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Association between Plasma Total Testosterone and Cardiovascular Risk Factors in Healthy Adult Men: The Telecom Study*

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ABSTRACT

The associations between androgens and cardiovascular risk factors in men are controversial. A nested case-control study was used to compare the levels of cardiovascular risk factors in two groups (n = 25 each) of healthy men contrasted by their plasma total testosterone (PTT) concentration, matched by age and ethnic origin.

Compared to the men with normal PTT (mean ± SEM, 19.8 ± 0.7 nmol/L), the men with low PTT (10.1 ± 0.3 nmol/L) had a significantly higher body mass index ($P < 0.01$), waist/hip ratio ($P < 0.001$), systolic blood pressure ($P < 0.05$), fasting and 2-h plasma glucose ($P < 0.04$ and $P < 0.02$ respectively), serum triglycerides ($P < 0.001$), total cholesterol ($P < 0.04$), low density lipoprotein cholesterol ($P < 0.01$), apolipoprotein B ($P < 0.01$), fasting and 2-h plasma insulin (both $P < 0.0001$), and lower values of serum high density lipoprotein cholesterol ($P < 0.01$) and apolipoprotein A1 ($P < 0.05$). After adjustment for both body mass index and waist/hip ratio, fasting and 2-h plasma insulin and triglyceride levels remained significantly different between the two groups ($P < 0.04$, $P < 0.001$, and $P < 0.03$ respectively).

Plasma sex hormone-binding globulin was markedly decreased in the low PTT group ($P < 0.0001$), whereas bioavailable testosterone was not significantly different.

This case-control study provides further and stronger evidence of a negative association between PTT and plasma insulin in men, as suggested by cross-sectional studies. Because these are observational data, neither causality nor the direction of the associations among PTT, sex hormone-binding globulin, and insulin sensitivity can be determined. Intervention studies are needed to better assess the metabolic and cardiovascular benefits of androgen treatment that have been suggested by preliminary clinical trials. (*J Clin Endocrinol Metab* **82:** 682–685, 1997)

FOR A LONG time, androgens have been considered to decrease glucose tolerance, induce hyperinsulinemia, and increase cardiovascular risk in women (1) as well as in men (2). Recently, these effects have been questioned in men. Indeed, from recent cross-sectional studies in healthy men, lower plasma total testosterone (PTT) levels seem to be associated with hyperinsulinemia, decreased glucose tolerance, and a higher level of cardiovascular risk factors (3–5). To investigate the role of endogenous testosterone and sex hormone-binding globulin (SHBG) in the association between sex hormones and cardiovascular risk factors in healthy males, in 1992–1993 we selected from the large male occupation-based population examined in the Telecom Study in 1985–1987 (3, 6), two groups of men contrasted by their PTT concentrations to compare their levels of cardiovascular risk factors, plasma SHBG, and plasma bioavailable testosterone.

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Materials and Methods

Study design

This study used a nested case-control design. The levels of plasma SHBG, plasma bioavailable testosterone, and cardiovascular risk factors were compared between males with low and normal PTT. As age and ethnicity influence cardiovascular risk factors (7–9), the subjects were matched on these covariates (±1 yr for age).

Selection of subjects

For the low PTT group, we selected healthy men not treated for diabetes, dyslipidemia, or hypertension from the lower percentiles of the PTT distribution of the 1718 adult men who participated in the cross-sectional study of 1985–1987 (3, 6). We recruited all healthy men with PTT levels of 11.8 nmol/L or less in 1985–1987 who could be traced and who agreed to be reexamined in 1992–1993. The fifth percentile of the PTT distribution in the background population was 11.8 nmol/L (Fig. 1) (6). Because of the large PTT intraindividual variability (10), for subjects to be classed into the low PTT group we only selected men who also had a low PTT level (≤13.2 nmol/L) at the examination in 1992–1993, with normal levels of plasma PRL, estradiol, and gonadotropins.

When a case with a confirmed low PTT level had been included, we then recruited a matched control subject, with PTT levels between 17.3–24.3 nmol/L in 1985–1987 and 13.9–28.4 nmol/L in 1992–1993. When several controls were available for a given case, we systematically chose the control who had been examined at the date closest to that of the case in 1985–1987.

To obtain the *a priori* calculated sample size of 25 men by group (see *Statistical methods*), we contacted 147 subjects (65 with low PTT in 1985–1987 and 82 with normal PTT in 1985–1987). The reasons for noninclusion are summarized in Table 1.

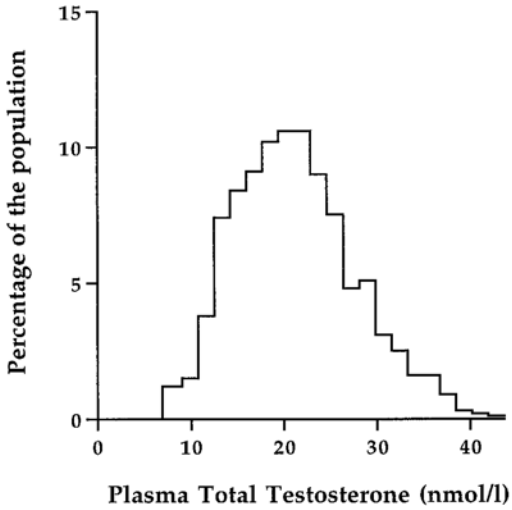

FIG. 1. Distribution of plasma total testosterone in men of the background population (Telecom Study in 1985–1987; n = 1718).

TABLE 1. Selection of subjects: reasons for noninclusion in low and normal PTT groups in 1992–1993 (n = 40 and 57, respectively)

Low PTT in 1985–1987	Normal PTT in 1985–1987
Dead: 1	Dead: 2
Treatment for hypertension: 4	Treatment for hypertension: 2
Treatment for dyslipidemia: 4	Treatment for dyslipidemia: 6
Treatment for diabetes: 3	Treatment by NSAID: 6
Treatment by NSAID: 2	Treatment by HMG: 1
Refusals: 10	Influenza: 1
PTT >13.2 nmol/L in 1992–1993: 16	HIV positive: 1
	Refusals: 20
	PTT <13.9 nmol/L in 1992–1993: 18

NSAID, Nonsteroid antiinflammatory drugs; HMG, human menopausal gonadotropins.

Evaluation of men

The men were examined between July 1992 and April 1993. They gave informed written consent and were examined by a physician who was blind as to the case or control status. Height, weight, and waist and hip circumferences were measured with the subject wearing only underpants to calculate the body mass index (BMI; kilograms per m^2) and the waist/hip ratio (WHR). Blood pressure was measured in the supine position after a 10-min rest. Drug, alcohol, and tobacco consumption was also recorded. Blood was drawn between 0830–0930 h after an overnight fast for the assay of fasting plasma glucose and insulin, sex hormones, serum cholesterol [total and high density lipoprotein (HDL)], lipoproteins [apolipoprotein A1 (Apo A1) and Apo B] and triglycerides. Low density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula (11). After a standard 75-g oral glucose tolerance test, 2-h plasma glucose and insulin levels were also assayed. The protocol had been approved by the Henri Mondor Hospital ethics committee.

Laboratory measurements

Plasma glucose was assayed the day of venipuncture, using the glucose oxidase method. Serum total cholesterol, HDL cholesterol, Apo A1, Apo B, and triglycerides were measured within 2 days after venipuncture. After centrifugation, plasma was separated and frozen at −20 C until the hormones were assayed an average of 8 days later: PTT by RIA after column chromatography on Celite (intraassay coefficients of variation, 8.3% and 7.6%; interassay coefficients of variation, 9.5% and 10.6% at PTT levels of 7.6 and 19.1 nmol/L, respectively) (12), plasma bioavailable testosterone by RIA on the supernatant obtained after precipitation of SHBG by half-saturated ammonium sulfate (5.5% intraassay and 5.7% interassay coefficients of variation at a bioavailable testosterone level of 7.6 nmol/L) (13), SHBG by electroimmunodiffusion using the kit SBP-Film (Sebia, Issy-les-Moulineaux, France; intraassay coefficients of variation, 6.2% and 2.5%; interassay coefficients of variation, 9.1% and 9.4% at SHBG levels of 16.2 and 39.3 nmol/L, respectively) (14), and plasma insulin by RIA using the INSI-PR method (CIS Bio-Industrie, Gif-sur-Yvette, France; intraassay coefficients of variation, 13.7% and 5.8% interassay coefficients of variation, 8.0% and 8.6%; at insulin levels of 72 and 118 pmol/L, respectively). The only missing data was one 2-h plasma insulin measurement in the low PTT group.

TABLE 2. Comparison of clinical features between the low and normal PTT groups in 1992–1993

	Low PTT (n = 25)	Normal PTT (n = 25)	*P*
Age (yr)	51.4 ± 2.1	51.6 ± 2.0	<0.95
Ethnic group (A/C)[a]	3/22	3/22	1
Body mass index (kg/m^2)	26.7 ± 0.5	23.9 ± 0.6	<0.01
Waist/hip ratio	0.96 ± 0.01	0.91 ± 0.01	<0.001
Systolic blood pressure (mm Hg)	139 ± 4	129 ± 3	<0.05
Diastolic blood pressure (mm Hg)	84 ± 2	80 ± 2	<0.26
Smokers (%)	28	20	<0.52
Alcohol consumption (g/day)	25.4 ± 16.0	23.1 ± 21.2	<0.67

Data are the mean ± SEM number of subjects for ethnic group and percentage for smokers.

[a] A, Afro-Caribbeans; C, Caucasians.

Statistical methods

The sample size of 25 subjects by group was adequate to detect a 1 SD difference for fasting plasma insulin between groups using an unpaired two-sided *t* test with type I and type II errors of 0.05.

Quantitative parameters were compared using nonparametric Kruskal-Wallis tests and analysis of covariance with adjustments for both BMI and WHR when no interaction was found between the level of PTT and these covariates. The level of statistical significance was set at 0.05. The mean ± SEM are given or the geometric mean (95% confidence interval of the mean) for the parameters with a distribution skewed to the right. Statistical analyses used SAS software (15).

Results

As expected from the study design, the two groups of men had different PTT levels (10.1 ± 0.3 *vs.* 19.8 ± 0.7 nmol/L; $P < 0.0001$), but identical age and ethnic composition (Table 2). Significant differences were observed for BMI ($P < 0.01$), WHR ($P < 0.001$), and systolic blood pressure ($P < 0.05$), which were higher in the low PTT group (Table 2).

All of the metabolic cardiovascular risk factors were increased in the low PTT group (Table 3). The subjects with low PTT had significantly higher fasting and 2-h plasma glucose, serum triglycerides, total cholesterol, LDL cholesterol, and Apo B lipoprotein and significantly lower HDL cholesterol and Apo A1 lipoprotein levels. Major differences were also seen for fasting and 2-h plasma insulin levels, which were higher in the low PTT group [68.6 (95% confidence interval of the mean, 57.1–82.6) *vs.* 40.3 (34.8–46.6) pmol/L ($P < 0.0001$) and 413.8 (314.6–544.1) *vs.* 147.1 (110.2–196.3) pmol/L ($P < 0.0001$), respectively; Table 3].

After adjustment for both BMI and WHR, fasting and 2-h plasma insulin levels remained significantly higher in the low PTT group [59.4 (51.1–68.9) *vs.* 46.6 (40.1–54.1) pmol/L ($P < 0.04$) and 391.0 (286.7–533.1) *vs.* 155.3 (114.7–210.2)

TABLE 3. Comparison of metabolic cardiovascular risk factors and plasma insulin between the low and normal PTT groups in 1992–1993

	Low PTT (n = 25)	Normal PTT (n = 25)	*P*
Fasting plasma glucose (mmol/L)	5.0 ± 0.1	4.8 ± 0.1	<0.04
2-h plasma glucose (mmol/L)	5.8 ± 0.4	4.7 ± 0.2	<0.02
Triglycerides (mmol/L)	1.45 (1.23–1.72)	0.93 (0.79–1.09)	<0.001
Total cholesterol (mmol/L)	5.87 ± 0.17	5.24 ± 0.24	<0.04
HDL cholesterol (mmol/L)	1.21 ± 0.06	1.46 ± 0.07	<0.01
LDL cholesterol (mmol/L)	4.34 ± 0.16	3.58 ± 0.23	<0.01
Apo A1 lipoprotein (mmol/L)	1.50 ± 0.06	1.67 ± 0.06	<0.05
Apo B lipoprotein (mmol/L)	1.40 ± 0.04	1.19 ± 0.06	<0.01
Fasting plasma insulin (pmol/L)	68.6 (57.1–82.6)	40.3 (34.8–46.6)	<0.0001
2-h plasma insulin (pmol/L)	413.8 (314.6–544.1)	147.1 (110.2–196.3)	<0.0001

Data are the mean ± SEM or geometric means (95% confidence intervals of the mean).

pmol/L ($P < 0.001$), respectively]. Triglycerides also remained significantly higher in the low PTT group [1.35 (1.13–1.61) *vs.* 1.00 (0.84–1.19) mmol/L; $P < 0.03$]. The differences were not statistically significant for the other variables.

We observed by univariate analysis a lower level of plasma SHBG in the low PTT group (20.0 ± 1.5 *vs.* 37.8 ± 1.6 nmol/L; $P < 0.0001$), whereas plasma bioavailable testosterone did not differ between the two PTT groups [6.9 ± 0.5 *vs.* 7.1 ± 0.5 nmol/L; $P < 0.84$). Adjustment for BMI and WHR did not modify the differences for plasma SHBG ($P < 0.0001$) and bioavailable testosterone ($P < 0.97$).

No significant difference was found for estrogens and gonadotropins between the two PTT groups [29.0 ± 2.0 *vs.* 28.5 ± 1.6 pg/mL ($P < 0.93$) for estrone, 18.2 ± 0.8 *vs.* 19.6 ± 1.1 pg/mL ($P < 0.28$) for estradiol, 3.2 (1.1–8.9) *vs.* 3.7 (1–14) U/L ($P < 0.12$) for FSH, and 2.3 (0.6–9.7) *vs.* 3.1 (1.2–7.9) U/L for LH, for low and normal PTT groups, respectively].

Discussion

From a healthy male population, systematic PTT measurements permitted the selection of two groups of men with different levels of PTT, matched by age and ethnic origin. Our data confirm the negative association between PTT and plasma insulin in men, previously described in cross-sectional studies (3–5). However, it provides stronger evidence for this relationship because this study was designed to verify the *a priori* hypothesis of a negative association between PTT and cardiovascular risk factors, mainly insulin, in men and because the PTT level was used as the only selection criterion in this nested case-control study and was evaluated by two measurements separated by 5–7 yr. Therefore, the probability of a chance finding was very low.

The recruitment of the background population was occupation-based and consisted of volunteers, probably more representative of healthy people than most samples in sex hormone studies that are often based on patient populations consulting for diseases or sexual dysfunctions. The process of subject selection in this case-control study appears not to have biased the relationship between androgen levels and cardiovascular risk factors in the sense of an overestimation. On the contrary, it has probably underestimated the difference in the level of cardiovascular risk factors between the two groups; 11 of 65 (16.9%) subjects were not included in the low PTT group because of treatment for diabetes, dyslipidemia, or hypertension *vs.* only 8 of 82 (9.8%) subjects in the normal PTT group. The refusal rate was not significantly different between the low (15.4%) and normal (24.4%) PTT groups. Therefore, the relationship between low PTT and reduced insulin sensitivity that we observed in this case-control study can probably be extrapolated to individuals in the lowest percentiles of the PTT distribution of a general male population.

It can be hypothesized that the link between PTT level and insulin sensitivity in men is mediated by the body fat distribution. Indeed, a low PTT level has been shown to predict abdominal adiposity in men (16), and central obesity is related to alterations in carbohydrate and lipid metabolism (17) as well as to cardiovascular disease and mortality in men (18) via a putative mechanism involving portal free fatty acids (19). If low PTT is responsible for an abdominal distribution of body fat, adjusting for WHR to assess the relationship between PTT and cardiovascular risk factors can be considered an overadjustment, but, indeed, adjusting for BMI alone was sufficient to decrease the differences in the classical cardiovascular risk factors to nonsignificant levels, except for insulin and triglycerides.

The respective roles of PTT, plasma free testosterone, and SHBG in the relationship between sex hormones and insulin sensitivity should be more closely evaluated in men. Our data can be interpreted by hypothesizing that the link between PTT and plasma insulin is explained by a negative association between SHBG and plasma insulin; low PTT could be due to low SHBG, which could explain the similar levels of bioavailable testosterone in the two groups, in the middle of the normal range for healthy adult men in our laboratory (3.5–12.8 nmol/L) (13). Indeed, SHBG has been shown to be positively correlated with PTT in men (20), and in type 2 diabetic men, a stronger positive correlation has been found between sensitivity to insulin and SHBG levels than to PTT levels (21). Moreover, in MRFIT, a decreased SHBG concentration has recently been found to be a risk factor for insulin resistance and noninsulin-dependent diabetes mellitus in men (22), but this association has not been observed in other male populations (23). On the other hand, it can also be hypothesized that a low PTT level induces hyperinsulinism, which, in turn, is the cause of the low SHBG level; insulin is known to inhibit the production and secretion of SHBG *in vitro* (24), whereas insulin pulses (25) and the portal insulin concentration (26) appear to regulate SHBG production in men. In this hypothesis, a low PTT level could be the cause and not the consequence of a low SHBG level.

To clarify these complex relationships among PTT, free

and bioavailable testosterone, SHBG, insulin, and cardiovascular risk factors in men, intervention studies are needed. Up to now, few clinical trials have been performed, and these studied small samples of middle-aged obese men with slightly decreased PTT levels. They have shown marked effects of androgens on adipose tissue metabolism, with trends for a reduction of abdominal fat tissue and an improvement in insulin sensitivity and lipid metabolism (27, 28). After short term androgen treatment, normal healthy men have also shown a tendency for a decrease in insulin response curves (29) and a decline in total and LDL cholesterol (30). These preliminary data support the hypothesis that a causal relationship could explain the association we have shown between low PTT and insulin resistance. Additional larger clinical trials are needed in healthy adult men with low PTT concentrations to further investigate the metabolic and cardiovascular benefits of androgen treatment and its cost-effectiveness.

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