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THE ROLE OF NUTRITION AND INSULIN IN THE REGULATION OF SEX HORMONE BINDING GLOBULIN

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Summary—In an analysis of 263 women with polycystic ovary syndrome (PCOS), 91 (35%) of whom were obese (body mass index > 25 kg/m^2), it was found that obese women with PCOS were more likely to be anovulatory and had a higher prevalence of hirsutism than the non-obese subgroup. Although serum concentrations of gonadotrophins, androstenedione and total testosterone were similar in obese and lean women with PCO, sex hormone binding globulin (SHBG) levels were significantly lower, and free testosterone correspondingly higher, in obese women. Serum concentrations of SHBG were inversely correlated with those of both fasting and glucose-stimulated insulin. A short-term, very-low-calorie diet resulted in a 2-fold increase in SHBG which was mirrored by a fall in serum insulin. Similar biochemical changes were also observed during a long-term (6–7 months) 1000 kcal diet and were associated with an improvement of menstrual function and fertility. This encourages the view that calorie restriction has an important part to play in the management of obese women with PCOS.

EFFECT OF OBESITY ON CLINICAL AND ENDOCRINE PRESENTATION OF WOMEN WITH POLYCYSTIC OVARY SYNDROME

Obese women with polycystic ovary syndrome (PCOS) are more likely to have menstrual disturbances and have a higher prevalence of hirsutism than lean women with this syndrome. In a group of 263 women with PCO, 88% of 91 obese women had menstrual disturbances and 73% had significant hirsutism compared with 72 and 56%, respectively in non-obese patients [1] (Fig. 1).

Despite these differences in clinical presentation between obese and lean women with PCO, the biochemical profiles of the two sub-groups were similar. Gonadotrophin, total testosterone and androstenedione concentrations were not significantly different in obese and lean women with PCO. The one striking endocrine feature of the obese women however, is that sex hormone binding globulin (SHBG) concentrations were significantly lower in obese compared with lean women and there was a negative correlation of SHBG with body mass index (BMI). Correspondingly, the concentration of free testosterone was elevated in obese compared with lean women with PCO. These abnormalities are consistent with the observation that the metabolic clearance rate of androgen is increased in obesity [2].

Recently, much interest has focused on the role of insulin in hyperandrogenaemic women [3–6]. The following studies report the relationship between insulin and SHBG and demonstrate how insulin may mediate the effect of obesity on suppression of SHBG concentrations.

RELATIONSHIP OF SERUM INSULIN TO SHBG

A negative correlation of SHBG with fasting and glucose stimulated insulin levels has been reported by Dunaif *et al.* [5] and has been confirmed in our own studies (Fig. 2).

These data support the concept that insulin mediates the weight related changes in SHBG. Interestingly, in a recent study confined to examination of obese women only, we found that SHBG was, as expected, inversely related to serum insulin (fasting insulin vs SHBG $r_s = -0.53$, $P < 0.01$) whereas the relationship between BMI and SHBG in this obese group of women did not reach statistical significance. Furthermore the correlation of SHBG with total testosterone ($r = -0.37$) did not reach statistical significance, suggesting that insulin has a more important inhibitory effect on SHBG than does testosterone [7]. The correlation of androgens and SHBG to clinical indices, insulin and insulin-like growth factor-I (IGF-I) are summarized in Table 1.

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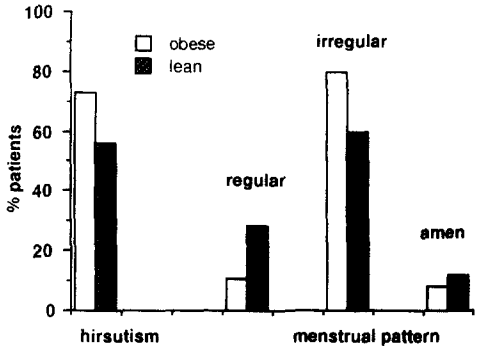

Fig. 1. Distribution, expressed as percentage of patients in each group, of clinical features in obese and lean women with PCOS. Hirsutism (χ^2 6.3, $P < 0.02$) and menstrual disorders ($\chi^2 = 11.6$, $P < 0.01$) were significantly more common in obese compared with lean subjects.

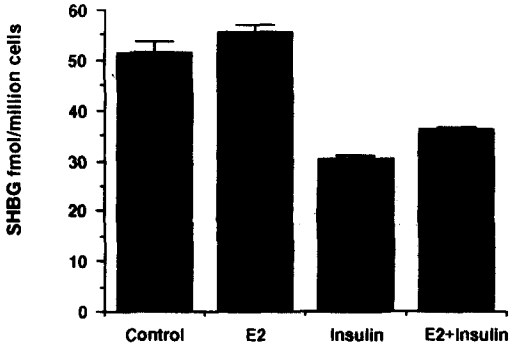

Fig. 3. Inhibition of SHBG secretion in HepG2 cells by insulin (10^{-7} mol/l) in the absence or presence of oestradiol (10–10^{-7} mol/l) in the medium. Cells were incubated for 48 h in the presence of 5% fetal calf serum. SHBG concentrations were measured by an immunoradiometric method [1, 9, 10].

These data are supported by observations from *in vitro* studies of SHBG secretion by hepatoma cells (HepG2) in culture. Insulin has been shown to have a direct inhibitory effect on secretion of SHBG by HepG2 cell [8, 9] (Fig. 3).

EFFECT OF CALORIE RESTRICTION ON CIRCULATING INSULIN AND SHBG CONCENTRATIONS

In a short-term study we examined the effect of a very-low-calorie diet (350 kcal/day), administered for 2 weeks on serum concentrations of insulin androgens and SHBG [10]. The data for women with PCO are summarized in Fig. 4 but similar changes were noted in six control subjects with normal ovaries.

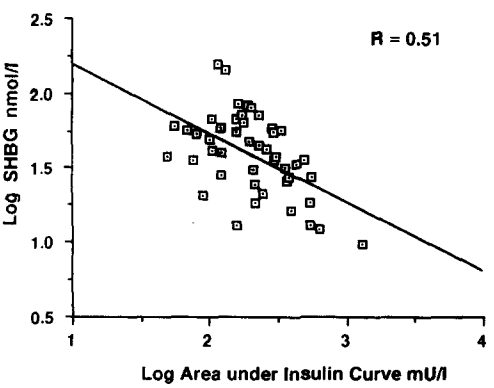

Fig. 2. Inverse correlation of SHBG with the sum of the insulin levels during a 75G oral glucose tolerance test.

Total testosterone concentrations were unchanged but those of SHBG doubled and there was a corresponding fall in free testosterone. The changes in SHBG were mirrored by, and correlated with, those in fasting insulin [10].

Biochemical and clinical consequences of long-term dieting in obese women with PCOS

Preliminary data from our long-term diet study suggest that calorie restriction results in an improvement in clinical as well as endocrine abnormalities [11]. Twenty-four obese women with PCO (of whom 19 were anovulatory) were recruited for treatment with a 1000 calorie per day, low-fat diet for 6 months. The mean weight loss during the study was 8.4% (SD 5.7) of the pre-treatment weight. Nine of 14 women who had lost >5% of their starting weight experienced regular ovulatory cycles and 6 of 9 subjects with infertility became pregnant during the study (a further subject conceiving in the month after the study had been formally completed).

Most subjects reported an improvement in seborrhoea and reduction in hirsutism, as gauged by the Ferriman and Gallwey Score was noted in 50% of women who had successfully lost weight.

Table 1. Correlation of androgens and SHBG with BMI, FG, basINS, sumINS and IGF-I in 24 obese woman with PCO

	BMI	FG	basINS	sumINS	IGF-I
Total testosterone	0.365	0.177	0.222	0.239	−0.099
SHBG	0.204	−0.523**	−0.531	−0.520**	−0.196
Free testosterone (%)	0.320	0.468*	0.285	0.439*	−0.372
Free testosterone (concentration)	0.401	0.458*	0.081	0.284	−0.430

BMI, body mass index; FG, Ferriman-Gallwey score; basINS, fasting insulin; sumINS, sum of the insulin response to 75G oral glucose and IGF-I, insulin-like growth factor-I. Values indicate Spearman's correlation coefficient (r_s). *$P < 0.05$; **$P < 0.01$.

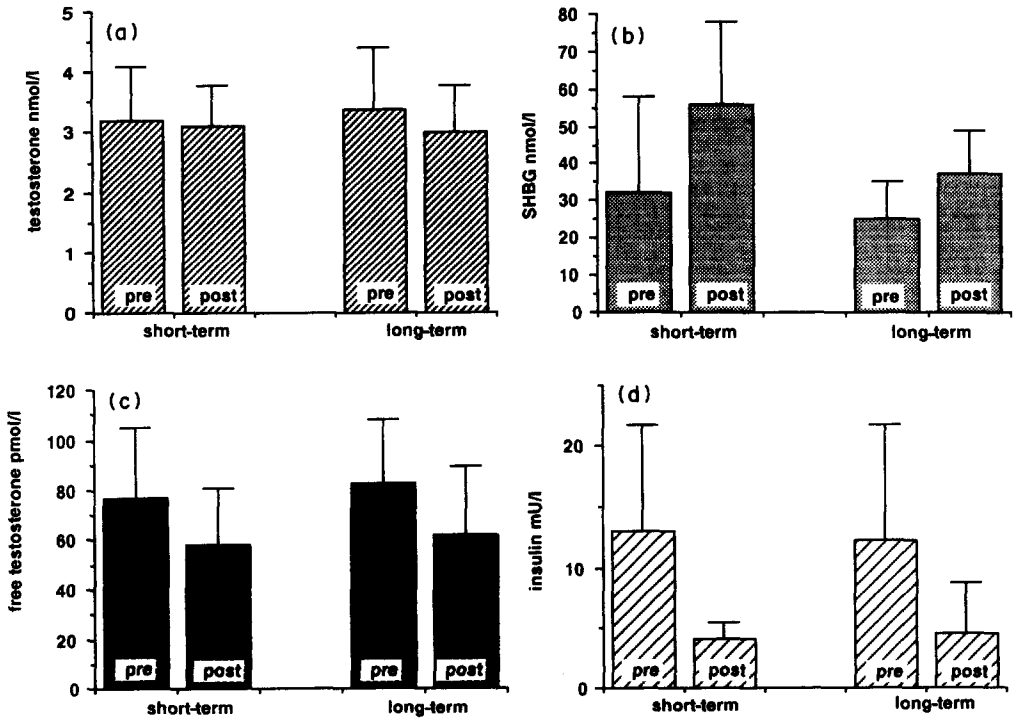

Fig. 4. Concentrations (mean + SD) of SHBG, free testosterone and fasting insulin before and after treatment with 2 weeks of a 350 kcal/day diet and after 7 months of a 1000 kcal/day, low-fat diet. Changes in SHBG, free testosterone and insulin were all significant ($P < 0.02$), comparing pre- and post-levels by paired t test.

Biochemical analysis revealed that an increase in SHBG and corresponding decrease in free testosterone was also observed during the long-term, 1000 calorie diet and, as in the short-term diet study, these indices were related to a significant decrease in fasting and glucose-stimulated serum insulin levels (Fig. 4).

CONCLUSIONS

The major difference in the endocrine profile between obese and lean women with PCOS in that the former have significantly lower levels of SHBG, the levels of which are inversely related to those of insulin. Insulin has a direct inhibitory effect on the synthesis and or secretion of SHBG by the liver. Weight reduction in obese women with PCOS results in a fall in fasting and glucose-induced insulin and a rise in SHBG. The clinical importance of these findings is illustrated by the improvement in menstrual function and hirsutism observed during 6 months of a 1000 calorie per day low-fat diet.

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