0021-972X/96/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 81, No. 5
Printed in U.S.A.

Influence of Some Biological Indexes on Sex Hormone-Binding Globulin and Androgen Levels in Aging or Obese Males*

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ABSTRACT

Several aspects of the regulation of androgen secretion and plasma levels in males remain controversial. Among these, we cite the problem of whether the age-related decrease in testosterone (T) levels is an intrinsic aging phenomenon or is a sequel of previous illness, the mechanisms underlying the increase in sex hormone-binding globulin (SHBG)-binding capacity in aging men and the supranormal capacity observed immediately after a weight-reducing diet, and the role of insulin in the age-associated decrease in dehydroepiandrosterone (sulfate) [DHEA (DHEAS)] levels. To gain further insight into these issues, we investigated the influence of age, smoking, body mass index (BMI), serum albumin, insulin, GH, and insulin-like growth factor I (IGF-I) levels, respectively, on androgen levels and SHBG-binding capacity in a nonobese healthy population (n = 250) as well as in an obese population (n = 50) before and after weight loss. The influence of GH supplementation on SHBG, DHEAS, DHEA, and insulin levels was studied in a small group of men (n = 8) with isolated GH deficiency.

In nonobese healthy men, age was inversely correlated with serum levels of all androgens studied (although total T levels stayed relatively stable until age 55 yr) as well as with albumin, GH, and IGF-I levels and positively correlated with BMI, insulin levels, and SHBG-binding capacity. Nevertheless, SHBG levels were significantly negatively correlated with insulin levels ($P < 0.001$) as well as with mean 24-h GH and IGF-I levels. Among possible confounding factors affecting (free) T [(FT)] levels in healthy men, smoking appeared to be accompanied by higher (F)T levels than those in nonsmokers. BMI increased with age, but although BMI was negatively correlated with T, FT, and SHBG, respectively, the age-dependent decrease in T levels persisted after correction for BMI. Data not corrected for BMI may, nevertheless, overestimate the age-associated decrease in T levels. The albumin concentration decreased with age, and if FT is the feedback regulator of plasma T levels, albumin concentration might be a codeterminant (although, evidently, less important than SHBG) of T levels and contribute to the age-associated decrease in T levels. In any case, albumin concentration is a codeterminant of DHEAS concentration. T, DHEA, and DHEAS levels were significantly correlated, but this correlation disappeared after controlling for age; hence, there is no evidence for an adrenal-gonadal interaction in men.

In obese men, T, FT, and SHBG levels were significantly lower than those in the nonobese men and inversely correlated with BMI; DHEAS levels were slightly lower than those in the nonobese controls, but no significant correlation between DHEA or DHEAS, and insulin levels was observed.

After a weight-reducing, protein-rich diet, resulting in a mean weight loss of ±15 kg, SHBG-binding capacity increased to normal values notwithstanding the fact that the subjects were still obese and that the insulin levels remained higher than those in the nonobese controls. Considering that after weight loss, GH and IGF-I levels remained lower than those in the nonobese controls, that adult men with isolated GH deficiency presented with higher SHBG levels than normal controls, which decreased to normal levels during GH substitution, and that elderly men have elevated SHBG levels notwithstanding high insulin levels, we suggest that the low GH and/or IGF-I levels might play a role in the elevated SHBG levels observed in both elderly males and obese men after a weight-reducing diet. As weight loss did not influence DHEAS levels notwithstanding an important decrease in insulin levels, our data do not support a role of insulin in the regulation of plasma DHEAS levels. (*J Clin Endocrinol Metab* **81:** 1821–1826, 1996)

SEVERAL PROBLEMS related to secretion and plasma levels of androgens in healthy males remain the subject of controversy. Do testosterone (T) levels decrease as a consequence of aging in healthy males or is the decrease a sequel of previous illness (1–3)? What factors are responsible for the age-associated increase in sex hormone-binding globulin (SHBG)-binding capacity in men? Are increased insulin levels responsible for the decrease in dehydroepiandrosterone sulfate (DHEAS) levels (3–5) in the presence of normal cortisol levels observed in aging as well as in obese men (6, 7)? It was the purpose of the present study to gain some further insight into the factors determining serum SHBG, T, DHEA, and DHEAS levels in elderly and obese men.

Received August 11, 1995. Revision received October 19, 1995. Rerevision received December 13, 1995. Accepted December 18, 1995.

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* This work was supported by Grant 3.0062.92 from the National Foundation for Medical Research (Belgium).

Subjects and Methods

The effects of age on hormone levels were studied in a group of 250 healthy nonobese (body mass index [BMI; wt(kg)/length^2 (m)], 20–26) men, aged 25–100 yr, living in a semiindustrial area. None was taking any medication or reported excessive alcohol consumption, and all were in good health, as evaluated by clinical examination and routine blood biochemistry. All were consuming the usual Western-style diet. Smokers were considered as a separate group. The effects of obesity on hormone levels were studied by comparing these levels in a group of 50 obese nondiabetic men (BMI, 34–54), aged 25–62 yr, with those in an age-matched subgroup of healthy nonobese men. The immediate effects of a weight-reducing diet on hormone levels were evaluated by determining the latter the day before and at the end of a protein-sparing modified fast (PSMF), as described previously (8), followed over 6 weeks. In all obese subjects and their controls, fasting insulin levels were measured; to obtain a better index of the hyperinsulinism, an oral glucose tolerance test (OGTT) using 75 g glucose was performed in 30 obese subjects before the start as well as at the end of the diet. Plasma samples for glucose and

insulin determinations were taken 0, 30, 60, 90, and 120 min after glucose intake; the cumulative insulin response was obtained as the sum of all insulin levels.

The influence of age on GH and insulin-like growth factor I (IGF-I) levels as well as the relation of the latter to T and SHBG levels were studied by determining the mean 24-h GH levels, *i.e.* the mean of 72 samples, taken at 20-min intervals, as described previously (9), in 24 nonobese healthy males, aged 25–85 yr. Finally, the influence of GH treatment on IGF-I, SHBG, insulin, DHEA, and DHEAS levels, respectively, was studied in 8 adult males with isolated GH deficiency. All had been treated with GH in their youth, but had not received treatment since. GH deficiency was ascertained by absent or insufficient GH responses to hypoglycemia and clonidine as well as by IGF-I levels. Hormone levels were determined before treatment as well as after 3, 6, and 9 months of treatment with 0.25 IU (0.120 μg) recombinant GH/kg BW·week, divided over 7 equal daily doses.

Plasma T, estradiol (E_2), androstenedione (A), DHEA, and DHEAS levels were determined by RIA, as previously described (10–13), whereas SHBG was measured by equilibrium dialysis (14). All methods involved a chromatographic step(s), eliminating interfering steroids before RIA. The sensitivity and the interassay coefficient of variation (CV) of the methods were 0.10 nmol/L and 6.7%, respectively, for T, 0.7 nmol/L and 9.2% for DHEA, 50 nmol/L and 10% for DHEAS, and 20 pmol/L and 6.7% for E_2 at mean concentrations for healthy men.

Insulin was measured using a commercial RIA kit (Riagnost Insulin, Behringwerke, Marburg, Germany). GH was measured using a commercial immunoradiometric assay (IRE, Fleurus, Belgium); the detection limit was 0.2 ng/mL, and the interassay CV was 12% at a concentration less than 0.5 ng/mL, 8% at concentrations between 0.5–5 ng/mL, and 6% at concentrations above 5 ng/mL (9). All samples from an individual subject were run in one assay. IGF-I levels were measured after extraction from acidified sera, using a commercial RIA kit (Nichols Institute, San Juan Capistrano, CA). The intraassay CV was 6.4%, the interassay CV was 11.2%, and the sensitivity was 10 ng/mL. Albumin was determined using a sequential analyzer (SMA-20). All blood samples were obtained between 800-1000 h after an overnight fast.

Statistical analysis

All data are the mean ± SD. Groups were compared using nonparametric methods; the Wilcoxon two-sample signed rank test was used to compare pre- and posttreatment values, and the Spearman (partial) correlation coefficient was used to assess the association between variables. For multiple comparisons, the Kruskal-Wallis test was used. All values for significance were two tailed; $P < 0.05$ was considered significant.

Results

In our nonobese subjects, T levels remained relatively stable until age 55–60 yr and declined rapidly thereafter. The decline in free T (FT) levels started at an earlier age; the discordance with total T levels was the consequence of the early increase in SHBG binding capacity, and at age 85 yr, levels were only 45% of those at age 30 yr. Plasma levels of FT, DHEA, and DHEAS showed a log linear decrease with age, whereas A levels remained stable up to age 75 yr, but declined rapidly afterward, and E_2 levels did not vary with age (Table 1). In all age groups, smokers had higher levels of both FT, T, and DHEAS than nonsmokers (Table 2). In both the nonobese and the obese population, BMI as well as insulin levels were negatively correlated with T and SHBG levels and positively correlated with age (Tables 3 and 4). Obese subjects had significantly lower SHBG, FT, T, DHEA, GH, and IGF-I levels than age-matched nonobese controls, whereas E_2 as well as insulin levels were significantly higher in the obese. Immediately after weight loss, the SHBG binding capacity normalized, notwithstanding persisting obesity and still elevated insulin levels (Table 5). The *right panel* of Table 5 shows that SHBG binding capacity was higher in subjects who consumed a PSMF diet than in nondieting weight-stable subjects with identical BMI values. Mean 24-h GH and IGF-I levels decreased with age, in parallel with the increase in SHBG (Table 6). The SHBG capacity of adult men with isolated GH deficiency was increased compared with that in age-matched controls, and GH treatment significantly decreased the SHBG binding capacity, but did not influence FT, T, or DHEAS levels (Table 7).

Discussion

One of the aims of this study was to explore some of the factors that might affect T levels in healthy aging men and, eventually, to explain the absence of a decrease with age reported by some researchers (1–3). In our nonobese men, aged 25–100 yr, serum FT levels decreased approximately log linearly (1.2%/yr) with age. Total T levels, however, stayed relatively stable until age 55 yr and decreased afterward at a rate of ±0.85%/yr. As we stressed previously (15), an age-associated decrease in T levels will only be observed if the population studied covers a wide age range and includes a sufficient number of subjects over age 60 yr. Other researchers also (16, 17) reported that the T levels stay almost stable until age 50 yr. Gray *et al.* (18) observed a decrease in total T levels of 0.4%/yr and in FT of 1.2%/yr. Our data confirm again that smokers have 5–15% higher T levels than nonsmokers (3, 15, 19, 20). In contrast to Field *et al.* (3), we observed, confirming our previous observations (15), that FT levels are higher in smokers than in nonsmokers. As the percentage of smokers is often higher in the elderly population, the absence of a correction for smoking might result in higher mean T levels in the older population, partially masking the age-associated decrease.

An inverse correlation between BMI and SHBG or T levels, respectively, has been reported in studies involving groups of men covering a wide range of BMI (3, 21–25). Our data show that this inverse correlation exists in nonobese (BMI,

TABLE 1. Influence of age (yr) on serum hormone levels in healthy men

Age	n	T	FT	SHBG	DHEA	DHEAS	A	E_2
25–34	45	21.38 ± 5.90	0.428 ± 0.098	35.5 ± 8.8	15.91 ± 6.05	6.79 ± 1.96	3.85 ± 1.25	136.8 ± 50.4
35–44	22	23.14 ± 7.36	0.356 ± 0.043	40.1 ± 7.9	12.65 ± 3.69	6.02 ± 2.18	3.81 ± 1.01	134.2 ± 56.3
45–54	23	21.02 ± 7.37	0.314 ± 0.075	44.6 ± 8.2	11.31 ± 5.39	5.34 ± 2.62	3.36 ± 0.90	142.3 ± 37.1
55–64	43	19.49 ± 6.75	0.288 ± 0.073	45.5 ± 8.8	10.20 ± 5.21	3.25 ± 1.48	4.66 ± 1.28	128.7 ± 40.4
65–74	47	18.15 ± 6.83	0.239 ± 0.078	48.7 ± 14.2	7.71 ± 4.15	2.65 ± 1.68	4.47 ± 2.17	132.3 ± 38.2
75–84	48	16.32 ± 5.85	0.207 ± 0.081	51.0 ± 22.7	5.39 ± 2.76	1.15 ± 0.52	2.18 ± 1.49	138.7 ± 43.4
85–100	21	13.05 ± 4.63	0.186 ± 0.080	65.9 ± 22.8	3.18 ± 0.69	1.23 ± 0.52	1.85 ± 0.91	136.4 ± 39.5

All values are expressed as nanomoles per L, except for DHEAS (micromoles per L) and E_2 (picomoles per L).

TABLE 2. Influence of smoking on sex hormone levels in healthy men

Age (yr)	T (nmol/L)	FT (nmol/L)	DHEAS (μmol/L)
25–44			
Sm (n = 16)	24.46 ± 4.69[a]	0.445 ± 0.099[a]	7.29 ± 1.66[a]
NSm (n = 51)	21.18 ± 7.12	0.392 ± 0.062	5.99 ± 3.01
45–64			
Sm (n = 18)	22.60 ± 2.85[a]	0.343 ± 0.064[a]	4.85 ± 0.88[b]
NSm (n = 48)	19.05 ± 6.73	0.280 ± 0.092	3.37 ± 1.63
65–84			
Sm (n = 32)	17.94 ± 3.92[a]	0.236 ± 0.051[a]	2.26 ± 0.92[b]
NSm (n = 63)	16.29 ± 6.12	0.216 ± 0.083	1.71 ± 0.48

Sm, Smokers; NSm, nonsmokers. [a] $P < 0.05$, Sm *vs.* NSm.
[b] $P < 0.01$, Sm *vs.* NSm.

TABLE 3. Parameter correlations in the nonobese population (n = 250)

	SHBG	BMI	Insulin	DHEAS	DHEA	Age
T	0.58[a]	−0.48[a]	−0.62[a]	0.51[a]	0.41[a]	−0.44[a]
SHBG		−0.34[a]	−0.69[a]	ND	ND	0.34[a]
BMI			0.63[a]	−0.28[b]	0.09	0.25[b]
Insulin				−0.09	−0.07	0.19[b]
DHEAS					0.29[b]	−0.69[a]
DHEA						−0.63[a]

ND, Not determined.
[a] $P < 0.001$.
[b] $P < 0.01$.

<26) healthy men ($P < 0.001$) as well as in our obese population. The consistency of this correlation found in all studies as well as the fact that insulin is known to decrease SHBG synthesis suggest a causal relationship between obesity and the decrease in SHBG levels, probably via the accompanying hyperinsulinism.

As BMI often increases with age, failure to correct for BMI may lead to an overestimation of the age-associated decline of T levels.

Another factor that might affect T levels, is the serum albumin concentration. Albumin-bound T depends on both the albumin concentration and the FT fraction and, in young adults, corresponds roughly to 20 times the FT fraction. Notwithstanding important interindividual variations (up to 25% in elderly men), the mean albumin concentration decreases with age, from 38.2 ± 4.0 (±SD) g/L at age 25 yr to 32.9 ± 3.2 g/L at age 75 yr ($r = -0.24$ for age *vs.* albumin; $P < 0.01$). If FT only (and not FT plus albumin-bound T) is the feedback regulator of plasma T levels, it follows that this decrease might contribute to a mean decrease of ±7% in T levels in the elderly, which might be more important in individual cases.

The cause of the increase in SHBG levels with age remains unclear. Neither the age-associated decrease in T levels nor the E_2 levels appear to play a role. Indeed, SHBG levels increase at an earlier age than the decrease in T levels, whereas E_2 levels in the elderly are similar to levels in young men, and Longcope *et al.* (25) did not find any independent correlation between E_2 and SHBG levels in middle-aged men. As GH is known to decrease SHBG levels (26, 27), the well known age-associated decrease in GH and IGF-I levels (9, 28) might contribute to the increased SHBG levels, as suggested by the highly significant correlation ($r = -0.51$; $P < 0.01$) between SHBG and 24-h GH or IGF-I levels, respectively. A

TABLE 4. Parameter correlations in obese men (aged 25–62 yr; BMI, 40.5 ± 7.2) before the start of a protein-sparing modified fast

	SHBG	BMI	Insulin	DHEAS	DHEA	Age
T	0.15	−0.50	−0.47[a]	0.16	0.18	0.05
SHBG		−0.10	−0.18	ND	ND	0.24
BMI			0.55[a]	0.09	0.09	0.01
Insulin				−0.01	−0.25	−0.12
DHEAS					0.67[a]	−0.42[b]
DHEA						−0.37[b]

ND, Not determined.
[a] $P < 0.001$.
[b] $P < 0.01$.

further argument in support of this hypothesis is the fact that in our adult men with isolated GH deficiency, SHBG levels are significantly ($P < 0.01$) increased compared to levels in healthy men of similar age, whereas treatment with substitutive doses of GH results in a significant decrease in SHBG levels. The fact that in patients with anorexia nervosa, SHBG levels are increased in the presence of high GH but low IGF-I levels suggests that the effects of GH on SHBG may be mediated by IGF-I (29). One could object that as GH increases insulin resistance (30, 31), the GH-induced decrease in SHBG may merely be the consequence of the hyperinsulinism. In our subjects, however, the fasting insulin levels did not increase significantly, and recently, Riedl *et al.* (32) reported that total insulin secretion during OGTT also remained unchanged after 6 months of treatment with GH at a similar dose. These results are in contradiction with those of Gafny *et al.* (33), who concluded that any effect of GH on SHBG is mediated by insulin. This seems unlikely, considering that the increase in SHBG in elderly males or obese men after PSMF (see below) occurs in the presence of high insulin levels; GH and IGF-I levels, however, are low.

Confirming the data reported by Strain *et al.* (22), we observed that in the mixed group of nonobese and obese subjects with a wide range of insulin levels, a hyperbolic regression equation [SHBG (nmol/L) = 1.2/insulin (nmol/L) + 31.1] represented best the correlation between insulin and SHBG ($r = -0.46$; $P < 0.01$ *vs.* −0.30 for the linear correlation of SHBG/insulin). This suggests that inhibition of SHBG secretion by insulin is practically at its maximum at a concentration of ±150 pmol/L.

The pronounced age-associated decrease in DHEA and DHEAS levels by ±2%/yr confirms that DHEAS is a most sensitive hormonal index of aging. The positive correlation between T, DHEA, and DHEAS levels disappeared almost completely after adjustment for age. Hence, there does not appear to exist an adrenal-gonadal interaction in men, as suggested by Parker and Lifrak (34). Besides higher FT levels, smokers also have higher DHEAS levels than nonsmokers. Decreased GH secretion does not seem to play a role in the age-associated decrease in DHEA and DHEAS levels, as GH treatment of adults with isolated GH deficiency does not affect DHEAS levels (35).

It has been proposed that this age-associated decrease in DHEA and DHEAS levels might be induced by the increase in insulin levels (7). Several researchers (6, 7, 36–42) reported an inverse correlation, sometimes limited to males, between insulin and DHEAS levels under various experimental con-

TABLE 5. Hormone levels (mean ± SD) in obese men (n = 50) before and after weight loss and in age-matched nonobese controls

	Nonobese controls	Obese baseline	Obese post-PSMF	Obese, baseline, BMI matched	Obese, post-PSMF, BMI matched
Age	25–62	25–62	25–62	30–56	27–61
Wt	74 ± 8	124 ± 27[a]	109 ± 25	120 ± 17	121 ± 21
BMI	23.7 ± 1.5	40.5 ± 7.2[a]	35.8 ± 7.2[b]	39.5 ± 4.3	38.8 ± 4.9
T	21.28 ± 7.08	14.61 ± 4.9[c]	17.47 ± 6.18[d]	14.29 ± 4.71	16.25 ± 5.62
SHBG	50 ± 11	39 ± 8[c]	59 ± 28[e]	37 ± 14	57 ± 22[f]
FT	0.42 ± 0.13	0.32 ± 0.15	0.31 ± 0.12	0.31 ± 0.11	0.29 ± 0.08
DHEA	16.3 ± 9.8	13.3 ± 8.1[g]	11.2 ± 7.5	11.9 ± 6.9	9.8 ± 8.3
DHEAS	5.85 ± 3.13	4.97 ± 2.87	5.16 ± 3.44	5.24 ± 2.37	4.32 ± 4.67
A	4.05 ± 1.12	5.26 ± 2.41	4.61 ± 1.77	4.93 ± 2.50	4.54 ± 1.61
E_2	122 ± 41	199 ± 74[a]	176 ± 96	201 ± 57	156 ± 61[h]
Insulin	72.6 ± 16.2	200 ± 117[c]	106 ± 86[e]	131 ± 42[g]	130 ± 52[g]
Serum insulin	ND	2660 ± 1461	1735 ± 785[d]	2736 ± 1163	1822 ± 847
GH	1.15 ± 0.29	0.64 ± 0.20[c]	0.73 ± 0.21[c]	0.63 ± 0.19[c]	0.71 ± 0.20[g]
IGF-I	204 ± 111	73 ± 62[c]	120 ± 54[c,d]	75 ± 37[c]	97 ± 72[c]

Steroid and SHBG levels are expressed as nanomoles per L, except E_2 (picomoles per L) and DHEAS (micromoles per L). Insulin are expressed as picomoles per L; IGF-I, and GH as nanograms per mL. Age in years; Wt, weight in Kg.

[a] $P < 0.001$ *vs.* nonobese controls.
[b] $P < 0.001$, after PSMF *vs.* baseline.
[c] $P < 0.01$ *vs.* nonobese controls.
[d] $P < 0.01$ *vs.* 0.05 *vs.* nonobese controls.
[e] $P < 0.01$, after PSMF *vs.* baseline.
[f] $P < 0.05$ *vs.* BMI-matched obese before PSMF.
[g] $P < 0.05$ *vs.* nonobese controls.

TABLE 6. Mean 24-h GH levels, IGF-I, T, and SHBG levels in adult men in relation to age

	Age (yr)		
	25–45 (n = 8)	45–65 (n = 8)	65–85 (n = 8)
mGH (ng/mL)	1.67 ± 0.78	1.23 ± 0.71[a]	0.88 ± 0.26[b]
T (nmol/L)	20.1 ± 5.8	16.4 ± 4.8	13.4 ± 3.3[b]
SHBG (nmol/L)	38.4 ± 14.4	45.4 ± 17.5	60.1 ± 10.3[b]
IGF-I (ng/mL)	203 ± 112	141 ± 68[a]	104 ± 41[b]

[a] $P > 0.05$ *vs.* 25–45 yr age group.
[b] $P < 0.01$ *vs.* 25–45 yr age group.

ditions. Surprisingly, other researchers (43–45) reported, at least in women, a positive correlation between insulin and levels of DHEA and DHEAS. The reported rapid variations in DHEAS levels during an OGTT (37) or euglycemic clamp (46) are, however, surprising in the view of the long half-life (8–11 h) (47) and the low MCR (±15 L/24 h) of DHEAS. In neither our nonobese nor obese population did we observe a significant correlation between fasting insulin and levels of DHEA and DHEAS. We also did not observe a significant correlation between the sum of insulin levels after OGTT and DHEAS levels. Our data are in agreement with those of Leenen *et al.* (48) and Phillips (49). The discrepancy in the literature concerning the relation between insulin and DHEAS levels is difficult to explain, but suggests that another factor(s) might codetermine DHEAS levels. The plasma albumin concentration also influences DHEAS levels, as albumin has a high affinity for DHEAS (2×10^5 L/mol) (50), and there does is no feedback for free DHEAS. Hence, it is not surprising that we observed a positive correlation between DHEAS levels and albumin ($r = 0.27$; $P < 0.01$), which persisted after correction for age and BMI. A similar positive correlation was reported by Tegelman *et al.* (51), whereas Rudman *et al.* (52) reported that both albumin and DHEAS levels were significantly lower in an elderly population residing in a nursing home than in independently community-dwelling men.

A significant age-associated decrease in A levels in our nonobese population was only observed in the group over 75 yr of age, in accordance with data on adrenal reactivity in elderly subjects (53, 54); no correlation with either BMI or insulin levels was observed.

Obese subjects had, as expected, lower SHBG, FT, T, and DHEA levels, but higher E_2 and insulin levels than nonobese controls. After a 6-week hypocaloric protein-rich diet, all subjects had lost weight (mean, 14.7 ± 6.6 kg), but were clearly still obese. Insulin levels, although significantly decreased compared with pretreatment levels, were still elevated, and notwithstanding these elevated levels and the decrease in E_2 levels, the SHBG binding capacity increased to levels comparable with or even higher than those in nondieting weight-stable obese men. At identical BMI, SHBG levels were significantly higher after PSMF than in nondieting weight-stable obese men, although insulin levels were comparable, and E_2 levels were significantly lower after PSMF. Other researchers (22, 55) also observed that during weight loss, SHBG levels increased more than expected from the BMI/SHBG relationship before weight loss. As after weight loss, fasting GH levels as well as IGF-I levels remained below those in nonobese controls ($P < 0.01$), it is tempting to hypothesize that besides the decrease in insulin levels, the low GH and/or IGF-I levels play a role in the elevated SHBG levels.

Notwithstanding the significant decrease in insulin levels after weight loss, DHEA and DHEAS levels as well as A levels did not change significantly, suggesting that insulin is not a major regulator of DHEA and DHEAS levels.

The prevailing hormonal milieu immediately after the PSMF diet is similar to that in elderly men, characterized by moderately increased insulin and SHBG levels, but decreased GH and IGF-I levels. In this context, it is interesting to mention that in *in vitro* studies, Plymate *et al.* (56) as well

TABLE 7. Effects of GH treatment of adult men (n = 8) with isolated GH deficiency (aged 19–29 yr; mean 24 ± 5) on DHEAS, T, FT, IGF-I, and insulin levels

	IGF-I (ng/mL)	Insulin (pmol/L)	DHEAS (μmol/L)	T (nmol/L)	FT (nmol/L)	SHBG (nmol/L)
Basal	88.1 ± 52.1	62.2 ± 22.3	6.44 ± 1.80	28.37 ± 6.84	0.522 ± 0.132	62 ± 17
3 months of treatment	286 ± 120	85.0 ± 18.7	6.09 ± 2.70	26.22 ± 5.31	0.517 ± 0.163	46 ± 19[b]
6 months of treatment	220 ± 60[a]	73.4 ± 30.2	6.64 ± 2.28	23.26 ± 6.53	0.535 ± 0.115	37 ± 12[a]
9 months of treatment	247 ± 44[a]	54.7 ± 21.6	5.30 ± 2.12	24.76 ± 5.14	0.531 ± 0.100	46 ± 11[b]

[a] $P > 0.001$ *vs.* basal values.
[b] $P < 0.01$ *vs.* basal values.

as Singh *et al.* (57) observed that both insulin and IGF-I decrease the rate of SHBG release from hepatocytes.

In conclusion, our data show that in healthy men, all androgen levels decrease with age, although total T levels stay relatively stable until age 55 yr. This age-dependent decline in androgen levels appears to be accentuated by the increase in BMI in elderly subjects, but may be partially masked when data are not corrected for the influence of smoking. The decrease in the serum albumin concentration observed in elderly men may contribute to the age-associated decrease in T and DHEAS levels. Furthermore, our data suggest that GH or IGF-I may be modulators of SHBG levels and that the prevailing low GH/IGF-I levels may explain the age-related increase in the SHBG binding capacity, which occurs despite an increase in insulin levels. Similarly, the prevailing low GH/IGF-I levels may explain the normalization of SHBG levels in obese men during the weight-reducing diet, which occurs despite persisting hyperinsulinism. Finally, our data do not support the hypothesis that insulin is a major determinant of DHEAS levels.

Acknowledgment

We thank Dr. M. Vandeweghe, who provided us with blood samples from adults with isolated GH deficiency before and during GH treatment.

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