

Testosterone Concentrations in Women and Men With NIDDM

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OBJECTIVE — To evaluate androgen concentrations in relation to insulin resistance in men and women with and without NIDDM. Recent studies have indicated the potential importance of the regulation of insulin sensitivity by androgens in both women and men. Low sex hormone binding globulin (SHBG) concentration is an independent risk factor for the development of non-insulin-dependent diabetes mellitus (NIDDM) in women and is strongly associated statistically with signs of insulin resistance.

RESEARCH DESIGN AND METHODS — We compared measurements of anthropometric variables and SHBG, steroid hormone, and insulin concentrations of women and men who have NIDDM with those of control subjects.

RESULTS — Women with NIDDM had somewhat higher plasma insulin concentrations, lower SHBG, and higher free testosterone values than did control subjects with similar body mass index (BMI). Women with NIDDM had marginally higher waist-to-hip ratios (WHR). Plasma insulin concentrations correlated positively with BMI, WHR, and free testosterone and negatively with SHBG. In multivariate analyses, insulin concentrations remained positively associated with BMI and free testosterone. Men with NIDDM had higher fasting plasma insulin concentrations than did the nondiabetic control subjects. Testosterone and SHBG were lower in the diabetic men than in both control groups. The derived value of free testosterone was not different between groups. Univariate correlation analyses revealed tight statistical couplings between plasma insulin on the one hand and SHBG and testosterone concentrations (negative) on the other. In multivariate analyses, only the insulin-testosterone association remained.

CONCLUSIONS — Women with NIDDM have high levels of free testosterone and low levels of SHBG. Insulin resistance is closely correlated with these signs of hyperandrogenicity as well as with obesity. Men with NIDDM also have low levels of SHBG and, in contrast to women, low testosterone values. Insulin values correlate negatively with these hormonal factors. Based on the results of experimental work and intervention studies, we suggest that these androgen abnormalities might be causally related to insulin resistance in NIDDM.

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Received for publication 12 January 1993 and accepted in revised form 2 December 1993.

NIDDM, non-insulin-dependent diabetes mellitus; SHBG, sex hormone binding globulin; BMI, body mass index; WHR, waist-to-hip ratio; WHO, World Health Organization; LBM, lean body mass; DHEA, dihydroepiandrosterone; DHEAS, dihydroepiandrosterone sulfate; E₂, 17- β -estradiol; E₁, estrone.

Insulin resistance is considered to be one of the cornerstones in the state that ultimately leads to clinically established non-insulin-dependent diabetes mellitus (NIDDM) (1–5). The main tissue responsible for this insensitivity to the action of insulin has been believed to be muscle (3,6). However, several studies suggest that the insulin stimulation of nonoxidative metabolic glucose pathways are involved, specifically the synthesis of glycogen (4–7). The rate-limiting enzyme for glycogen synthesis in muscle is glycogen synthase (8). Some studies have shown that steroid hormones, including both adrenal and sex steroid hormones, probably regulate the insulin sensitivity of the glycogen synthase system (9–11).

Hyperandrogenicity is a well-known correlate to insulin resistance in the polycystic ovarian syndrome (with or without concomitant obesity) and in non-diabetic women with abdominal obesity (12,13). The primary factor in this statistical relationship has not been identified (14), but androgen administration has been shown to induce insulin resistance and impaired glucose tolerance in women (15). Moderate increases of testosterone concentrations in female rats are followed by a marked decrease in whole-body insulin sensitivity, localized primarily to glycogen synthesis and glycogen synthase in muscle (9,10). Furthermore, a low sex hormone binding globulin (SHBG) concentration, an indicator of a relative hyperandrogenicity, is a powerful, independent risk factor for the development of NIDDM (16).

With this background, we hypothesized that androgens may be of importance for the development of insulin resistance in women. This insulin resistance might occur in muscle tissue where glycogen synthase, apparently regulated by androgens, may play a key role. An involvement of these factors has been suggested previously by statistical associations with abdominal obesity in women (13), a frequent precursor state to NIDDM (17).

These factors, however, have not been examined in women with clinical NIDDM. Therefore, we evaluated steroid hormone concentrations in relation to insulin concentrations in women with and without NIDDM.

The relation between testosterone and insulin sensitivity in men has been studied much less. Exposure to excess androgens seems to be followed by insulin resistance (18). Also, population studies of men (20,21) confirm that low testosterone values are associated with insulin resistance in men with abdominal obesity (19). The combination of these observations suggests that both too-high and too-low levels of testosterone might be associated with insulin resistance; this is not the case in a "window" of normal testosterone values. This notion is supported by recent work in which we found that castration of male rats is followed by insulin resistance. This resistance is totally alleviated by substitution of testosterone to normal levels but is again seen with doses of testosterone producing higher than normal serum concentrations (22). Furthermore, in nondiabetic men with abdominal obesity, who are insulin resistant in proportion to their relative hypogonadism, substitution with testosterone is followed by an improvement of insulin resistance measured with the hyperinsulinemic, euglycemic glucose clamp technique (23,24). These observations suggest a close statistical interaction between androgens and muscular insulin resistance in men. To our knowledge, however, this problem has not been examined in men with NIDDM. Therefore, we decided to study this question in diabetic men compared with control subjects.

RESEARCH DESIGN AND METHODS

— Women with NIDDM ($n = 39$) were recruited from outpatient diabetes clinics or through an advertisement in a local newspaper. Their diabetes was diagnosed at least 6 months previously and an average of 4.5 years previously. All women were in menopause and no woman was taking hormonal replace-

ment therapy or had a diagnosis of polycystic ovarian syndrome. Other characteristics of this group are found in Table 1. All women reported a stable body weight (<3 kg change) within the preceding 6 months. The patients were treated with diet alone ($n = 21$) or diet together with drugs ($n = 18$). The drugs included sulfonylurea preparations only. The recommended diet consisted of sufficient energy to maintain body weight and a macronutrient distribution of 20:40:40 for percentage of energy as protein, fat, and carbohydrate, respectively, with an intake mainly of slowly absorbed carbohydrate. The diet was prescribed by a dietitian, and patients were examined, on average, every 3 months by a physician confirm that their diabetes was under control.

A group of nondiabetic women of similar age served as control subjects ($n = 20$). These women were recruited as a subgroup from a cohort of women born between 1926–1934 and selected at random from a population register in the city of Göteborg. All women were menopausal. Women taking hormonal replacement therapy ($n = 3$) were excluded. None had a diagnosis of polycystic ovarian syndrome.

Diabetic men ($n = 46$) were recruited by an advertisement in a local newspaper. Their diabetes had the same minimal duration and was treated by diet similar to the women. They were also considered to be in a clinically well-controlled state and of stable weight. None was on drug treatment.

A control group consisted of 11 men with an age range comparable to that of the men with NIDDM. They were nondiabetic as defined by World Health Organization (WHO) criteria (25) and were recruited in the same way as the men with NIDDM. They were apparently healthy by history and physical examination.

The study commenced after the subjects gave their informed consent and after it was approved by the University of Göteborg Ethical Committee.

Body weight of subjects in their

underwear was recorded to the nearest 0.1 kg and height to the nearest centimeter. Based on these measurements, the subjects' body mass indexes (BMIs) [$\text{weight}/(\text{height})^2$, $\text{kg}/(\text{m})^2$] were calculated. Waist and hip circumferences were measured as recommended in a WHO report (26), and waist-to-hip ratios (WHRs) were calculated from those measurements. In the men, sagittal abdominal diameter, which correlates closely with visceral fat mass, was also recorded (27). Lean body mass (LBM) was calculated from total body potassium measured in a whole body counter (28). Body fat was then calculated from LBM and body weight (29). Blood pressure was measured with a mercury manometer in the right arm while subjects were in the supine position after a 5-min rest, and two measurements were averaged. Diastolic blood pressure was recorded at the Korotkoff phase IV.

Venous blood was drawn in the morning after an overnight fast for the determination of blood glucose and serum insulin (analyzed by radioimmunoassay; Phadebas, Pharmacia, Uppsala, Sweden). In men, serum cholesterol and triglycerides were analyzed by automated enzymatic methods. In women, testosterone, Δ -4-androstenedione, dihydroepiandrosterone (DHEA) and its sulfate (DHEAS), 17- β -estradiol (E2), and estrone (E1) were determined with radioimmunoassays (30–32). In the men, testosterone was determined with a nonextraction method using an antiserum against testosterone, coupled to serum albumin at carbon no. 19 (RSL 125 testosterone; ICN Biochemicals, Costa Mesa, CA). SHBG was determined by an immunoradiometric assay (Farma, Diagnostica, Tulunsalo, Finland). The ratio of testosterone:SHBG was used as an index of free testosterone.

The statistical methods used were the Student's t test or analysis of variance (when more than two groups were compared), as available in the statistical package Statview from Macintosh. $P < 0.05$ was considered significant.

Table 1—Anthropometric data, blood pressures, glucose and insulin values in diabetic women and control subjects

	Control subjects	Diabetic women	P values
n	17	39	
Age (years)	60 ± 1	62 ± 1	NS
Body weight (kg)	71.2 ± 2.3	75.5 ± 2.0	NS
Waist circumference (cm)	88.9 ± 3.0	94.9 ± 1.7	0.07
Hip circumference (cm)	103.0 ± 1.3	105.0 ± 1.3	NS
WHR	0.86 ± 0.02	0.90 ± 0.01	0.07
BMI (kg/m ²)	26.8 ± 0.01	28.3 ± 0.01	NS
LBM (kg)	43.5 ± 1.3	40.7 ± 1.1	NS
Body fat (kg)	30.6 ± 1.7	32.0 ± 1.8	NS
Fasting glucose (mM)	4.4 ± 0.2	8.6 ± 0.4	<0.01
Fasting insulin (mU/L)	10.0 ± 2.0	17.0 ± 2.3	0.08

Data are means ± SE.

RESULTS— Table 1 shows the results of the measurements of anthropometry, blood pressures, glucose, and insulin in the diabetic women and control subjects. Age and body weight did not differ significantly between groups. Waist circumference ($P = 0.07$) and WHR ($P = 0.07$) tended to be higher in the diabetic women. BMI, LBM, and body fat were not different. Glucose ($P < 0.01$) was higher and insulin values also tended to be higher in the diabetic women ($P = 0.08$), as expected.

The diabetic women with drug treatment differed from those without drug treatment only with regard to WHR and blood glucose, which were higher in the drug-treated subjects (not shown).

The steroid hormone data are listed in Table 2. Compared with the control subjects, the diabetic women had higher E_1 and derived free testosterone concentrations and lower DHEA and SHBG values. No differences were noted between diabetic women treated or not treated with drugs (not shown).

Univariate correlations were calculated in diabetic and nondiabetic subjects separately. Because the study was designed to analyze the relationship between insulin and anthropometric and steroid hormone data, these measurements were focused on for the correlation

analyses (Table 3). Insulin values showed consistent correlations with BMI, LBM, and derived free testosterone in both diabetic and control subjects (free testosterone only marginally in control subjects). However, although WHR, E_1 , and E_2 concentrations correlated significantly with insulin in control subjects, this was not the case in diabetic women, where a trend to a negative correlation with SHBG was found.

Glucose values showed no significant correlations with body composition or anthropometric variables. Significant correlations were found with E_2 and free testosterone and with E_1 and E_2 in control subjects. Free testosterone correlated sig-

nificantly and positively with LBM and E_2 and negatively with SHBG in both diabetic and control subjects. In control subjects, positive correlations also were found with BMI (borderline) and WHR. SHBG correlated strongly and negatively with free testosterone and showed essentially the same negative relationships as free testosterone with the other variables. Exceptions were a lack of correlation with E_2 . Androstenedione correlated with LBM ($r = 0.53$, $P < 0.05$) in the diabetic group. Finally, DHEA, DHEAS, total testosterone, and androstenedione did not correlate significantly with anthropometric, glucose, or insulin values (not shown).

Because of the intercorrelations between insulin and the anthropometric clusters of observations (BMI, WHR, LBM), as well as with the steroid hormones, these observations were subjected to multivariate regression analysis to determine which anthropometric and hormonal factors correlated independently with insulin. For the diabetic women, the strongest positive independent correlations with insulin were BMI ($r = 0.41$, $P < 0.01$) and derived free testosterone ($r = 0.32$, $P < 0.05$). In control subjects, however, glucose ($r = 0.87$, $P < 0.01$) and E_2 ($r = 0.89$, $P < 0.001$) were the strongest independent correlates of insulin, after adjusting for the other factors.

Table 4 shows the anthropometric, metabolic, and hormonal data for

Table 2—Steroid hormone values in diabetic women and control subjects

	Control subjects	Diabetic women	P values
n	17	39	
Estrone (ng/100 ml)	3.92 ± 0.39	5.82 ± 0.56	<0.05
17- β -estradiol (ng/100 ml)	1.72 ± 0.17	1.50 ± 0.10	NS
Androstenedione (ng/100 ml)	85.7 ± 9.7	71.6 ± 4.9	NS
DHEA (ng/100 ml)	378 ± 30	229 ± 28	<0.01
DHEAS (ng/100 ml)	68 ± 12	53 ± 4	NS
Total testosterone (ng/100 ml)	26.0 ± 2.7	24.7 ± 2.5	NS
Free testosterone	3.14 ± 0.76	5.86 ± 0.76	<0.05
SHBG (mole $\times 10^8$)	13.1 ± 1.82	5.59 ± 0.46	<0.001

Data are means ± SE. Free testosterone calculated as the molar ratio of total testosterone:SHBG.

Table 3—Selected correlations between variables in diabetic women and control subjects

	Insulin	Glucose	Free testosterone	SHBG
BMI				
NIDDM	0.53*	0.21	0.43	−0.38†
Control	0.64‡	0.23	0.49§	−0.53†
WHR				
NIDDM	0.17	0.19	0.12	−0.33†
Control	0.48†	0.24	0.57†	−0.33
LBM				
NIDDM	0.49†	0.33	0.69*	−0.42§
Control	0.65*	0.32	0.75*	−0.59†
Free testosterone				
NIDDM	0.41‡	0.30	—	−0.61*
Control	0.49§	0.57†	—	−0.72‡
SHBG				
NIDDM	−0.32§	−0.22	−0.61*	—
Control	−0.41	−0.27	−0.72‡	—
E ₁				
NIDDM	0.07	−0.06	0.22	−0.12
Control	0.72‡	0.49†	0.37	−0.38
E ₂				
NIDDM	0.14	0.05	0.38†	−0.19
Control	0.88*	0.69†	0.52†	−0.35

* $P < 0.001$. † $P < 0.05$. ‡ $P < 0.01$. § $0.05 < P < 0.10$.

men. The groups of control subjects and men with NIDDM were not different in age, BMI, cholesterol, or blood pressure. WHR and abdominal sagittal diameter were significantly higher in the group of diabetic men compared with control subjects. Insulin, glucose, and triglyceride values were higher in the diabetic men than in the nondiabetic group. Both testosterone and SHBG concentrations were found to be lower in the diabetic men. Testosterone:SHBG was not significantly different. Correlation analyses were performed where insulin values were treated as independent variables. Testosterone and SHBG concentrations correlated significantly and negatively with insulin (r values = 0.72–0.80, $P < 0.001$).

CONCLUSIONS— Women with NIDDM had higher values of derived free testosterone and lower SHBG than did control subjects. Although age and BMI did not differ in diabetic versus control subjects, the WHR was marginally higher

in the diabetic women, particularly those who were treated with drugs. This finding is similar to results reported previously in diabetic men (33). Insulin and WHR are

closely related (13,16,17,34), and although insulin correlated independently with derived free testosterone in multivariate analyses, obesity factors were also related to insulin.

These results indicate that women with NIDDM have higher concentrations of testosterone, and low SHBG values (which suggests a relative hyperandrogenicity), that correlate strongly and independently with insulin values. Hyperandrogenicity was also closely statistically related to an elevated WHR. Such tight statistical relationships between WHR, insulin, and a low SHBG previously have been found in a population study of nondiabetic women selected at random (16).

Thus, the coupling between diabetes and hyperandrogenicity apparently is found not only in specific syndromes, such as the polycystic ovary syndrome (34–36), but also in women with ordinary NIDDM. It seems that the hyperandrogenicity is related to the plasma insulin concentrations, which probably are an index of insulin resistance.

Estrone levels were higher in diabetic women. This has been found previously in postmenopausal, insulin-dependent diabetic women (37–39). In nondiabetic postmenopausal women, the

Table 4—Age, anthropometric and metabolic variables, blood pressure, and concentrations of testosterone and SHBG in normal and NIDDM men

	Normal men	NIDDM men	P value
n	11	46	
Age (years)	57.2 ± 2.2	56.3 ± 2.1	NS
BMI (kg/m ²)	25.1 ± 0.6	26.8 ± 0.7	NS
WHR	0.904 ± 0.009	0.993 ± 0.015	<0.05
Sagittal diameter (cm)	21.6 ± 0.6	24.0 ± 0.6	<0.5
Insulin (mU/L)	6.5 ± 0.4	18.5 ± 1.8	<0.05
Glucose (mM)	4.9 ± 0.6	9.1 ± 0.7	<0.05
Cholesterol (mM)	5.8 ± 0.3	5.3 ± 0.2	NS
Triglycerides (mM)	1.5 ± 0.2	2.3 ± 0.3	<0.05
Systolic blood pressure (mmHg)	129 ± 4	137 ± 3	NS
Diastolic blood pressure (mmHg)	79 ± 3	79 ± 2	NS
Total testosterone (nM)	22.6 ± 3.2	16.0 ± 1.1	≤0.05
SHBG (nM)	41.3 ± 5.9	25.0 ± 2.4	<0.05
Free testosterone	0.644 ± 0.05	0.712 ± 0.07	NS

Data are means ± SE. Free testosterone calculated as the molar ratio of total testosterone:SHBG.

source of circulating estrogens is the peripheral conversion of androstenedione to estrone (40–42), which, at least in part, takes place in adipose tissue (42). Estrogen concentrations in serum, however, were not related to the measurements of adipose tissue mass in this study. Furthermore, adrenal androgens were not elevated; in fact, DHEA was lower in diabetic women. Why estrone concentrations were elevated in the diabetic women is not clear.

Another rather striking relationship was the strong positive correlation between insulin and both estrone and 17- β -estradiol that was found only in the nondiabetic women. We presume that these estrogens are derived mainly from adrenal precursors in these women, but no relationships between these precursors and insulin were seen. The relationships between estrogens and insulin are difficult to interpret with the data currently available and require additional studies.

There was a strong correlation between LBM and free testosterone, and this was observed in both normal and diabetic women. Testosterone is known to have anabolic effects, including increasing LBM, particularly muscle (43). These data suggest that free testosterone might be an important factor regulating LBM in women.

Any potential cause-effect sequence between these statistically correlated factors must remain speculative. The relationship between insulin and hyperandrogenism has been observed repeatedly before, although not in women with ordinary NIDDM. Several arguments suggest that hyperinsulinemia may cause increased androgen production, and amelioration of hyperandrogenism is, in the polycystic ovary syndrome, usually not followed by normal insulin sensitivity (14). Hyperandrogenism may possibly cause insulin resistance. Supporting the latter alternative are observations that women receiving anabolic steroids develop insulin resistance (15). Furthermore, we have demonstrated previously

that small doses of testosterone cause a dramatic insulin resistance in female rats, seemingly because of an effect at the level of glycogen synthase in muscle (9,10). It is then possible that hyperandrogenicity in women, via an effect on muscle, decreases insulin sensitivity. Whether or not this is the correct alternative can only be determined by intervention experiments that alleviate the hyperandrogenicity in insulin-resistant women with or without NIDDM.

Further research in this area is important because of the therapeutic implications for NIDDM, where insulin resistance is a common phenomenon that hampers effective therapy. Furthermore, hyperandrogenicity, as indicated by a low SHBG, is a strong, independent risk factor for NIDDM in women (16), which raises interesting possibilities for screening women at risk for NIDDM.

Fasting serum insulin values were higher in men with NIDDM than in the normal men, which indicates insulin resistance. Insulin resistance and the elevated triglycerides also found in this study are well-established associates to NIDDM.

Testosterone and SHBG concentrations were lower in men with NIDDM than in control subjects. Lower testosterone and SHBG values have been reported previously in men with an excess of body fat in the abdomen (19–21).

The low testosterone concentrations suggest that NIDDM in men is associated with a relative hypogonadism. This finding is in agreement with another study (44). The signs of hypogonadism were statistically closely associated with fasting insulin values, indicating a coupling to insulin resistance. The testosterone:SHBG ratio provides an estimation of the fraction of free, active testosterone (45). This ratio was, however, not different between control subjects and men with NIDDM. An alternate explanation to the findings might therefore be discussed. Insulin is known to diminish SHBG production in the liver (46). Therefore, hyperinsulinemia may be associated with

low SHBG levels, which in turn influence testosterone. It can therefore not be discounted that insulin resistance with hyperinsulinemia is the primary event, followed by changes in testosterone and SHBG concentrations.

In previous experiments in a rat model, we showed that castration is followed by a marked insulin resistance, which is fully restituted to normal by testosterone substitution (22). Furthermore, men with abdominal obesity have an increased risk of developing NIDDM (47). They are characterized by a relative hypogonadism tightly coupled statistically to insulin resistance (19–21). Testosterone has been administered to such men and results in an improvement of their insulin resistance (23,24). These results in prediabetic conditions suggest that testosterone is partly regulating insulin sensitivity. In analogy, the possibility should be considered that a relative hypogonadism in men with NIDDM may contribute to their insulin resistance.

Taken together, the results in women and men with NIDDM indicate that women are hyperandrogenic and men might be relatively hypogonadal. Both conditions are statistically associated with insulin resistance. Data from experimental work as well as from intervention studies suggest the possibility of a cause-effect relationship with insulin resistance. This possibility needs more attention.

Acknowledgments— This study was supported by the Swedish Medical Research Council (B 93–19X-251), Asker's Foundation, and the Research Fund of Hjalmar Svensson.

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