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Sex hormone-binding globulin is linked to the risk of type 2 Diabetes Mellitus

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Until recently, the main function of the sex hormone-binding globulin (SHBG) was thought to be the binding of circulating free hormones, thus regulating their plasma levels. In the last years, both experimental and clinical studies suggested low circulating levels of SHBG are associated with impaired glucose control. Also, recent studies emphasize the important roles of endogenous sex hormones in the pathogenesis of type 2 diabetes mellitus.

Moreover, the plasma levels of SHBG may be influenced by several gene polymorphisms, as well as insulin resistance, but data regarding the association between SHBG polymorphisms and the risk of diabetes mellitus are still needed for a better understanding and therapeutic implications.

The Women's Health Study was a randomized, double-blind, placebo-controlled study, started in 1993 in 39,876 women from United States of America, using low-dose of aspirin and vitamin E for the primary prevention of cardiovascular disease and cancer. 12,304 were postmenopausal and not using hormone – replacement therapy and they were included in another study and during a 10-year follow-up period, 366 cases of newly diagnosed type 2 diabetes were reported. Randomly selected controls from women who remained free of diabetes matched the case patients.

At the same time, a replication study was conducted with men (patients and control subjects) included in the "Physicians Health Study II" (170 cases and 170 controls).

Plasma levels of the SHBG were measured and genotyping of SHBG polymorphisms was performed.

The results showed that in women, higher plasma levels of sex hormone–binding globulin were prospectively associated with a lower risk of type 2 diabetes: multivariable odds ratios were 1.00 for the first (lowest) quartile of plasma levels, 0.16 (95% confidence interval [CI], 0.08 to 0.33) for the second quartile, 0.04 (95% CI, 0.01 to 0.12) for the third quartile, and 0.09 (95% CI, 0.03 to 0.21) for the fourth (highest) quartile ($P<0.001$ for trend). These associations were replicated among men (odds ratio for the highest quartile of plasma levels vs. the lowest quartile, 0.10; 95% CI, 0.03 to 0.36; $P<0.001$ for trend). As compared with homozygotes of the respective wild-type allele, carriers of a variant allele of the SHBG single-nucleotide polymorphism (SNP) rs6259 had 10% higher sex hormone–binding globulin levels ($P=0.005$), and carriers of an rs6257 variant had 10% lower plasma levels ($P=0.004$); variants of both SNPs were also associated with a risk of type 2 diabetes in directions corresponding to their associated sex hormone–binding globulin levels.

In conclusion, low-levels of circulating sex hormone-binding globulin predict type 2 diabetes development both in women and men. Further studies are still needed for a better understanding of the clinical implications of SHBG genotypes. ❑

Comment on a paper:

Ding EL, Song Y, Manson JE et al – Sex Hormone-Binding Globulin and Risk of Type 2 Diabetes in Women and Men. *N Engl J Med* 2009 Sep 17; 361:1152-1163