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Interrelations Between Sex Hormone-Binding Globulin (SHBG), Plasma Lipoproteins and Cardiovascular Risk

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The incidence of coronary artery disease is significantly higher in men than in women, at least until menopause. This gender difference could be explained by the action of sex steroids on the lipoprotein profile. In prepubertal children, high-density lipoprotein (HDL) cholesterol and triglyceride levels are similar between sexes, while adult men have generally lower HDL cholesterol and higher triglyceride levels than premenopausal adult women. Most cross-sectional studies have reported that sex hormone binding globulin (SHBG) and testosterone levels correlate positively with HDL cholesterol levels between sexes. Thus SHBG by modulating the balance in the biodisposal of testosterone and estradiol, might have a profound effect on the risk of cardiovascular disease. However, adjustment for body weight and body fat distribution weakens the association between SHBG, testosterone and HDL cholesterol. The negative correlation of fasting insulin with SHBG and HDL cholesterol levels in both sexes, and some evidence that insulin is an inhibitor of SHBG production *in vitro*, has suggested that hyperinsulinism might negatively regulate SHBG and HDL levels. It remains to be determined whether the inverse relationship between SHBG and insulin levels is coincidental or has a causal effect on the increase of atherosclerosis. Decreased SHBG has been shown to be predictive of the incidence of non-insulin-dependent diabetes mellitus in women but not in men, and of subsequent development of cardiovascular disease and overall mortality in postmenopausal women. SHBG is an index of androgenism in women and of insulin-resistance in both sexes, and might be useful in epidemiological studies of cardiovascular risk. However, in men, SHBG is not predictive of the occurrence of cardiovascular disease. Whether SHBG might have an intrinsic protective effect on the arterial wall through SHBG-receptors is still highly speculative.

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INTRODUCTION

It is now recognized that the incidence of coronary artery disease is significantly lower in premenopausal women than in men and increases in women after menopause. Because sex hormone steroids have been shown to regulate lipoprotein metabolism, differences in lipoprotein concentration due to sex hormone steroids might contribute to the relative protection of premenopausal women. This review will be devoted to the tight relationship observed between sex hormone-binding globulin (SHBG), which modulates the biodisposal of androgens and estrogens (D. C. Anderson: *Clin. Endocr.* **33** (1974) 69–96), and plasma lipoproteins. The present literature reveals that low SHBG concentrations occur in insulin resistance states, a clinical setting associated with an increased risk of ischemic cardiovascular disease.

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SEX HORMONES, SHBG AND LIPIPOPROTEIN PROFILE IN HUMANS

Prepuberty and puberty

At birth, high-density lipoprotein (HDL) cholesterol and triglyceride levels are similar between sexes. However, HDL cholesterol concentrations decrease significantly in boys at the age of puberty, while they remain unchanged in girls [1]. Adult males have lower HDL cholesterol levels and higher triglyceride levels than adult females [2]. Interestingly, most cross-sectional studies have reported that HDL cholesterol and SHBG concentrations correlate significantly and positively between sexes.

Adult males

A study by Hämäläinen *et al.* [3], reported that, in a group of 30 healthy middle-aged Finns with similar dietary habits, the serum concentrations of dihydrotestosterone (DHT), total and free (protein-unbound) testosterone as well as SHBG correlated positively and highly significantly with serum concentrations of HDL cholesterol and apolipoprotein A-I (Apo A-I), the main apoprotein of HDL. In contrast, free-17β-estradiol correlated negatively with HDL cholesterol and Apo A-I levels. A previous study by Miller *et al.* [4] also reported that HDL cholesterol level was associated positively with SHBG level independently of total or protein-free testosterone level in a group of 300 adult men. Additionally, HDL_2 cholesterol, which is associated with the cardiovascular protective effect of HDL, was positively and independently correlated with SHBG and testosterone levels, whereas HDL_3 cholesterol was unrelated to androgen status. Some other studies have confirmed that SHBG and endogenous testosterone levels correlated positively with HDL cholesterol in large populations of middle-aged men [5].

These results suggest that the androgen–estrogen balance, mainly regulated by circulating SHBG [6], influences the lipid profile in men. The independent positive and highly significant relationship of SHBG to HDL cholesterol levels further suggests that SHBG might also have some intrinsic effects on the metabolism of HDL cholesterol, in addition to its influence on the androgen–estrogen balance.

Influence of ageing. Ageing is an exception to the usual parallel variation of SHBG and HDL cholesterol concentrations. The age-dependent decrease in bioavailable testosterone is greater than the age-dependent decrease in total testosterone. This well-documented observation is mainly explained by the age-dependent increase in the binding capacity as well as the immunoreactive concentration of SHBG (see Vermeulen [7]). This increase in SHBG level, might be due to reduced androgen secretion by the reduced number of Leydig cells in ageing testes and by the decrease in growth hormone and IGF-I production with ageing [8]. In this clinical setting no significant variation in HDL cholesterol level has been observed, while testosterone supplements in ageing males by weekly injection of testosterone enanthate 100 mg, increases both testosterone and estradiol and decreases SHBG, total cholesterol and LDL cholesterol levels [9]. Inconsistent change in HDL and VLDL cholesterol but a progressive increase in LDL cholesterol levels has been reported with age in men [2] as well as insulin resistance and decreased glucose tolerance [10]. These results suggest that HDL cholesterol may remain stable because testosterone production tends to decrease and SHBG level to increase with age, both mechanisms having favorable effects on the metabolism of HDL cholesterol, hence explaining the apparent discrepancy of change in SHBG without noticable concomitant variation in HDL cholesterol levels.

Influence of body fat mass and body composition. In men, adipose tissue distribution is related to plasma lipid levels and risk of cardiovascular disease. In most studies, the waist-to-hip ratio (WHR) correlates positively with plasma triglyceride, LDL and VLDL cholesterol and inversely with HDL cholesterol levels. The independence of the correlations between SHBG and lipoprotein according to adipose tissue are highly controversial. Terry *et al.* [11] reported that SHBG levels and percentage free testosterone were associated with regional adiposity but did not account for the correlations between WHR and lipoproteins. In another study, the significant association of SHBG with triglyceride, HDL2 and apoprotein A1 levels was eliminated by adjustment for WHR [12]. However, in The San Antonio Heart Study [13], SHBG was positively and significantly correlated to HDL cholesterol and negatively to triglyceride levels in men after adjustment for age, BMI and WHR. Taking the influence of insulin on these parameters into account reduced, but did not suppress, the positive correlation of SHBG with HDL cholesterol.

In the Telecom Study, involving 1292 healthy French men, a significant graded inverse association between testosterone and insulin levels after correction for age, cigarette smoking, alcohol consumption and plasma glucose was found [14]. Phillips [15] reported that testosterone correlated negatively in non-obese and obese men with insulin and glucose levels and that, conversely, the estradiol–testosterone ratio correlated positively with insulin and glucose levels. These data suggest that the sex-hormone milieu underlines the glucose–insulin–lipid defect associated with coronary heart disease in men.

Adult females

Evans *et al.* [16] reported that increasing androgenicity, as reflected by a decrease in SHBG and an increase in free testosterone levels, was accompanied by an increase of fat mass with upward distribution. It is

now-well documented, in pre- [17] as well as in postmenopausal [18] women, that the SHBG level is partly related to adiposity and to the degree of physical fitness [19, 20]. The San Antonio Heart Study [21] carefully examined the relationship of SHBG to overall adiposity and body fat distribution in two populations of non-Hispanic and of Mexican American premenopausal white women. In this study, premenopausal Mexican American women showed greater overall and upper body adiposity and lower SHBG levels than premenopausal non-Hispanic white women. In both populations, SHBG correlated negatively with BMI, WHR and the centrality index. The lower level of SHBG in premenopausal Mexican American women was interpreted as greater androgenicity and seems to be related to a higher prevalence of non-insulin dependent diabetes mellitus (NIDDM) as compared to non-Hispanic white American women [22].

In obese women, hypertestosteronemia was found to be associated with a significant decrease in HDL cholesterol and a significant increase in LDL cholesterol and triglyceride levels [23]. In women with polycystic ovary syndrome (PCOS), hyperandrogenia results in a male pattern of the lipoprotein profile. A significant positive correlation between SHBG and HDL cholesterol remaining after adjustment for weight [24, 25] as well as insulin resistance have been reported [26, 27].

From these results, it emerges that the low SHBG concentration observed in women with abdominal obesity is associated with low HDL cholesterol levels. This decrease, whether or not driven by insulin resistance, might increase the risk of cardiovascular disease in women.

CONFOUNDING FACTORS INTERFERING WITH THE INTERRELATION OF SHBG AND LIPOPROTEINS

Diet and exercise

Men with good physical fitness have high HDL levels, and various prospective studies have shown an increase in HDL cholesterol level in obese men subjected to an exercise training program. Some studies have emphasized the importance of diet on the plasma levels of SHBG [28]. In normal men on a high carbohydrate diet, both testosterone and SHBG levels increase [29]; in an other study, when given a low fat diet containing less than 20 g of fat per day (necessarily a high carbohydrate diet) for 2 weeks, all subjects increased their SHBG levels [30]. In contrast, under high fat diet for 2 weeks, cholesterol levels increased while SHBG levels decreased significantly in normal men [30]. The combined effect of exercise and food intake on hormonal profile has been investigated in male volunteers giving either a marginally negative [less than 15%] or a balanced energy diet [31]. When the energy expenditure increased by 15% with 2 h of exercise per day, food intake increased so as to maintain the energy balance. In these conditions of diet and exercise to increase insulin sensitivity, a significant rise in SHBG concentration was observed.

Alcohol consumption

Alcohol intake is generally linked to abdominal obesity and is negatively correlated with SHBG and, in some studies [5], but not all [12], with total testosterone levels in men.

Cigarette smoking

In men, it has been shown by most studies that cigarette smoking correlates positively to estrogen levels [32] and also has some positive relationship to adrenal androgen secretion and DHEAS levels in both men and postmenopausal women [33, 34]. The relationship of cigarette smoking to SHBG levels remains unclear.

Thyroid hormones

It is well-documented that hyperthyroidism is associated with high SHBG levels [6] and that thyroid hormones increase SHBG production *in vitro* [6, 35]. There is a highly significant relationship between circulating thyroid hormone and SHBG levels in hyperthyroidism and, to a less extent, in hypothyroid patients. Thyroid hormones regulate cholesterol levels by enhancing LDL cholesterol clearance and have a complex effect on HDL metabolism. However, it is unlikely that the small fluctuations in thyroid hormone levels, in normal physiological circumstances have an influence on SHBG production and HDL cholesterol metabolism.

Androgens

Depending on the dose and on the route of administration, synthetic androgens decrease HDL and HDL2 cholesterol levels [6], but also decrease both testosterone and SHBG concentrations. High doses of testosterone (200 mg i.m. week for 20 weeks) decrease HDL cholesterol levels [36], and conversely GnRH antagonist [Nal–Glu] administration decreases testosterone levels in healthy young men and increases HDL cholesterol levels by 26% and HDL2 cholesterol levels by 63% with unchanged LDL cholesterol and triglyceride concentrations. These acute changes in testosterone suppression were prevented by coadministration of testosterone with GnRH to maintain physiological testosterone levels [37]. These results are in agreement with those of a previous study [38], and suggest that the physiological concentration of testosterone has a suppressive effect on HDL cholesterol levels in healthy men. The mechanism of this effect remains obscure but could again be related to a change in insulin secretion or action when androgens are suppressed in men. However, it might also be hypothesized that a decrease

in testosterone levels is accompanied by an increase in the fraction of SHBG unoccupied by endogenous testosterone. As SHBG has been shown to bind membrane receptors on a few target cells [39–41], it is tempting to suggest that "steroid-free SHBG" could have some influence on the metabolism of HDL cholesterol.

Estrogen and progestogen

The administration of estrogen in postmenopausal women protects against coronary heart disease. This effect is mediated, in part, by beneficial effects on lipid and lipoprotein metabolism, i.e. an increased HDL cholesterol level [see 42]. Conversely, androgenic progestogen administration, by decreasing HDL cholesterol may have a deleterious effect on the incidence of cardiovascular disease and is not recommended in treating postmenopausal women [43]. Administration of estrogen–progesterone, particularly progestogen without androgenic activity, to protect against an increase in endometrial cancer rates, may maintain the beneficial effects of estrogen therapy alone. However, the non-lipid effects of estrogen, on insulin resistance and glucose metabolism, coagulation and fibrinolysis, as well as direct effects on the arterial wall, improving blood flow and reducing blood pressure, are now well-recognized [44]. Whether the increase in SHBG observed in postmenopausal women receiving estrogen substitute therapy is directly or indirectly associated to the mechanism of cardiovascular risk protection is unknown.

Adrenal function

A recent study by Hautanen *et al.* [45] investigated the influence of cortisol secretion on cardiovascular risk and reported that SHBG correlated negatively with insulin and triglyceride, corticosteroid-binding globulin and corticotropin-stimulated cortisol levels, the last of which was positively correlated to insulin levels. The authors suggested that cortisol-induced insulin resistance may be a common determinant of the regulation of SHBG, and of carbohydrate and lipid metabolism. In both sexes, several confounding factors must be considered in the interpretation of the relationship between sex hormones, plasma lipoproteins and cardiovascular disease. The serum levels of DHEA and DHEAS gradually decline in both men and women with ageing [46], falling in normal men by more than 70% [47]. Interestingly, low DHEA levels have been found associated with increased cardiovascular morbidity in men [33]. The effects of DHEA on SHBG and lipid metabolism are unknown.

SHBG AND CARDIOVASCULAR RISK

The predictive value of SHBG level for risk of cardiovascular disease has been investigated by a few studies and is highly controversial. Earlier studies suggesting a positive relationship between SHBG level and cardiovascular risk have failed to be confirmed by further transversal or longitudinal studies.

The Swedish study by Lapidus *et al.* [48] reported that low SHBG levels increased the incidence of cardiovascular disease and overall mortality in postmenopausal women. Another study by Phillips *et al.* [49] reported an association of hypotestosteronemia with coronary artery disease in men undergoing angiography without previous myocardial infarction. SHBG was not measured in this study, but it was found that total but not free testosterone concentration, correlated negatively with fibrinogen and plasminogen activator inhibitor-1 and positively with HDL cholesterol levels. This discrepancy suggests that SHBG might be involved in the correlation between testosterone and risk factors of coronary disease.

However, in men with angiographically assessed coronary heart disease compared with joggers and/or healthy men, Hämäläinen *et al.* [50] reported that coronary heart disease patients had higher LDL cholesterol and triglyceride levels and lower HDL cholesterol concentrations. In these patients, SHBG correlated positively with HDL cholesterol levels in all groups. A study by Slowinska-Srzednicka *et al.* [51] compared a group of normo-cholesterolemic men with a recent history of myocardial infarction with a control group of healthy men of matched age and reported no significant difference in testosterone and SHBG concentrations between the two groups although significantly lower concentrations of DHEAS and dihydrotestosterone were observed in patients with myocardial infarction compared with healthy men. The Helsinki Heart Study [52] compared 62 men with cardiac endpoints (non-fatal myocardial infarction) and 97 controls on placebo over 4 years and reported that patients had higher DHEAS levels than controls and that SHBG seemed to be of minor importance as a risk factor for cardiovascular heart disease, in agreement with a longitudinal study by Barrett-Conor and Kaw [53]. These findings suggest that the concentration of SHBG is not predictive of the occurrence of cardiovascular disease in men.

HYPOTHETICAL MECHANISMS OF A POSSIBLE IMPACT OF SHBG ON ATHEROGENESIS

The positive correlation of SHBG with HDL cholesterol levels reported in most studies in both men and women suggests that SHBG influence the metabolism and/or the production of HDL cholesterol; this effect could be direct or indirect through the equilibrium of the estradiol–testosterone balance. On the other hand, the relationship of SHBG with insulin resistance and hyperinsulinism may point to insulin as the main regulatory factor for both SHBG and HDL.

However, a supposed direct effect of SHBG on HDL metabolism in men is supported by the independence

of the correlation of plasma SHBG and HDL cholesterol concentrations when different parameters related to insulin resistance are introduced in multivariate analysis. SHBG could exert some direct effect on HDL metabolism. Consensual data from several groups have shown that steroid unbound SHBG interacts on the membrane of target cells by a still unidentified receptor [39–41]. It is interesting to speculate that the interaction of SHBG with this receptor might have some influence on the metabolism of HDL cholesterol. This potential new field of SHBG physiology merits further investigations.

A less speculative mechanism for SHBG–HDL interaction is the effect of sex steroids on hepatic lipase biosynthesis. This enzyme, synthesized by hepatocytes, plays a key role in the regulation of HDL concentration, increasing the conversion rate of HDL2 into HDL3. It is stimulated by androgens and inhibited by estrogens, the latter explaining the higher HDL2 cholesterol levels in females than in males or under estrogen administration [54]. On the other hand, SHBG, by the modulation of the steroidogenic biodisposal balance, might enhance some protective effect of estrogens independently of lipoproteins, either acting on hemostasis (i.e. coagulation factors) and fibrinolytic process or directly on the arterial wall, improving blood flow and reducing blood pressure. It is not known whether the increase in SHBG levels, observed in postmenopausal women receiving estrogen substitute therapy is directly or indirectly associated to the mechanisms of cardiovascular risk, but it is probably related to the increased level of estrogens.

On the other hand, there are several lines of evidence that SHBG level is reduced in insulin resistant states, particularly in women [55], and that insulin is an inhibitor of SHBG production by human hepatoma carcinoma cells [Hep G2] [56]. Hepatic lipase activity is also increased in insulin resistant states [57]. Therefore, insulin resistance may concomitantly and independently induce a decrease in SHBG production and an increase in hepatic lipase which in turn would induce two major atherogenic changes in lipoprotein: conversion of apo B containing lipoprotein into small LDL, and reduction of HDL cholesterol levels. Moreover, SHBG may also regulate the biosynthesis of hepatic lipase by controlling the androgen–estrogen balance in the microenvironment of the hepatocyte. Finally, molecular analysis of SHBG's interaction with cell membranes might also reveal some new properties and functions of SHBG [58, 59] in the process of atherogenesis.

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