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Sex Hormone-binding Globulin and Female Reproductive Function

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Although sex steroids have long been known to influence serum concentrations of SHBG, it is now recognized that nutritional factors may be more important in the regulation of SHBG in women. Thus, SHBG concentrations are negatively correlated with body mass index (BMI) and, more particularly, to indices of central adiposity. Polycystic ovary syndrome (PCOS), the most common cause of anovulatory infertility, is associated with truncal obesity, hyperandrogenism and hyperinsulinaemia. There is evidence that insulin may be the humoral mediator of the weight-dependent changes in SHBG. Serum SHBG concentrations are inversely correlated with both fasting and glucose-stimulated insulin levels, and insulin has been shown to have a direct inhibitory effect on SHBG synthesis and secretion by hepatocytes in culture. However, the interrelationship of BMI, insulin and SHBG appears to be different in women with PCOS from that in normal subjects. The clinical importance of the weight-related suppression of SHBG is illustrated by the finding of a greater prevalence of hirsutism in obese women with PCOS compared with their lean counterparts. Obese subjects with PCOS have similar total testosterone concentrations to lean PCO women but have lower SHBG and reciprocally higher free testosterone levels. Calorie restriction results in reduction of serum insulin followed by an increase in SHBG and a fall in free testosterone but an isocaloric, low-fat diet has no significant effect on SHBG concentrations. Weight reduction in obese, hyperandrogenaemic women with PCO is an important approach to the management of both anovulation and hirsutism.

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INTRODUCTION

Serum concentrations of SHBG influence the expression of androgen action in women and thereby play a part in the development of hirsutism in hyperandrogenaemic women. Serum SHBG levels are subject to regulation not only by steroidal hormones but also, more importantly, by nutritional factors. The central role of insulin in this process and the effects of calorie restriction on SHBG, insulin and reproductive function will be reviewed.

SHBG AND HYPERANDROGENISM IN WOMEN

SHBG is the major transport protein for testosterone (and oestradiol) in women. In normal, adult women up to 95% of circulating testosterone is SHBG-bound (average around 66%). The concentration of SHBG in plasma is inversely proportional to the metabolic clearance rate (MCR) of testosterone and, therefore, to androgen action on target tissues [1]. Thus, depression of plasma concentrations of SHBG appears to be a significant factor in the aetiology and degree of hirsutism in women.

The interrelationship of SHBG and androgen action is clinically most relevant in the context of polycystic ovary syndrome (PCOS). PCOS is the most common cause of hyperandrogenism in women and is often associated with anovulation and obesity [2, 3]. The characteristic biochemical features include hypersecretion of androgens (primarily ovarian), luteinizing hormone and insulin. Serum levels of SHBG are significantly lower in women with PCOS than in weight-matched, control subjects (Fig. 1) [4]. This implies that, in PCOS, for a given level of serum testosterone, androgen target tissues are exposed to a higher local concentration of testosterone than in non-

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PCOS subjects and that the degree of hirsutism is likely to be greater than in equally hyperandrogenaemic women. Interestingly, there is a clear cut (inverse) correlation ($r = -0.52$, $P < 0.01$) of SHBG with the Ferriman–Gallwey Score (a semiquantitative index of hirsutism) [5, D. S. Kiddy, D. Hamilton-Fairley and S. Franks, unpublished data].

REGULATION OF SHBG IN WOMEN

Factors associated with either increased or decreased serum levels of SHBG are summarized in Table 1 [for reviews see refs 6–8]. Sex steroids and thyroid hormones are well known humoral factors which influence SHBG synthesis and secretion but, in recent years, the important role of nutritional factors has become recognized. Acute fasting or chronic undernutrition (as in anorexia nervosa) are associated with increased serum SHBG and, conversely, obesity is characterized by suppression of SHBG concentrations.

As might be predicted, SHBG concentrations in obese women with PCOS are even lower than in obese controls [4]. In women with PCOS, there is an inverse correlation of SHBG concentrations with body mass index (BMI) [4, 9, 10]. PCOS is characterized by hyperinsulinaemia and insulin resistance; and recent studies have demonstrated that SHBG in women with PCOS is negatively correlated with fasting and glucose-stimulated insulin levels [4, 9–11].

Furthermore, insulin has been shown to exert a direct inhibitory effect on production of SHBG by human hepatoma cells (Hep G2) *in vitro* [12, 13] supporting the view that insulin is an important regulator of SHBG production and is a likely candidate for the humoral mediator of the effects of nutritional status on SHBG. This interrelationship of insulin and SHBG may be relevant to normal pubertal development in girls (and boys) as well as in the aetiology of hirsutism. During adolescence, there is a striking inverse relationship of insulin and SHBG [14] which suggests that the nutritionally-dependent changes in insulin secretion in puberty may influence the expression of sex steroids (oestrogens and androgens in girls, androgens in boys) in determining secondary sexual characteristics.

Table 1. Factors associated with increased or decreased serum concentrations of SHBG [see refs 6–8]

Regulation of SHBG in women
Factors associated with increased SHBG
• oestrogens: luteal phase, pregnancy; exogenous oestrogen
• thyroid hormones
• liver disease
• diet: fasting; anorexia nervosa
Factors associated with decreased SHBG
• oestrogen deficiency: menopause
• androgens: hyperandrogenaemia; exogenous androgen
• glucocorticoids
• hypersecretion of growth hormone and prolactin
• obesity

EFFECTS OF DIET ON SHBG AND REPRODUCTIVE FUNCTION

Both short-term and long-term calorie restriction in women with PCOS are associated with significant biochemical changes, notably a fall in fasting insulin concentrations, which is mirrored by a rise in SHBG (Fig. 2); there is a reciprocal fall in free testosterone levels [15–17]. In longer term studies, there are indications of an objective improvement in the hirsutism score within 6 months of starting a 1000 calorie, low-fat diet [16, 17]. Importantly, long-term calorie restriction and the parallel fall in serum insulin levels are associated with improved menstrual cyclicity and fertility [17]. It is not clear whether the related increase in SHBG plays a part in the improved ovarian function but, if so, the mechanism remains obscure.

It has been suggested that fat intake may be the most significant component of the diet in the regulation of SHBG [18]. In a related study, we therefore examined the effects of a short-term (2-week), low fat, isocaloric diet in a group of 5 women with PCOS (mean BMI 64 kg/m^2) and 4 weight-matched controls (mean BMI

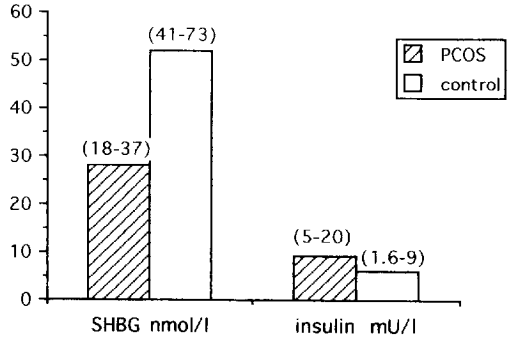

Fig. 1. Serum concentrations [median (range)] of SHBG and fasting insulin in oligomenorrhoeic women with PCOS [mean (SE) BMI 28.5 (0.8)] and in weight-matched controls [BMI 26.7 (1.2)]. Note significantly lower SHBG ($P < 0.001$) and higher fasting insulin ($P < 0.05$) in PCOS [4].

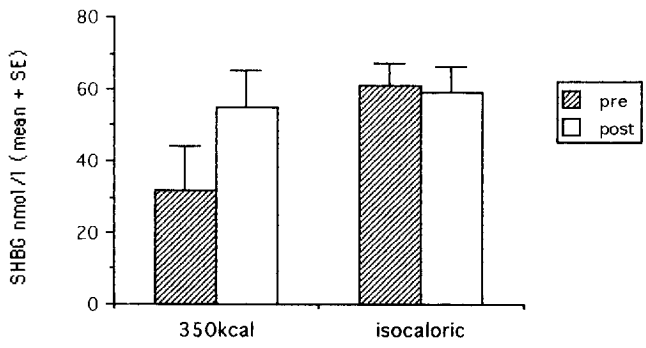

Fig. 2. Serum SHBG concentrations before and 2 weeks after either a low-fat hypocaloric (350 kcal/day) or low-fat isocaloric diet in 2 groups of 5 PCO women. Note rise in SHBG in calorie restricted group only.

60 kg/m^2). Although there was a small decline in mean (SD) fasting insulin levels [4.5 (2.0) vs 7.3 (2.2) mU/l; $P < 0.05$, paired t-test] in the PCO group (but not controls) following the diet, there was no significant change in either group in SHBG concentrations [PCO post-diet: 61 (13) vs PCO prediet: 59 (15) nmol/l]. These findings suggest that it is calorie restriction *per se* which is the principal determinant of the diet-related change in SHBG, at least in women with PCOS.

In conclusion, obesity is associated with suppression of SHBG. SHBG levels are lower in obese women with PCOS than in weight-matched controls and, in turn, are associated with (and are almost certainly caused by) a greater degree of hyperinsulinaemia in PCOS. Insulin has a direct suppressive action on SHBG production by the liver. Calorie restriction in obese women with PCOS leads to a fall in fasting and glucose-stimulated insulin levels, a reciprocal rise in SHBG and an improvement in hyperandrogenism. This has practical implications in the management of hyperandrogenism in obese women with PCOS.

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