Sex hormone-binding globulin predicts the incidence of hyperglycemia in women: interactions with adiponectin levels

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Abstract

**Objective:** Previous evidence has suggested that a low sex hormone-binding globulin (SHBG) concentration is associated with insulin-resistance and a low adiponectin concentration. We investigated the association between SHBG and the risk of hyperglycemia in each sex and we determined potential interactions between SHBG and adiponectin levels in the development of dysglycemia.

**Design:** We used a nested case–control design in the large prospective study, Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR). We studied 227 men and women who were normoglycemic at baseline but hyperglycemic at 3 years (glycemia ≥ 6.1 mmol/l or type 2 diabetes). They were matched for sex, age, and body mass index with 227 subjects who remained normoglycemic at 3 years.

**Results:** At baseline, the concentration of SHBG was significantly lower in women who subsequently developed hyperglycemia than in those who remained normoglycemic, with no difference for men. In multiple regression, SHBG at baseline was an independent determinant of plasma adiponectin levels, in both women \( P < 0.0001 \) and men \( P = 0.002 \). In multivariate conditional logistic regression taking into account physical activity and changes in waist circumference over the follow-up, plasma SHBG remained significantly associated with the development of hyperglycemia in women but not in men. These associations persisted after adjustment for fasting insulinemia, high fasting glucose, and adiponectin levels.

**Conclusions:** These findings suggest that a low SHBG level is a strong risk marker for dysglycemia in women, independently of both adiponectinemia and insulinemia. SHBG may therefore improve the identification of women at risk of diabetes.

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Introduction

Cross-sectional studies have suggested that a low sex hormone-binding globulin (SHBG) concentration is associated with insulin-resistance and type 2 diabetes. In women with polycystic ovary syndrome, a low SHBG level is associated with insulin resistance. The inhibitory effect of insulin on SHBG secretion suggests that increased hyperinsulinemia could decrease SHBG concentration (1, 2).

Because SHBG concentrations differ between men and women, the association between this variable and incident diabetes may differ by sex. The relationship between low SHBG and the risk of incident type 2 diabetes has been reported to be stronger in women than in men (3, 4).

Adiponectin is an adipokine, which has a higher concentration in women than in men, and it is strongly correlated with insulin resistance. Low-plasma adiponectin is associated with decreased insulin sensitivity and predicts the future development of type 2 diabetes (5, 6). Concomitant low-plasma levels of adiponectin and SHBG have been reported in women with polycystic ovary syndrome (7). However, the relationship between SHBG and adiponectin and the potential confounding between them in the prediction of type 2 diabetes has not been fully studied in healthy individuals.

The aim of our study was to investigate the relationship between SHBG concentration and the development of hyperglycemia at 3 years, separately in men and women, using a nested case–control design.
in the large prospective study, DESIR Furthermore, we determined the interactions between SHBG and adiponectin levels in the development of hyperglycemia.

Materials and methods

Participants
The study population was men and women, aged 30–64 years, who participated in the cohort Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR), a 9-year-follow-up study that aims to clarify the development of the insulin-resistance syndrome (8). Participants were recruited from volunteers who were offered periodic health examinations free of charge by the French Social Security system in ten Health Examinations Centres from the western part of France. All subjects signed an informed consent form and the protocol was approved by an ethics committee. Subjects had the first visit at entry (T0) and the second 3 years later (T3). A total of 5212 subjects were included at T0, and 4501 had a second examination at T3. Visits were at 3-year intervals, and the final examination took place at 9 years. Hyperglycemia (type 2 diabetes or impaired fasting glucose (IFG)) was determined according to the American Diabetes Association criteria (9), in which diabetes is defined as fasting plasma glucose ≥7.0 mmol/l or treatment by glucose-lowering agents and IFG as fasting plasma glucose between 6.1 and 6.9 mmol/l. A total of 3982 men and women, who participated in both examinations, were normoglycemic at T0. Among them, 227 were hyperglycemic at T3 (IFG or type 2 diabetes). They were matched for sex, age, and body mass index (BMI) with 227 people who were still normoglycemic at T3.

Methods
Weight, height, and waist circumferences were measured and BMI (kg/m²) calculated. Family history of diabetes and menopausal status were noted in a clinical questionnaire by the examining physician. Degree of physical activity (at home, at work, and sport) was assessed using a self-administered questionnaire (10). Blood samples were taken in the fasting state to assess biochemical parameters including lipids, glucose, and insulin. Fasting serum insulin was measured by an enzymimmunoassay with IMX (Abbott). The insulin resistance index homeostasis model assessment (HOMA) was calculated. Fasting plasma adiponectin at baseline was measured by RIA (Linco, St Charles, MO, USA; sensibility 1 ng/ml, intra- and interassay coefficients of variation (CV) 4.4 and 9.9% respectively) (8) and SHBG by a commercially available RIA (SHBG-IRMA Kit Cis-Bio International, Gif-sur-Yvette, France), with mean intra-batch and inter-batch CVs lower than 6%.

Statistical analysis
Data from men and women were analyzed separately. Quantitative data are expressed as means with s.d.s (skewed variables as medians with inter-quartile ranges) and categorical data as percentages. Changes in waist circumference over time were defined as (waist at follow-up waist at baseline)/waist at baseline. Changes in physical activity was defined as (activity at follow-up – activity at baseline)/activity at baseline. Characteristics were compared, according to the presence or absence of hyperglycemia at 3 years, by Student’s paired t-tests for continuous variables and McNemar χ²-tests for categorical variables. Skewed variables (triglycerides, insulin, adiponectin, and SHBG) were log transformed before statistical analyses. Pearson correlation coefficients between SHBG and various metabolic parameters were evaluated. Multiple linear regression was used to assess whether plasma SHBG was an independent determinant of adiponectin levels. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) of risk for hyperglycemia at 3 years associated with SHBG levels. We kept SHBG as a continuous variable because quartile analyses supported linearity in the logit. Logistic regression models were used to examine the effects of potential confounders other than those controlled for by matching, including changes in physical activity and waist circumference over the follow-up. In addition, we examined whether plasma levels of adiponectin mediated the association between SHBG and hyperglycemia risk by including this variable in the regression model. A P value of 0.05 or less was considered to indicate statistical significance. Analyses were conducted using SAS version 8.2.

Results
Main clinical characteristics of the population studied are presented in Table 1. The mean BMI was 26.5 ±4.0 kg/m². Both groups (cases and controls) were matched for age, BMI, and sex. The percentage of women with menopause or being treated with hormonal replacement therapy was similar between cases and controls.

At baseline, the plasma concentration of SHBG was negatively correlated with waist circumference, fasting insulin, triglycerides, and HOMA levels. SHBG concentration was positively correlated with adiponectin levels, in both women (r=0.28, P=0.0003) and men (r=0.25, P<0.0001).

In multiple linear regression, SHBG was an independent determinant of plasma adiponectin levels, after controlling for age, BMI, waist circumference, and fasting glycemia in both women (P<0.0001) and men (P=0.002).
The baseline plasma concentration of SHBG was significantly lower in women who subsequently developed hyperglycemia, than in those who remained normoglycemic (Table 1). These relationships were not modified after adjustment for physical activity and waist circumference over the follow-up (model 1 in Table 2). By contrast, in men, the association did not reach statistical significance (OR, 0.98; 95% CI, 0.95–1.02; \( P = 0.4 \)).

In women, the significant association between SHBG and occurrence of hyperglycemia persisted after adjustment for fasting insulinemia and the presence of mild hyperglycemia (fasting plasma glucose 5.6–5.9 mmol/l; models 2 and 4 in Table 2).

The association between SHBG and hyperglycemia was attenuated, but still significant after introducing plasma adiponectin concentration into the logistic model in women (Table 2). Similarly, this association was not substantially altered after controlling for menopause status, hormonal replacement, and oral contraceptive treatments. There was no significant interaction between SHBG and adiponectin levels for the risk of hyperglycemia in either sex.

### Discussion

The main finding of the present study is that the SHBG concentration is significantly associated with the risk of development of hyperglycemia among women but not among men. A low SHBG concentration in women appears to be associated with incident hyperglycemia independently of metabolic parameters such as insulinemia or the HOMA insulin-resistance index.

A number of cross-sectional studies in women with polycystic ovary syndrome have suggested that a low SHBG concentration is associated with enhanced insulin resistance. Only a few prospective studies have assessed the relationship between SHBG and the risk of diabetes (3, 11). An inhibitory effect of insulin on SHBG secretion has been reported, suggesting that increased hyperinsulinemia could decrease SHBG concentration (1, 2, 12). However, in the present study, the association between low SHBG and the development of hyperglycemia is independent of plasma insulin levels, suggesting that hyperinsulinemia may not entirely account for the predictive value of SHBG.

A recent study showed that monosaccharides, including glucose or fructose, regulate human SHBG gene expression and protein secretion by altering gene expression and protein secretion by altering.
hepatic hepatocyte nuclear factor (HNF)-4α levels (13). The reduction of SHBG secretion in response to increased concentrations of glucose may provide a mechanism for the link between low-plasma levels of SHBG and insulin resistance. In our study, baseline plasma glucose levels between 5.0 and 5.9 mmol/l (defined as IFG) was the strongest predictive factor for the onset of hyperglycemia. However, the relationship between low SHBG levels and the risk of hyperglycemia was attenuated, yet persisted, after the addition of increased baseline glucose levels into the statistical model, suggesting that the association between low SHBG and the risk of diabetes is at least partially independent of chronic hyperglycemia. The lower SHBG levels may be due in part to a reduced acute insulin response to glucose and/or higher glycaemia peak in response to meals, underlying the strong association between low SHBG and subsequent increased risk of diabetes.

Alternative underlying mechanisms must therefore explain this association between SHBG and the risk of hyperglycemia. In this regard, our findings of a strong correlation between SHBG concentrations and adiponectin levels in women suggest the potential implication of adiponectin. Adiponectin is viewed as an important adipokine involved in the metabolism of glucose. Low-plasma adiponectin is associated with insulin resistance and predicts the future development of type 2 diabetes (5, 6). Furthermore, in women with polycystic ovary syndrome, plasma adiponectin concentration has been reported to be decreased, in parallel with low SHBG levels (7). Recent in vitro studies have shown an inhibitory effect of testosterone on adiponectin gene transcription, suggesting direct interactions between testosterone and adiponectin gene regulation (14). Thus, adiponectin may have a role in mediating the effects of sex hormones on insulin sensitivity and metabolic risk among women. There is a specific receptor of type 2 for adiponectin in the liver, suggesting the potential implication of adiponectin in the regulation of the secretion of SHBG. Further in vitro studies are needed to determine whether adiponectin may modulate liver SHBG synthesis and if so if it is through the adiponectin type 2 receptor.

The present study displays a tight correlation between SHBG and adiponectin concentrations in each sex, and shows for the first time that the association between SHBG and the risk of hyperglycemia is independent of adiponectin levels. Metabolic interactions between these two variables need further investigations.

Furthermore, the existence of an endocytic receptor and pathways for the cellular uptake of SHBG-bound sex steroids have been recently discovered, providing a novel paradigm for a biological role of SHBG-bound steroids in hormone action (15). These findings reinforce therefore the potential importance of the plasma concentration of SHBG in modulating biological action.

In our study, SHBG levels were not associated with hyperglycemia at 3 years in men, in contrast to that observed among women. The association between SHBG and the risk of diabetes remains debated with contrasting findings among men. Some other studies reported the absence of an association in men (3, 4), but others described that low levels of serum SHBG predicted the subsequent development of type 2 diabetes or the metabolic syndrome among aging or middle-aged men (16–18). These discrepancies may relate to differences in age or BMI of men as the association is more evident among aging and obese men in the literature. Furthermore, the lower plasma concentration of adiponectin in men may also preclude the ability to demonstrate an association between SHBG levels and the risk of hyperglycemia among men, in contrast to women.

Limitations of the present study included its case–control nature and a relative short follow-up. The strengths of the present study of the DESIR cohort are its prospective design with assessment of changes in waist circumference and physical activity over time. In addition, these findings provide insights into the role of SHBG in the risk of hyperglycemia among healthy and mostly non-obese women, who have rarely been investigated in previous reports.

In conclusion, the present study showed that in a European cohort with a low prevalence of obesity, low-plasma SHBG levels are significantly associated with the onset of hyperglycemia or diabetes in women but not in men. This significant association between SHBG and hyperglycemia is partially independent of insulin and adiponectin concentrations, supporting low SHBG levels as a strong and independent marker of enhanced risk of diabetes in women.

Declaration of interest

F Bonnet, B Balkau, J M Malecot, P Picard, C Lange, F Fumeron, R Aubert, V Raverot, H Déchaud, T Tichet, P Lecomte, and M Pugeat have nothing to declare.

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