

Sex differences in the control of sex-hormone-binding globulin in the elderly: role of insulin-like growth factor-I and insulin

P Lecomte, N Lecureuil³, M Lecureuil³, Y Lemonnier⁴, N Mariotte⁵, C Valat¹ and M A Garrigue²

Endocrinology, ¹Nuclear Medicine, ²Biochemistry, CHU, Tours 37044 Cedex, France, ³Biomathematics, UFR Pharmacy, 37200 Tours, France, ⁴Geriatrics, CHR, Orleans, France, ⁵IRSA, 37521 La Riche, France

(Correspondence should be addressed to N Lecureuil, Laboratoire de Biophysique et Biomathématiques, 31 avenue Monge, 37200 Tours, France)

Abstract

Objective: Serum levels of sex-hormone-binding globulin (SHBG) have been reported in the literature to increase with age in both sexes. We have investigated the variations in levels of androgens, insulin and IGF-I with age and have evaluated their putative roles to obtain a better understanding of the increase in SHBG.

Design: Cross-sectional pilot study of blood samples in healthy elderly subjects aged 50 to 90 years.

Patients and Methods: Forty-four postmenopausal women and 40 men were classified into three age groups. Subjects who were obese, undernourished or smokers and postmenopausal women receiving hormone replacement therapy were excluded from the study. Body mass index and waist/hip ratio were evaluated in each subject.

Fasting levels of blood glucose, insulin, triglycerides, cholesterol, SHBG, testosterone, dehydroepiandrosterone sulfate (DHEAS) and IGF-I were measured. Free testosterone and glucose/insulin ratio were calculated.

Results: The results are based on variance analysis of the mean of each parameter in the three age groups. Multiple regression analysis was performed to define the role of age, insulin and IGF-I in the increase in SHBG. The increase in SHBG with age in older men was significant but that in postmenopausal women was not. Decreasing DHEAS with age was confirmed. No significant variations in glucose and insulin were observed with age in our selected population. A positive correlation was observed between insulin and triglycerides in elderly men and women. IGF-I decreased significantly with age in both sexes. Insulin was the main factor explaining SHBG increase with age in women. In men, both age and IGF-I contributed to the SHBG increase.

Conclusions: The factors regulating the increase in SHBG with age appear to be different in the two sexes. Insulin plays a major role in women, whereas a decrease in IGF-I is the predominant regulating factor in men. These results should be thought of as a working hypothesis rather than a reflection of physiology.

European Journal of Endocrinology 139 178–183

Introduction

We showed in a previous study that sex-hormone-binding globulin (SHBG) increases with age in both sexes (1). Vermeulen *et al.* (2) recently investigated the influence of aging and obesity upon androgen levels in men and looked for factors that influence the variations in SHBG. They found that SHBG increased with age but that the levels were lower in obese subjects. Maruyama *et al.* (3) described an increase in SHBG levels with age in men, in good agreement with previous findings (4–6). In contrast, there have been conflicting reports concerning similar variations in women, mainly attributable to the perimenopausal period. SHBG increases with age in premenopausal women (7) and decreases transiently during the immediate postmenopausal period (8). Other reports (3, 9, 10) have shown it to increase with age in women.

According to Von Schoultz & Carlstrom (11), the current thinking tends to be that SHBG levels are related to general metabolic factors, nutritional status, growth and aging rather than estrogen/androgen balance or thyroid hormones.

The aim of our pilot study was to evaluate SHBG further in a selected population of old and very old non-obese males and females and to investigate several parameters known to influence it, e.g. androgens (12), insulin (13) and insulin-like growth factor-I (IGF-I) (14, 15).

Subjects and methods

Three different age groups of women and men recruited from a geriatrics department were studied: group A, aged 50–60 years (19 women, 55.5 ± 2.8 years; 15 men, 53.8 ± 3.1 years); group B, aged 61–70 years (12

Table 1 Comparison of the mean metabolic factors and androgen levels within the three age groups in women and men. Values are means \pm s.d.

Variable	Women			Men			ANOVA
	Group A	Group B	Group C	Group A	Group B	Group C	
BMI	22.4 \pm 1.8	22.1 \pm 2.1	22.9 \pm 1.9	24.5 \pm 1.9	24.0 \pm 2.4	23.7 \pm 2.1	-
WHR	0.80 \pm 0.04	0.84 \pm 0.09	0.84 \pm 0.04	0.92 \pm 0.04	0.93 \pm 0.08	0.96 \pm 0.06	NS
SHBG (nmol/l)	49.0 \pm 20.0	55.1 \pm 37.3	61.2 \pm 34.5	29.3 \pm 10.4	34.8 \pm 15.6	47.3 \pm 18.0	A, B vs C P = 0.009
Total testosterone (nmol/l)	1.30 \pm 0.66	1.05 \pm 0.89	0.96 \pm 0.38	17.5 \pm 6.5	19.9 \pm 5.7	18.7 \pm 4.2	NS
Free testosterone (pmol/l)	21 \pm 14	18.7 \pm 17.6	14.6 \pm 9	428 \pm 155	461 \pm 17	358 \pm 119	NS
DHEAS (mol/l)	2424 \pm 1530	2616 \pm 1718	892 \pm 622	4300 \pm 1862	2949 \pm 1634	1921 \pm 1115	A, B vs C P = 0.001
Glucose (mmol/l)	5.30 \pm 0.63	5.30 \pm 0.53	5.37 \pm 0.84	5.58 \pm 0.47	5.17 \pm 0.55	5.57 \pm 0.58	NS
Insulin (pmol/l)	68.6 \pm 24.5	64.3 \pm 24.2	58.6 \pm 26.2	76.5 \pm 31.0	65.2 \pm 23.7	59.2 \pm 18.0	NS
Glucose/insulin \times 1000	86 \pm 30	90 \pm 25	106 \pm 40	85 \pm 34	88 \pm 29	102 \pm 30	NS
Triglycerides (mmol/l)	0.88 \pm 0.44	1.01 \pm 0.67	1.18 \pm 0.35	1.15 \pm 0.53	1.01 \pm 0.41	1.25 \pm 0.50	NS
IGF-I (nmol/l)	26.3 \pm 10.5	14.8 \pm 5.8	18.8 \pm 12.2	27.7 \pm 4.6	21.3 \pm 5.2	23.6 \pm 9.1	A vs B P = 0.009

See the text for a description of the age groups.

women, 62.7 \pm 2.4 years; 11 men, 63.5 \pm 3.1 years); group C, aged above 70 years (13 women, 87.1 \pm 8.3 years; 14 men, 80.2 \pm 5.3 years) (ages are means \pm s.d.). Obese subjects, smokers and patients taking drugs that may interfere with the results (liver-inducing drugs, hormones, neuroleptics) were excluded. All women were postmenopausal and not receiving hormone replacement therapy. Malnutrition was evaluated by measuring prealbumin and retinol-binding protein. Severely ill patients (cancer, thyroid disease, coronary heart disease, renal and liver dysfunction, diabetes, prostatic cancer in male patients) were excluded. Body mass index (BMI) and waist/hip ratio (WHR) were evaluated. Waist circumference was measured as the smallest value between iliac crests and lower ribs, and hip circumference was measured at the level of the great trochanter. WHR was chosen as a simple measurement of upper body adiposity.

Fasting blood glucose and insulin levels (RIA, Institut Pasteur, Paris, France), triglycerides, cholesterol, SHBG (Biomerieux, Craponne, France), total testosterone, dehydroepiandrosterone sulfate (DHEAS) and IGF-I (Nichols Institute, Paris, France) were measured. Free testosterone was calculated as described by Rosner (16), and the glucose/insulin ratio was calculated to evaluate insulin resistance.

Statistical analysis

Group means for each androgen or metabolic factor were compared by ANOVA. When a significant difference was found, Newman-Keuls test was used. The interrelationships between the various independent variables and the androgen- and metabolic-dependent variables in question were assessed by multiple regression analysis.

Results

SHBG

SHBG increased with age; by ANOVA, this was not significant in women but was highly significant in men (P = 0.009) (Table 1). Moreover, a correlation with age was significant only in men (Table 2).

Androgens

By ANOVA, free testosterone decreased with age in both sexes but this was not significant (Table 1). This

Table 2 Correlations with age in both sexes.

	SHBG	Free testosterone	DHEAS	IGF-I
Women (n = 44)	0.15	-0.21	-0.46*	-0.32†
Men (n = 40)	0.37†	-0.15	-0.56*	-0.19

* P < 0.002, † P < 0.01.

Table 3 Parameter correlations in women and men.

	Women (n = 44)			Men (n = 40)		
	SHBG	Insulin	Triglyceride	SHBG	Insulin	Triglyceride
IGF-I	-0.29	0.44†	0.37†	-0.41†	0.09	0.20
SHBG		-0.41†	-0.34†		-0.125	0.10
Insulin			0.48*			0.39†

* $P < 0.001$, † $P < 0.02$.

decrease was more obvious in men and women over 70.

DHEAS significantly decreased with age in both sexes (Table 1) and moreover correlated inversely with age in both sexes (Table 2).

Metabolic parameters

By ANOVA, fasting blood glucose levels were normal in both sexes, even in older subjects (Table 1). Fasting insulin levels were not significantly modified by age. Glucose/insulin ratio increased mainly in the group of oldest subjects, but this increase was not significant.

A positive correlation between insulin and triglyceride levels was found in both sexes ($P=0.0009$ for women; $P=0.013$ for men) (Table 3). A significant positive correlation between WHR and triglyceride levels was observed only in women ($P=0.03$) (data not shown). A significant negative correlation between SHBG and triglyceride levels was also observed only in women ($P < 0.02$) (Table 3).

By ANOVA, IGF-I levels were observed to decrease significantly with age in the women (Table 1). Correlations with age confirmed a significant relationship only in women (Table 2). There was a positive correlation between insulin and IGF-I ($P=0.003$) and a positive correlation between triglyceride and IGF-I levels only in women ($P=0.01$) (Table 3).

Correlations between SHBG levels and metabolic parameters (Table 3)

An inverse correlation between SHBG and insulin was significant only in women ($r=-0.41$; $P=0.005$). SHBG correlated negatively with IGF-I in women but this was not significant. In contrast, SHBG was significantly negatively correlated with IGF-I in men ($r=-0.41$; $P=0.01$).

Multiple regression analysis

Using multiple regression analysis to assess the relative contributions of the various factors (age, insulin, IGF-I, free testosterone, triglycerides) to explain the increase in SHBG, we found that insulin was the main factor contributing to SHBG increase with age in women

($P=0.005$) whereas age and IGF-I both contributed to SHBG variations in men ($P=0.003$).

Discussion

The cause of the increase in SHBG levels with age remains unclear; however, androgens and metabolic factors (insulin, growth hormone, IGF-I) need to be taken into account. What are the influences of decreased androgens and IGF-I upon SHBG levels in the elderly? Is there a relationship between the well-demonstrated trend toward insulin resistance and SHBG?

SHBG and age

Maruyama *et al.* (3) showed a twofold increase in SHBG with age in both sexes and they emphasized that there is a wide range of variations in women. In our own previous data (1), we observed significantly higher levels of SHBG in older women ($n=48$, 63–98 years) than young premenopausal women ($n=30$, 25–47 years) not taking oral contraceptives (69 ± 28 vs 43 ± 11 nmol/l; $P < 0.0001$). Similar results were observed in older men ($n=30$, 65–92 years) compared with young untreated men ($n=30$, 22–58 years) (54 ± 22 vs 27 ± 9 nmol/l; $P < 0.0001$). We found a twofold increase in SHBG in older men whereas the increase with age was smaller (1.6 times) in women. Gray *et al.* (17) found an increase in SHBG with age in 450 men (39–70 years) not suffering from obesity or illness. In a recent study, Vermeulen *et al.* (2) showed a significant increase in SHBG with age in 250 non-obese healthy men (25–100 years) ($P < 0.001$).

Data on variations in SHBG with age in women are scarce. Van Hemert *et al.* (9) reported a significant increase in SHBG with age ($P < 0.01$) in 746 postmenopausal women (53–76 years). Recently, Pasquali *et al.* (18) found no increase in SHBG with age in 196 postmenopausal women. The mean time after menopause was 6.6 ± 5.6 years and BMI was 25.9 ± 4.4 ; therefore our population was different because we excluded obese patients and our postmenopausal women were older.

In our study we did not find a significant increase in SHBG in women with age, in contrast with the findings

in men and our previous data. These discrepancies may be explained by: (i) the great variability in SHBG levels in women, the effect of which was reduced by the larger number of subjects in the study of Van Hemert *et al.* (9) and (ii) the smaller increase with age in women than in men. However, in this study, we compared aging postmenopausal women rather than young versus postmenopausal women in the previous work (1). In a recent paper, Pfeilschifter *et al.* (15) observed a similar positive relationship between SHBG and age in both sexes. The relationship was significant in older men but not in older women in a similar population (50–80 years), showing a striking similarity to our results in a larger group of subjects. This suggests that other potent regulators of SHBG may exist in women.

Androgens

Vermeulen *et al.* (2) showed a decrease in testosterone in men starting at age 55–60 years and an earlier decrease in free testosterone. We observed a non-significant decrease in free testosterone with age in men.

In postmenopausal women, circulating androgens decrease as a result of lower secretion by the ovaries and a slow decrease in adrenal secretions (19). A significant decrease in the free androgen index was recently observed by Bancroft & Cawood (20) in postmenopausal women. We observed a non-significant decrease in free testosterone with age in women. This decrease could be explained, at least in part, by the increase in SHBG with age in both sexes in elderly subjects.

DHEAS decreased significantly with age in our elderly men and women. This was also observed in men in the study of Vermeulen *et al.* (2) ($P < 0.001$) and in postmenopausal women (21). DHEAS levels were measured in both sexes in 981 men and 481 women aged 11–89 years by Orentreich *et al.* (22) and a progressive decrease was observed. In a recent Italian study (23) involving over-90-year-olds, fivefold lower DHEAS levels were observed in elderly men and women than in the youngest subjects. There was no correlation between DHEAS and SHBG, insulin or IGF-I in either sex in our study.

Metabolic parameters

The impairment of oral and intravenous glucose tolerance with advancing age is well known (24). Because of their age and the cost, we could not evaluate insulin resistance in our elderly patients with sophisticated methods. Only fasting insulin and glucose were evaluated. This simple method is considered to be accurate by Nestler (25) in non-diabetic humans. Nevertheless, we found a non-significant increase in the glucose/insulin ratio in our population. Similarly, in the Rancho Bernardo study, a decrease in insulin levels with age was observed in both sexes (26). This is not

surprising if we hypothesize that the most elderly are probably less insulin resistant and also since we excluded obese subjects.

An inverse relationship between the serum concentrations of insulin and SHBG in women has been demonstrated in numerous studies (7, 18, 27, 28). Few data are available for men (29, 30) and they mostly involve middle-aged men. In both the latter papers, a significant negative correlation between insulin and SHBG was observed in healthy obese and non-obese men. Vermeulen *et al.* (2) similarly found the same significant negative correlation in aging non-obese males.

In our study, we found a significant negative correlation between insulin and SHBG only in elderly women. A similar significant negative correlation was shown by Haffner *et al.* (28) and Pasquali *et al.* (18) in postmenopausal women.

We found a positive correlation between insulin and triglycerides in both sexes. It is accepted that triglycerides are elevated in the case of insulin resistance. We emphasize the significant relationship between WHR and triglycerides in our group of elderly women, as also shown by Lapidus *et al.* (31). We observed a significant negative correlation between SHBG and triglycerides. The same results were also found by Haffner *et al.* (28) and Lapidus *et al.* (31) in postmenopausal women.

Cross-sectional studies have shown a decrease in IGF-I with age in both men and women (32–34) in relation to impairment of GH secretion. We obtained similar data.

The relationship between SHBG and IGF-I is complex. The influence of nutrition on the regulation of SHBG has been emphasized. It was shown by Kiddy *et al.* (35) in young normal women that SHBG increased under fasting conditions while insulin and IGF-I decreased, and by Pugeat *et al.* (13) that inverse relationships were observed with refeeding. *In vitro* studies demonstrated similar negative effects of insulin and IGF-I on SHBG production by the liver (36, 37) but the effects on the SHBG/total protein ratio were not significant, suggesting less specific effects compared with results on cortisol-binding globulin (CBG) (37). Moreover, although it is accepted that insulin receptors are present in the human liver, the absence of IGF-I receptors on normal human hepatocytes has been suggested (38). Taking the results together, it seems doubtful that IGF-I directly modifies SHBG levels *in vivo*. An inverse relationship between SHBG and IGF-I was observed in our elderly women, but this was not significant. In contrast, SHBG was negatively and significantly correlated with IGF-I in elderly men. We underline the discrepancy between sexes with respect to the relation between SHBG and IGF-I since similar results have recently been shown in a larger group of elderly subjects (15): an inverse relationship between SHBG and IGF-I was also observed which was barely significant in women ($P < 0.05$) but highly significant in men ($P < 0.001$). Similar findings were observed in middle-aged men by Erfurth *et al.* (39) ($P = 0.002$). As suggested by Copeland *et al.* (32), a true sexual dimorphism could

clearly exist: higher levels of androgens in men may contribute to a unique vulnerability of the male to the development of abdominal obesity when growth hormone (and IGF-I) production declines.

The discrepancies between the sexes and the roles of IGF-I and insulin in the regulation of SHBG levels in men and women were evaluated in our study. Gafny *et al.* (14) investigated these relationships. In a group of growth hormone-deficient patients receiving growth hormone supplementation, SHBG decreased while IGF-I and insulin increased. An inverse relationship between SHBG and insulin was observed in these patients, as with our findings. IGF-I increased and SHBG decreased, showing a similar inverse relationship in this group of growth hormone-deficient patients.

Multivariate analysis of our data suggested that SHBG was highly dependent on age and IGF-I in men and on insulin in women. However, our cross-sectional study was not designed to elucidate causative relationships between parameters, and the small number of patients introduced several limitations and possible bias.

The increase in SHBG with age remains unexplained. The age-associated decrease in testosterone levels probably partly explains the increase in SHBG with age. Increasing insulin resistance with age and modification of adiposity from peripheral to abdominal areas should decrease SHBG levels.

In agreement with Gafny *et al.* (14) and Vermeulen *et al.* (2), we believe that low IGF-I might partly explain the increase in SHBG with age in men in spite of insulin resistance. The findings for women are less clear. There is still disagreement about whether levels of SHBG increase with age. The cause of the discrepancies could be age itself: when SHBG was measured in elderly women, it was found to be increased (3, 15). We therefore would favor a predominant effect of insulin upon the liver and SHBG synthesis in aging women. This could be due to the collapse of steroid synthesis in postmenopausal women or to modification of the distribution of adiposity towards the abdomen.

The respective effects of age, IGF-I and insulin on the regulation of SHBG levels in elderly subjects merit further study. A greater knowledge of the role of modification of insulin and/or IGF-I levels should contribute to a better understanding of SHBG regulation in the elderly of both sexes.

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Received 9 December 1997

Accepted 30 March 1998