 6.1 and 48.5 ± 17.9 nmol/l, respectively.

There was a significant positive correlation of QUICKI with SHBG (Pearson's correlation, $r = 0.364$, $P < 0.001$) and total testosterone ($r = 0.217$, $P < 0.001$). After adjusting for total testosterone, the positive correlation between QUICKI and SHBG remained ($r = 0.297$, $P < 0.001$), but adjustment for SHBG rendered the correlation between QUICKI and total testosterone nonsignificant ($r = 0.015$, $P = 0.799$). The Pearson's partial correlation for QUICKI and SHBG remained significant ($r = 0.236$, $P < 0.001$) even after adjustment for BMI, total testosterone, LDL cholesterol, triglycerides, high-sensitivity C-reactive protein, alcohol consumption, smoking, physical exercise, and education.

The results of this population-based study showed that both total testosterone and SHBG levels were positively associated with insulin sensitivity. Further, the association between SHBG and insulin sensitivity was independent of total testosterone, while the association between total testosterone and insulin sensitivity was mediated by SHBG.

The strengths of the present study were that it was based on a general population with a fairly high participation rate. Secondly, QUICKI has been shown to be a reliable instrument for measuring insulin sensitivity in population studies (4). The cross-sectional nature of the study is a limitation that prevents conclusions from being drawn about causality. In addition, we were unable to use a reliable method for measuring free testosterone, which is suggested to be the biologically active fraction of the hormone, although, according to another view, SHBG-bound hormones may also be biologically active (2). Further studies are needed to better understand the role of free testosterone with respect to insulin sensitivity.

ULLA M. RAJALA, MD, PHD[1,2]
SIRKKA M. KEINÄNEN-KIUKAANNIEMI, MD, PHD[1,2,3]
PAIVI K. HIRSSO, MD[1,2]
JARI J. JOKELAINEN, MSC[1,2]
MAURI A. LAAKSO, MD[1,2]
LIISA A. HILTUNEN, MD, PHD[1,2,3]
AIMO O. RUOKONEN, MD, PHD[4]
PIRJO K. HÄRKÖNEN, MNSC[5]
MARKKU J. TIMONEN, MD, PHD[1]

From the [1]Department of Public Health Science and General Practice, University of Oulu, Oulu, Finland; the [2]Unit of General Practice, Oulu University Hospital, Oulu, Finland; the [3]Oulu Health Center, Oulu, Finland; the [4]Unit of Clinical Chemistry, Oulu University Hospital, Oulu, Finland; and the [5]Oulu Deaconess Institute, Sports Medicine, Oulu, Finland.

Address correspondence to Ulla Rajala, MD, University of Oulu, Public Health Science and General Practice, Box 5000, FIN-90014, Finland. E-mail: ulla.rajala@oulu.fi.

DOI: 10.2337/dc06-1979

References

1. Pitteloud N, Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson K-F, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ: Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. *Diabetes Care* 28:1636–1642, 2005
2. Ding EL, Song Y, Malik VS, Liu S: Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 295: 1288–1299, 2006
3. Tsai EC, Matsumoto AM, Fujimoto WY, Boyko EJ: Association of bioavailable, free, and total testosterone with insulin resistance: influence of sex hormone–binding globulin and body fat. *Diabetes Care* 27:861–868, 2004
4. Hrebicek J, Janout V, Malincikova J, Horakova D, Cizek L: Detection of insulin resistance by simple quantitative insulin check index QUICKI for epidemiological assessment and prevention. *J Clin Endocr Metab* 87:144–147, 2002
5. Allison PD: *Logistic Regression Using the SAS System*. Cary, NC, SAS Institute, 1999