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Part of the Interindividual Variation in Serum Testosterone Levels in Healthy Men Reflects Differences in Androgen Sensitivity and Feedback Set Point: Contribution of the Androgen Receptor Polyglutamine Tract Polymorphism

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Context: There is a large interindividual variation in serum (free) testosterone (FT) levels in men, underlain in part by genetic components.

Objective: The objective of the study was to explore the hypothesis that this variability results in part from differences in androgen sensitivity and feedback loop set point and assess the role of the *androgen receptor (AR)* polyglutamine tract polymorphism encoded by a CAG repeat of variable length in exon 1 of the AR gene.

Design/Setting/Participants: We performed a cross-sectional analysis in two independent populations of healthy men, consisting of 2322 men aged 35–59 yr (Belstress study) and 358 men aged 25–45 yr (Siblos study), respectively.

Main Outcome Measures: Serum hormonal levels and the *AR* gene CAG repeat length were determined.

Results: In the Belstress population, serum testosterone and calculated FT showed a positive linear association with LH ($P < 0.001$). In the 200 men with lowest FT, CAG repeat number was lower than in the 200 men with highest FT ($P = 0.004$). As studied in a larger subset of the population consisting of 857 men covering the whole FT range, FT increased progressively with CAG repeat length ($P = 0.003$). These findings of a positive relation of FT with both LH and CAG repeat length were confirmed in the Siblos study population (both $P \leq 0.001$). Difference in FT between extreme quartiles of CAG repeat was 10 and 14% in the Belstress and Siblos study, respectively. In both study populations, CAG repeat length was also positively associated with serum total testosterone ($P \leq 0.004$).

Conclusions: The data support the view that between-subject variability in serum FT in healthy men is underlain in part by differences in androgen sensitivity and feedback set point, with a contributory role of *AR* polymorphism. These findings have potential implications for the interpretation of epidemiological studies, diagnosis of hypogonadism, and pharmacogenetics of androgen treatment in men. **(*J Clin Endocrinol Metab* 92: 3604–3610, 2007)**

THERE IS A LARGE interindividual variation of serum total and free testosterone (T and FT) levels at all ages in healthy adult men. The physiological basis and clinical significance of this phenomenon is still poorly understood. Whereas lifestyle-related factors such as adiposity and smoking (1, 2), besides other modifiable factors, are known to contribute to this between-subject variation (3), studies in twins indicate a substantial genetic component in the determination of T blood levels (4, 5). Consistent with the latter findings are observations that, notwithstanding the moment-to-moment variations entrained by episodic pituitary LH secretion, mean serum (F)T levels in individual men tend to remain rather stable over the mid to long term (6–8).

Serum T is regulated through the hypothalamic-pituitary-gonadal feedback loop. In this study we explored the hypothesis that differences in feedback loop set point contribute to interindividual variation in serum T, with part of the between-subject differences in serum T reflecting genetically determined, subtle differences in androgen sensitivity. To this end, we assessed in healthy adult men the relationship between serum LH and (F)T and the influence of the CAG repeat polymorphism in the *androgen receptor* (*AR*) gene, one of the more obvious candidate genes that might contribute to the genetic component of between-subject variability of serum T.

As to the relationship between serum LH and (F)T, the premise was that the finding of a positive association is compatible with a genetic effect modulating androgen sensitivity. Indeed, a same serum (F)T level will result in a lesser feedback suppression of serum LH in a men with relatively lower androgen sensitivity, which in turn will result in increased LH levels and a consequent increase of serum (F)T; both LH and (F)T are thus expected to increase with decreasing androgen sensitivity. On the other hand, in the absence of differences in androgen sensitivity, genetic factors affecting testicular responsiveness to LH and Leydig cell

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Abbreviations: ANCOVA, Analysis of covariance; AR, androgen receptor; BMI, body mass index; E_2, estradiol; FT, free T; HDL, high-density lipoprotein; T, testosterone.

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secretory capacity or the rate of inactivating T metabolism would rather be expected to result in no or a negative association between LH and (F)T. Indeed, men with a relatively lower Leydig cell responsiveness to LH or with increased T catabolism would require higher circulating LH to maintain a same level of serum (F)T in accordance with the feedback set point; this would result in no association between (F)T and LH or in a negative association if Leydig cell secretory capacity is a limiting factor.

Furthermore, we assessed the influence of the CAG repeat polymorphism in exon 1 of the *AR*. This trinucleotide repeat encodes a highly polymorphic polyglutamine tract, and its length has been reported to be inversely associated with *AR* transactivation (9). This CAG repeat polymorphism might affect androgen action (10) and thus contribute to the variability of serum T levels through modulation of the negative feedback control of the hypothalamic-pituitary-testicular axis. The CAG repeat length has been associated with a series of androgen-related clinical effects (11, 12), whereas information about its effect on circulating T levels is surprisingly scarce (13, 14).

The issue whether interindividual variation in serum (F)T in healthy men reflects differences in androgen sensitivity has potentially far-reaching implications, *e.g.* for a correct interpretation of epidemiological data on clinical correlates of serum T levels in men, for the diagnosis of hypoandrogenism in both young and elderly men, or eventually for individualization and optimization of T replacement therapy.

In the present study, the foregoing hypothesis that part of the interindividual variation of serum (F)T in healthy men reflects subtle differences in feedback loop set point with a contributory role of the CAG repeat polymorphism of the *AR*, was explored in two independent populations of healthy adult men.

Subjects and Methods

Study populations

Belstress population. This study was performed in a subsample of the Belstress project, a work-floor-based study focused on job stress, cardiovascular and other health issues, and sickness absence. Objectives, design, and methodology of the Belstress project have been extensively described elsewhere (15). The subsample used for this study included 2322 male subjects aged 35–59 yr, selected according to two main criteria, *i.e.* serum sampled before 1000 h and from companies located in Ghent or its neighborhood. All participants signed an informed consent and completed questionnaires. Exclusion criteria comprised potentially interfering medication or extreme low T levels (≤45 ng/dl). The relationship between serum (F)T and LH levels was studied in the whole study population of 2322 men. The impact of the AR gene CAG polymorphism was assessed in the 200 men with lowest FT, compared with the 200 men with highest FT as well as in a subset of 857 men representative of the whole FT range in the study population.

Siblos population. In the Siblos study, young men were recruited from population lists of semirural communities around Ghent (Belgium) to participate in a sibling-pair study on genetic contribution to the determination of bone mass, sex steroids, and their interaction. The primary condition to be recruited was to have a brother in the same age range also willing to participate. Exclusion criteria were defined as illnesses or medication use that may affect sex steroid levels, body composition, and bone metabolisms. After applying exclusion criteria, 276 pairs, 17 triplets, and two quartets of dizygotic brothers were included in the study; furthermore, 63 men were included as single participants when their brother could not participate in the study due to the presence of an exclusion criterion.

For the present cross-sectional analysis, we used a group of 358 unrelated men consisting of one randomly chosen brother (n = 295) of each pair, triplet, or quartet and the 63 single participants. All men were in good health and completed questionnaires about previous illness and smoking. The study protocol was approved by the ethical committee of the Ghent University Hospital, and a written informed consent was obtained from all participants.

Hormonal assays

Serum was obtained between 0800 and 1000 h and stored at −80 C until analysis. Commercial direct immunoassays were used to determine serum levels of LH (ECLIA; Roche Diagnostics, Mannheim, Germany), estradiol (E_2) (clinical assay; DiaSorin s.r.l., Saluggia, Italy, according to a modified protocol with doubling the amount of serum), total T, and SHBG (Orion Diagnostica, Espoo, Finland). Serum FT was calculated from serum total T, SHBG, and albumin concentrations using a previously validated equation (16, 17). For all measurements, intra- and interassay coefficients of variation were less than 10 and 15%, respectively; in particular interassay coefficient of variation was 7.5% for T (at a mean concentration of 320 ng/dl), 3.8% for SHBG (at a mean concentration of 39.7 nmol/liter), and was between 8.7 and 14.2% for FT (as calculated for two series of 10 assay runs each at a mean concentration of 13 ng/dl) (to convert T and FT to nanomoles per liter, multiply by 0.0347).

Genotyping

Genomic DNA was extracted from EDTA-treated blood using a commercial kit (Purgene kit; Gentra Systems, Minneapolis, MN). The *AR* exon 1 region encoding the CAG repeat was amplified using PCR with forward primer 5′-GAATCTGTTCCAGAGCGTGC-3′, fluorescently labeled with NED (Belstress study) or FAM (Siblos study) and reverse primer 5′-TTCCTCATCCAGGACCAGGTA-3′. Each PCR was initiated with a 5-min denaturation step at 95 C and terminated with a 20-min extension step at 72 C; in-between reaction profiles were as follows: denaturation at 95 C for 60 sec, annealing at 62 C for 60 sec, and extension at 72 C for 90 sec for 35 cycles. The PCR products were mixed with a Genescan 400HD ROX size standard and deionized formamide, heat denatured, and electrophoresed (Belstress study) on a ABI Prism 310 or (Siblos study) a 96-capillary 3730 *xl* genetic analyzer (ABI Prism; Perkin-Elmer Applied Biosystems, Foster City, CA).

Statistics

Comparison of the hormone levels between groups with low and high FT was performed by multiple regression analyses with additional correction for age, body mass index (BMI), and smoking. Association between LH and FT, as well as between the CAG repeat length and hormone levels, were assessed with partial Pearson correlations, using ln-transformed (for T, FT, and E_2) or sqrt-transformed (for LH and SHBG) variables when necessary. To evaluate the independent contribution of CAG repeat length in explaining the variability in hormonal levels, comparison of the distribution of hormonal levels between quartiles of *AR* CAG repeat length was performed using multiple regression analyses of covariance with correction for age, BMI, and smoking. To meet the necessary model assumptions, hormonal levels were ln or sqrt transformed when necessary. All statistical analyses were performed using SPSS 12.0 software. $P < 0.05$ was considered significant in all analyses.

Results

The working hypothesis of the existence in healthy men of a positive association between serum T and serum LH levels, on the one hand, and a positive association between serum T and the CAG repeat length in the AR receptor gene, on the other hand, was initially tested by comparing in the Belstress population men with highest and lowest (F)T levels, respectively. Findings for these extreme groups were subsequently

assessed for consistency in subgroups of the Belstress population representing the full (F)T concentration range. Finally, consistency with results obtained in the Belstress population was assessed in an independent population of healthy men, *i.e.* the Siblos population.

Belstress population

Clinical characteristics including age, BMI, smoking habits and hormones for the total study population of 2322 men are summarized in Table 1. Of this population of 2322 men, two groups of 200 men with the highest (≥15.26 ng/dl) and lowest (≤9.41 ng/dl) level of calculated FT, respectively, were selected for initial further comparison. Basic clinical characteristics of both subgroups are also presented in Table 1. Highly significant differences were observed between both groups for all hormonal levels after adjustment for age, BMI, and smoking as shown in Table 2. Men with the highest FT levels also showed the highest LH, SHBG, and E_2 levels as well as a higher T to E_2 ratio. The consistency of the finding for these two extreme subgroups, that high (F)T levels were associated with higher LH levels, was confirmed across the whole study population and complete FT range (n = 2322): T and FT were positively correlated with LH after adjustment for age, BMI, and smoking (r = 0.193, $P < 0.001$, and r = 0.239, $P > 0.001$, for FT and T, respectively). This positive association of both hormonal levels is illustrated in Fig. 1, A and C), representing the means of LH adjusted for age, BMI, and smoking per quartile of T and FT [analysis of covariance (ANCOVA), $P < 0.001$]. For SHBG no clear linear positive effect across the FT range could be demonstrated (results not shown).

In the 200 men with highest FT, the mean CAG repeat number in the *AR* was significantly higher, compared with the 200 men with lowest FT (Table 2). The consistency of this finding was confirmed in an enlarged study subset of 857 men representative of the full range of FT in the overall study population, consisting of the former 400 men and randomly selected subjects from the intermediate FT concentration strata, the numbers of included subjects being matched so that the different concentration strata covering the population range are equally represented. Their basic clinical characteristics are not different from the global study population (Table 1). The CAG repeat length ranged from nine to 41 (P25-P75: 20–24; median 21). Consistent with the findings for the men with extreme FT values, in those men representing the full range of FT, there was a significant partial correlation (adjusted for age, BMI, and smoking) between CAG repeat length and FT (r = 0.120; $P < 0.001$) or T (r = 0.103; $P = 0.003$) levels. There was no significant correlation with SHBG or LH. Quartile analysis of the CAG repeat length showed significant differences for serum levels of T ($P = 0.010$), FT ($P = 0.003$), LH ($P = 0.020$), and SHBG ($P = 0.032$). Serum LH, T, and FT were highest in the upper CAG quartiles, but for only FT, was there a progressive increase across all CAG repeat quartiles. Results for total T (ANCOVA: $P = 0.01$) and FT (ANCOVA: $P = 0.003$) are illustrated in Fig. 2, A and C); the adjusted means of T and FT in Q_4 were 6 and 10% higher than in Q_1, respectively.

TABLE 2. Comparison of hormonal levels and *AR* CAG repeat length between the men with lowest (≤9.41 ng/dl) and highest (≥15.26 ng/dl) FT levels in the Belstress population[a]

	Low FT (n = 200)	High FT (n = 200)	P^a
T (ng/dl)[b]	273.1	747.9	< 0.001
LH (U/liter)	3.70	5.31	< 0.001
SHBG (nmol/liter)	16.2	24.9	< 0.001
E_2 (pg/ml)[c]	12.6	19.5	< 0.001
T/E_2	217.0	381.5	< 0.001
$(CAG)_n$	21.4	22.5	0.004

Data are geometric means adjusted for age, BMI, and smoking.
[a] According to ANCOVA, adjusting for age, BMI, and smoking; LH and SHBG were sqrt transformed, and other dependent variables were ln transformed.
[b] To convert to nanomoles per liter, multiply by 0.0347.
[c] To convert to picomoles per liter, multiply by 3.676.

Siblos population

Analysis of this population was intended as independent confirmation of the findings in the Belstress population. The characteristics of this second study population, consisting of 358 younger men, are summarized in Table 1. Consistent with the findings for the Belstress study population, in this group both total T and calculated FT were positively correlated with LH after adjustment for age, BMI, and smoking (r = 0.358 and r = 0.323, respectively, both $P < 0.001$), and LH showed a progressive linear increase with higher T and FT quartiles (ANCOVA, $P < 0.001$) (Fig. 1, B and D). As for SHBG, no significant correlation could be established with FT.

In the Siblos study population of 358 men, the *AR* CAG

TABLE 1. Clinical characteristics of the Belstress study population and considered study population subsets and the Siblos study population

	Belstress				Siblos
	Study population (n = 2322)	Subset covering the population FT range (n = 857)	Lowest FT subset (n = 200)	Highest FT subset (n = 200)	Study population (n = 358)
Age (yr)	45.6 (6.1)	45.4 (6.2)	47.4 (5.6)	43.0 (6.0)	34.5 (5.0)
BMI (kg/m²)	26.2 (3.5)	26.2 (3.6)	27.3 (4.0)	25.0 (3.2)	25.4 (3.4)
Current smoking (%)	29.7	30.4	29.8	29.3	22.1
T (ng/dl)[a]	492.3 (146.6)	499.7 (190.2)	275.8 (53.5)	761.7 (107.9)	557.6 (136.6)
SHBG (nmol/liter)	24.1 (10.3)	23.0 (9.6)	16.4 (6.8)	25.9 (8.4)	24.6 (8.9)
FT (ng/dl)[a]	12.0 (3.3)	12.4 (4.4)	7.4 (1.1)	19.1 (2.3)	13.6 (3.1)
LH (U/liter)	4.7 (2.2)	4.7 (2.2)	3.9 (2.2)	5.6 (2.2)	4.5 (1.8)

Data are mean (SD).
[a] To convert to nanomoles per liter, multiply by 0.0347.

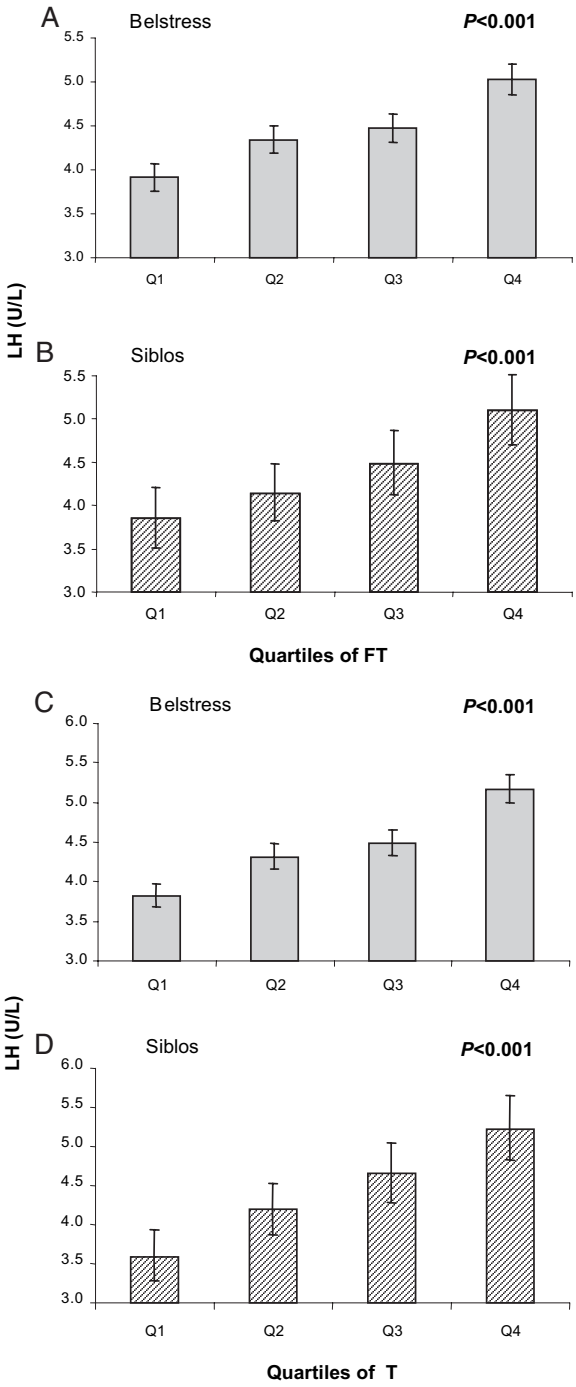

FIG. 1. Geometric means with 95% confidence interval of LH according to quintiles of FT or T in the total study Belstress population (n = 2322) (A and C) and the Siblos population (n = 358) (B and D) after adjustment for age, BMI, and smoking (ANCOVA, LH sqrt-transformed).

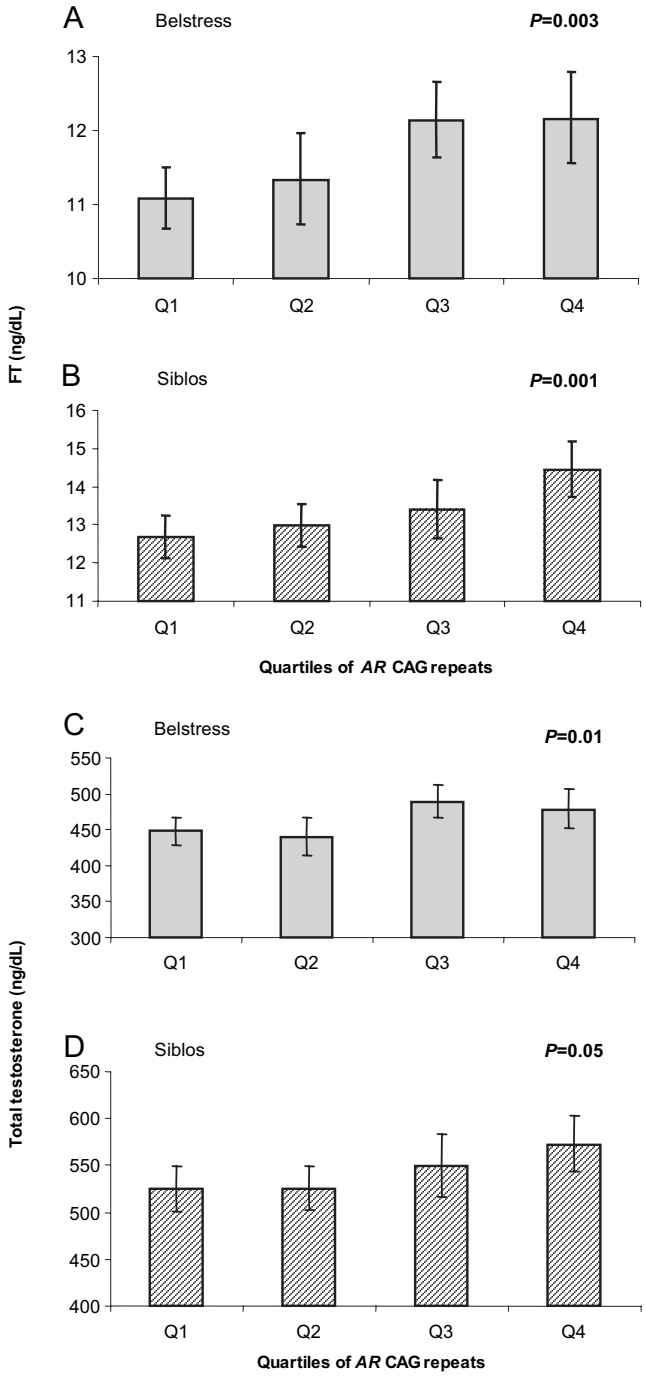

FIG. 2. Geometric means with 95% confidence interval of FT and T according to quartiles of CAG-repeat length in the Belstress subpopulation (n = 857) (A and C) and the Siblos population (n = 358) (B and D), after adjustment for age, BMI, and smoking (ANCOVA, FT and T ln-transformed). To convert T and FT to nanomoles per liter, multiply by 0.0347.

repeat length ranged from nine to 33 (P25-P75: 20–24; median 22). Significant partial correlations (adjusted for age, BMI, and smoking) were observed between the CAG repeat length and both T (r = 0.154; $P = 0.004$) or calculated FT (r = 0.226; $P < 0.001$) levels. There was no significant correlation with LH or SHBG.

Quartile analysis showed a progressive increase of FT and T with CAG repeat length (ANCOVA: $P < 0.001$ and $P = 0.05$, respectively) (Fig. 2, B and D), with the adjusted mean of T and FT in Q_4 being in average 8.5 and 14% higher than in Q_1, respectively. There was no difference across quartiles of CAG for LH ($P = 0.580$) and SHBG ($P = 0.675$).

Discussion

Whether considering either the extremes or the whole range of (F)T concentrations in the Belstress population of

2322 generally healthy men, we observed that higher (F)T levels are consistently associated with higher LH levels. These observations were confirmed in the independent younger Siblos study population. These findings are compatible with the hypothesis that between-subject variation of serum (F)T results in part from differences in androgen sensitivity and negative feedback loop set point. Furthermore, the hypothesis that the interindividual variation in serum (F)T reflects differences in androgen sensitivity is supported by the finding in both study populations of a positive association of (F)T with CAG repeat length in the *AR* gene, this single polymorphism explaining 6–8.5% of T and 10–14% of FT variability.

In men with functionally intact hypothalamo-pituitary compartment of the gonadal axis, serum LH levels are a marker of tissue exposure to sex steroids at the hypothalamo-pituitary level, with the combination of a low or normal serum T together with a high LH being the hallmark of primary deficiency of testicular Leydig cell secretory capacity. The association of an elevated serum LH together with increased serum (F)T is an expected and classical finding in patients with functional mutations of the *AR* and pathologically decreased androgen sensitivity. It has been suggested that determination of the product of serum LH and T concentrations might be useful in identifying patients with minimal forms of androgen insensitivity (18). However, it should be recognized that the combination of elevated LH and T levels is not pathognomonic of androgen insensitivity as other situations affecting the LH feedback regulation, in particular estrogen deficiency, can induce similar changes (19). In our study, it is unlikely that the observed positive association between LH and FT levels would have been underlain by variation in estrogen feedback action. Indeed, it has been shown that circulating estrogen levels rather than local aromatization of T in the hypothalamo-pituitary tissues is critical for estrogen feedback regulation of LH secretion (20), and when comparing the Belstress subgroups with low and high FT, we found that the latter group had not only higher LH but also higher serum E_2 concentrations. The latter higher serum E_2 is likely explained by higher T substrate availability for aromatization and possibly also plays a role in the observed higher SHBG concentrations in the subgroup with high FT.

Our study is based on single time point sampling in sizable populations. It is unlikely that temporal association of LH and T secretion within individuals would have contributed substantially to the observed cross-sectional association of LH and FT in the study population. Indeed, time of sampling was random relative to occurrence of endogenous LH pulses, and whereas intraindividual concentrations of LH and T are associated, this is with a time shift (21). Furthermore, single time point T levels have been reported to be fairly representative of midlong term mean serum T (6, 7).

The length of the CAG repeat of the *AR* affects *AR* mRNA and protein levels (10, 22) as well as transcriptional efficacy of the *AR* through changes in conformation and association with coactivators (10, 23). This *AR* polymorphism has been reported to affect tissular androgen action in men (24–26) and prostate cancer risk (27, 28). Along the same line, the CAG repeat polymorphism of the *AR* might be expected to affect hypothalamic-pituitary feedback regulation with longer CAG repeats being associated with diminished androgen feedback and relative elevation of circulating (F)T, as was indeed observed in our two study populations. Previous limited literature data on circulating T in relation to CAG repeat length have not been univocal. Mifsud *et al.* (11) reported a significant ($P = 0.046$) bivariate positive correlation between CAG repeat length and FT in a small group of 91 fertile men with mean age of 35.6 yr but did not discuss the impact of confounders. Walsh *et al.* (14) reported a nonsignificant trend of increasing bioavailable T according to tertiles of CAG repeat length in 294 men aged 55–93 yr; a significant similar trend in a second cohort of 171 men aged 19–90 yr appeared to be restricted to the older subjects. In a cohort of 882 men aged 40–70 yr from the Massachusetts Male Aging Study, Krithivas *et al.* (29) found no association between CAG repeat and T levels at baseline evaluation (mean age 53 ± 8 yr), although they did report a significantly sharper decline of (F)T on follow-up examination (mean age 61 ± 8 yr) in those men with shorter CAG repeat length of the *AR*. No significant association between serum T and CAG repeat was found in three other independent studies by Van Pottelbergh *et al.* (30) in 273 healthy community-dwelling men over 70 yr of age, Harkonen *et al.* (25) in 172 men aged 41–70 yr, and Canale *et al.* (31) in 91 healthy men aged 23–45 yr. Apparent discrepancies between studies may be underlain by differences in population genetic background, differences in subjects selection criteria, and small sample size for several of these studies, whereas in the older men, lack of association might be explained by age-related alterations in androgen feedback regulation (30).

In any case, the consistent positive association between CAG repeat length and (F)T in the present study as observed in two independent, sizable and more homogenous study populations is predicted and biologically plausible. The 10–14% of between-subject variability of FT explained by the CAG repeat polymorphism in the Belstress and Siblos study populations, respectively, is not negligible and is in the same order of magnitude as the effects of well-established modifiable factors affecting serum T levels, such as smoking (3). Moreover, from a genetic perspective, serum (F)T is undoubtedly a polygenic trait and the polymorphism of the *AR* is obviously only one of many potentially contributing genetic factors underlying the substantial heritability of serum (F)T (5).

In the Belstress population, the CAG repeat length was also associated with serum LH, although not consistently progressive over the four quartiles of CAG repeat length. This association was not observed in the Siblos population. In view of the much higher moment-to-moment variability of serum levels of LH, compared with (F)T, to demonstrate more consistently an association between *AR* CAG repeats and serum LH would probably require repeated sampling and/or larger study populations.

Results of this study, which support the view that interindividual differences in serum (F)T in healthy men partly reflect subtle differences in androgen sensitivity, strongly suggest that healthy men with (F)T in the upper normal range do not necessarily have a higher tissular androgen activity than those with lower (F)T levels. These findings

have obvious potential implications as to the interpretation of epidemiological reports on associations of T levels within the normal range with clinical and biological parameters, and they might help explain some apparently inconsistent findings. For example, below and above this normal range of serum T in men, a higher T tend to be associated with less favorable cardiovascular risk factors [*e.g.* with lower high-density lipoprotein (HDL)-cholesterol)], whereas, on the contrary, within the normal range, higher serum T is associated with more favorable cardiovascular risk factors (*e.g.* higher HDL-cholesterol) without having demonstrable positive effects in terms of clinical cardiovascular end point (32). If a higher serum T within the normal range does not reflect a higher androgen activity but is accompanied by higher E_2 levels, this might explain seemingly paradoxical findings such as a positive association of higher serum T with higher HDL-cholesterol seen only within the window of T levels around the normal range. When the feedback regulation of androgen levels is not fully operational, as is the case in elderly men (33), failure to compensate for AR CAG repeat polymorphism-related differences in androgen sensitivity might then translate into differences in androgen action. In this light Canale *et al.* (31) reported that given similar circulating T levels in hypoandrogenized men and controls, the final net androgenic phenotypical effect is related to *AR* polymorphism.

Our study results imply that assessment of androgen receptor polymorphisms may provide additional information when studying associations between clinical variables and androgen levels in men. Conversely, it seems preferable to take into account serum T levels when studying associations of clinical variables such as cardiovascular risk factors and the *AR* CAG repeat polymorphism, as was done in some (33) but not all (34, 35) studies. Whether and how integrated interpretation of serum (F)T level and CAG repeat polymorphism can have useful applications in the clinical management of individuals with suspected alteration of the androgen status remains to be established in studies with clinical end points.

Limitations of our study are those inherent to epidemiological studies with single time point assessment, in particular as far as the hormonal levels are concerned, and in the fact that in this explorative study a single candidate gene was considered. A strength of the study is that we had access to a large cohort of men, all sampled in the first part of the morning and for whom data were available to adjust our analyses for major confounders. Furthermore, we confirmed our findings on the relationship of FT with LH and *AR* CAG repeat length in a second, independent group of younger men.

In conclusion, this report presents evidence that between-subject variability in serum (F)T in healthy men is underlain in part by differences in androgen sensitivity, with a contributory role of the polymorphic glutamine tract in the AR encoded by the CAG repeat polymorphism in exon 1 of the *AR* gene. These findings have potential implications for interpretation of epidemiological studies, diagnosis of hypogonadism in borderline situations, and possibly individualization of androgen therapies in men.

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