Influence of Various Modes of Androgen Substitution on Serum Lipids and Lipoproteins in Hypogonadal Men

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We investigated whether the androgen type or application mode or testosterone (T) serum levels influence serum lipids and lipoprotein levels differentially in 55 hypogonadal men randomly assigned to the following treatment groups: mesterolone 100 mg orally daily ([MES] n = 12), testosterone undecanoate 160 mg orally daily ([TU] n = 13), testosterone enanthate 250 mg intramuscularly every 21 days ([TE] n = 15), or a single subcutaneous implantation of crystalline T 1,200 mg ([TPEL] n = 15). The dosages were based on standard treatment regimens. Previous androgen substitution was suspended for at least 3 months. Only metabolically healthy men with serum T less than 3.6 nmol/L and total cholesterol (TC) and triglyceride (TG) less than 200 mg/dL were included. After a screening period of 2 weeks, the study medication was taken from days 0 to 189, with follow-up visits on days 246 and 300. Before substitution, all men were clearly hypogonadal, with mean serum T less than 3 nmol/L in all groups. Androgen substitution led to no significant increase of serum T in the MES group, subnormal T in the TU group (5.7 ± 0.3 nmol/L), normal T in the TE group (13.5 ± 0.7 nmol/L), and high-normal T in the TPEL group (23.2 ± 1.1 nmol/L). 5 α-Dihydrotestosterone significantly increased in all treatment groups compared with baseline. Compared with presubstitution levels, a significant increase of TC was observed in all treatment groups (TU, 14.4% ± 3.0%; MES, 18.8% ± 2.5%; TE, 20.4% ± 3.0%; TPEL, 20.2% ± 2.6%). Low-density lipoprotein cholesterol (LDL-C) also increased significantly by 34.3% ± 5.5% (TU), 46.4% ± 4.1% (MES), 65.2% ± 5.7% (TE), and 47.5% ± 4.3% (TPEL). High-density lipoprotein cholesterol (HDL-C) showed a significant decrease by −30.9% ± 2.8% (TU), −34.9% ± 2.5% (MES), −35.7% ± 2.6% (TE), and −32.5% ± 3.5% (TPEL). Serum TG significantly increased by 37.3% ± 11.3% (TU), 46.4% ± 10.3% (MES), 29.4% ± 6.5% (TE), and 22.9% ± 6.7% (TPEL). TU caused a smaller increase of TC than TE and TPEL, whereas the parenteral treatment modes showed a lower increase of TG. There was no correlation between serum T and lipid concentrations. Despite the return of serum T to pretreatment levels, serum lipid and lipoprotein levels did not return to baseline during follow-up evaluation. In summary, androgen substitution in hypogonadal men increases TC, LDL-C, and TG and decreases HDL-C independently of the androgen type and application made and the serum androgen levels achieved. Due to the extended washout period for previous androgen medication and the exclusion of men with preexisting hyperlipidemia, this investigation demonstrates more clearly than previous studies the impact of androgen effects on serum lipids and lipoproteins. It is concluded that preexisting low serum androgens induce a "male-type" serum lipid profile, and increasing serum androgens further within the male normal range does not exert any additional effects. The threshold appears to be above the normal female androgen serum levels and far below the lower limit of normal serum T levels in adult men. These findings may have considerable implications for the use of androgens as a male contraceptive and for androgen therapy in elderly men.

THE RISK FOR DYING of coronary heart disease (CHD) is twice as high for men as for women. Furthermore, before menopause, the risk of deadly CHD in women is less than one fifth the risk in men.[1] This difference in the incidence of CHD led many investigators to focus on the influence of sex steroids on lipid metabolism. Epidemiological studies showed that prepubertal children do not exhibit any sex-specific differences in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs). With the onset of puberty, HDL-C decreases and LDL-C and TGs increase in boys compared with girls.[2-4] Only after the age of 50 years does HDL-C begin to increase in men, concomitant with the simultaneous decrease of serum testosterone (T) often observed in older men. However, HDL-C does not reach the higher levels observed in women of a similar age.

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These epidemiological observations led to the hypothesis of a suppressive effect of T on HDL-C and of estrogens on LDL-C. Whereas a vast amount of data exist for the influence of estrogens on lipid metabolism in women, information on the impact of T on serum lipid and lipoprotein levels in men is scarce and contradictory. With the renewed interest in T therapy as androgen substitution in elderly men or as a male contraceptive, the possible harmful effect of androgens on lipid metabolism is of major concern. We therefore investigated the influence of different modes of androgen substitution on lipid and lipoprotein levels in men with hypogonadism.

SUBJECTS AND METHODS

Patients

Fifty-five men with hypogonadism and serum T less than 3.6 nmol/L (normal, >10 nmol/L) on two separate occasions, free of neoplastic, inflammatory, renal, or metabolic disorders, and not on any medication known to influence lipid or androgen metabolism participated in the study (Table 1). Previous T treatment (testosterone enanthate [TE] or oral testosterone undecanoate [TU]) was suspended at least 3 months prior to the study. Men with secondary hypogonadism due to pituitary insufficiency were euthyroid and maintained on a constant dosage of cortisone or levothyroxine throughout the study period. None of the subjects received growth hormone substitution. All men provided written informed consent to participate in the study.

Table 1. Anthropometric, Biochemical, and Endocrine Data for the Patients (mean ± SEM)

Parameter	TU	MES	TE	TPEL
No. of subjects	13	12	15	15
Prim/sec	4/9	5/7	5/10	7/8
Cortisone/L-thyrox	1/2	1/1	1/2	2/2
Age (yr)	34.5 ± 3.9	31.3 ± 3.7	31.8 ± 2.6	35.8 ± 2.7
BMI (kg/m²)				
Day 0	25.71 ± 0.79	23.95 ± 1.04	24.83 ± 0.95	25.65 ± 0.76
Day 105	26.75 ± 1.08	24.47 ± 1.16	25.25 ± 0.95	26.20 ± 0.61
Day 300	26.20 ± 1.01	24.45 ± 1.26	25.23 ± 0.83	26.58 ± 0.69

NOTE. The BMI was determined before (day 0), during (day 105), and after (day 300) androgen substitution.

Abbreviations: Prim/sec, primary or secondary hypogonadism, cortisone/L-thyrox, hydrocortisone and/or levothyroxine.

Study Design

In this open-label randomized study, patients with clinically and biochemically confirmed androgen deficiency (serum T <3.6 nmol/L on at least two occasions) were randomly assigned to one of four treatment protocols: mesterolone ([MES] Proviron; Schering, Berlin, Germany) 100 mg/d, TU (Andriol; Organon International, Oss, The Netherlands) 160 mg/d, TE (Testoviron Depot 250 mg; Schering) 250 mg intramuscularly every 21 days, or T pellets ([TPEL] TestoImplant; Organon International) as a single subcutaneous implantation of six T pellets, each containing 200 mg crystalline T.[5] On days 0, 21, 42, 63, 84, 105, 126, 147, 168, and 189, blood samples were drawn after at least 8 hours of fasting, and medications and TE injections were administered. The study medication period lasted until day 210, and follow-up studies were performed on days 246 and 300.

The study was approved by the ethics committee of the University of Essen and followed the guidelines of the Declaration of Helsinki, 1975. Other results of this study have been published elsewhere.[6,7]

Laboratory Methods

Hormone levels were measured by commercially available immunoassays: T, estradiol, and sex hormone–binding globulin (SHBG) by radioimmunoassay (Diagnostic Products, Los Angeles, CA) and 5α-dihydrotestosterone (DHT) by radioimmunoassay after oxidative destruction of T (Amersham, Braunschweig, Germany). The male normal range for T is 10 to 35 nmol/L and for DHT 2 to 5 nmol/L. Interassay and intraassay variation was less than 8% for all assays except DHT (17%).[5,8] The percentage of free T was calculated by the formula, $-2.38 \cdot \log [\text{SHBG}] + 6.11$.[9,10]

Total cholesterol (TC) and TGs were determined enzymatically using routine kits from Boehringer (Mannheim, Germany). The plasma HDL-C level was measured after LDL-C precipitation with dextran sulfate and manganese chloride.[11] The concentration of LDL-C was calculated with the Friedewald formula.[12]

Statistics

Results are reported as the mean ± SEM. The androgen to estrogen ratio was derived by dividing the total androgen concentration (T + DHT in nanomolars) by the estrogen concentration (in picomolars). Changes in the body mass index ([BMI] body weight in kilograms divided by height in meters squared) were tested with the Wilcoxon matched-pairs sign test. Statistical comparisons were made with paired and unpaired *t* tests or repeated-measures ANOVA as appropriate, with the level of significance set at P less than .05 (Student-Newman-Keuls test). All statistical analyses, including multivariate analyses, were performed with the SPSS (Chicago, IL) software package. The area under the curve and lipids versus time was calculated by the trapezoidal rule. For different periods of the investigation, mean serum concentrations for hormonal and lipid parameters were calculated by dividing the AUC by the time period. Pearson's correlation analysis and linear regression analysis were used to assess the relation of hormone parameters and lipid concentrations (Table 2).

RESULTS

Hormones

Before androgen substitution, all subjects exhibited greatly reduced serum androgen concentrations, thereby confirming true hypogonadism. Whereas in the TU, TE, and TPEL groups, substitution induced a significant increase of serum T, the MES group did not show any increase of serum T. However, DHT increased in all groups significantly. The largest increase of androgens occurred in the TPEL group, followed by the TE group. TU induced a minor but significant increase of T; however, serum T levels were not normalized by TU. Comparing the mean androgen concentrations during substitution, TPEL increased T and DHT significantly versus the other substitution regimens ($P < .001$). TE stimulated T and DHT to a considerably lower extent than TPEL but still far higher than TU and MES ($P < .01$) (Fig 1 and Table 2).

Serum estradiol increased significantly in the TPEL group from days 21 to 105 and in the TE group from days 42 to 189 compared with the screening period ($P < .01$). In the TU and MES groups, serum estradiol during substitution was not different from baseline values. Serum SHBG levels decreased significantly in all groups during substitution ($P < .01$). Except for the MES group, neither serum T nor serum SHBG completely returned to baseline values during follow-up evaluation, resulting in significantly elevated levels of derived free T during follow-up study in the TU, TE, and TPEL groups (Fig 1 and Table 2).

Lipid and Lipoprotein Concentrations

During the screening phase, the TPEL group had significantly higher levels of TC and TG than all other groups ($P < .05$), and the TE group had lower levels of TC than the TPEL and MES groups and lower levels of LDL-C than all other groups ($P < .01$). HDL-C did not differ between the groups before androgen substitution (Fig 2 and Table 2).

Substitution of androgens induced a significant increase of TC, LDL-C, and TG in all treatment groups compared with presubstitution ($P < .01$). HDL-C decreased significantly during substitution ($P < .01$). When comparing the mean levels of the substitution period, the TPEL group exhibited significantly higher levels of TC and LDL-C than the other three groups ($P < .01$). Among the other groups, neither TC, LDL-C, nor HDL-C differed. During follow-up study, TC, LDL-C, and TG remained at elevated levels. However, HDL-C showed a tendency to return to baseline levels, although a significant increase versus the substitution period occurred only in the TU and TPEL groups ($P < .01$) (Fig 2 and Table 2).

The strong impact of androgen substitution on lipid parameters is demonstrated further by the percentage change of serum

Table 2. DHT, 17β-Estradiol, SHBG, TC, LDL-C, HDL-C, and TG During the Screening Phase, Substitution Period, and Follow-Up Period (mean ± SEM)

Parameter	TU	MES	TE	TPEL
T (nmol/L)				
Screening	2.90 ± 0.4	2.17 ± 0.4	2.29 ± 0.6	2.72 ± 0.4
Substitution	5.73 ± 0.3*	2.39 ± 0.3	13.51 ± 0.7*	23.18 ± 1.1*
Follow-up	3.55 ± 0.8	2.35 ± 0.5	5.20 ± 1.2*	5.03 ± 1.4*
Free T (pmol/L)				
Screening	61.8 ± 8.4	56.7 ± 11.4	34.6 ± 8.0	35.0 ± 4.9
Substitution	175.3 ± 9.4*	75.3 ± 8.6	311.8 ± 11.9*	591.8 ± 34.1*
Follow-up	96.5 ± 21.4*	74.2 ± 17.7	128.5 ± 22.8*	76.0 ± 18.1*
DHT (nmol/L)				
Screening	1.76 ± 0.3	1.99 ± 0.4	2.12 ± 0.4	1.37 ± 0.1
Substitution	3.27 ± 0.2*	4.34 ± 0.2*	4.04 ± 0.4*	5.50 ± 0.4*
Follow-up	1.76 ± 0.2	1.40 ± 0.2	2.10 ± 0.2	1.76 ± 0.2
Estradiol (pmol/L)				
Screening	84.7 ± 8.9	65.6 ± 7 2	66.9 ± 5.4	68.9 ± 8.1
Substitution	88.0 ± 3.2	73.7 ± 4.9	90.3 ± 3.0*	103.9 ± 4.3*
Follow-up	67.5 ± 7.2	84.2 ± 10.1	67.2 ± 7 4	57.8 ± 4.4
SHBG (nmol/L)				
Screening	42.2 ± 4.7	38.1 ± 5.5	61.0 ± 8.2	47.8 ± 3.7
Substitution	21.0 ± 0.7*	30.2 ± 2.0*	40.0 ± 2.7*	32.1 ± 1.3*
Follow-up	67.5 ± 3.2*	34.0 ± 4.2	42.6 ± 5.6*	38.7 ± 3.4*
TC (mg/dL)				
Screening	175.1 ± 4.4	176.6 ± 3.3	167.9 ± 5.1	188.4 ± 5.8
Substitution	208.2 ± 4.3*	202.0 ± 5.2*	202.2 ± 5.0*	226.4 ± 4.9*
Follow-up	208.2 ± 8.1*	217.1 ± 10.7*	194.5 ± 11.6*	246.3 ± 10.3*
LDL-C (mg/dL)				
Screening	91.8 ± 5.6	100.3 ± 6.7	79.6 ± 3.7	99.3 ± 8.6
Substitution	134.6 ± 3.8*	134.7 ± 5.5*	131.5 ± 4.5*	146.5 ± 4.3*
Follow-up	123.3 ± 6.7*	143.8 ± 10.8*	124.4 ± 10.7*	161.7 ± 9.5*
HDL-C (mg/dL)				
Screening	69.4 ± 2.7	65.9 ± 1.8	71.0 ± 3.8	72.0 ± 2.7
Substitution	45.2 ± 1.1*	45.5 ± 1.2*	45.7 ± 1 9*	48.5 ± 1.1*
Follow-up	53.6 ± 3.6*	48.7 ± 2.1*	49.6 ± 3.4*	54.7 ± 2.5*
TG (mg/dL)				
Screening	96.2 ± 5.2	85.7 ± 4.7	100.4 ± 4.7	122.9 ± 7 8
Substitution	140.8 ± 9.9*	117.7 ± 9.6*	130.0 ± 6.5*	151.0 ± 8.3*
Follow-up	152.5 ± 24.8*	133.5 ± 18.9*	123.8 ± 16.4*	150.1 ± 11.9*

NOTE. During the substitution period, androgen concentrations differed among the groups significantly ($P < .01$), except for DHT in MES and TE groups.

*$P \leq .01$ *v* screening period.

lipid levels during substitution. TC increased 14% to 20%, with significant differences between the parenteral substitution regimens (TE and TPEL) and the TU group. LDL-C increased 34% to 65%. The TU group had a significantly smaller increase of LDL-C than the other groups, and the TE group a significantly larger increase than the other groups ($P < .01$). A more uniform change was observed with the 31% to 36% decrease of HDL-C. No differences between the groups were noted. Serum TG increased in all groups; however, the elevation was significantly more pronounced in the oral treatment (TU and MES) groups ($P < .01$) (Table 3).

No significant correlation was detected between any hormonal parameter, either alone or in multivariate analysis including the ratio of androgens to estradiol with and without SHBG or derived free T, and lipid levels. However, HDL-C correlated significantly with SHBG concentrations in all treatment groups ($P < .001$; Fig 3).

DISCUSSION

This study investigated the influence of androgen substitution therapy on serum lipid and lipoprotein levels in hypogonadal men. The investigation of hypogonadal men offers the opportunity to study the same individual before and during androgen substitution, thus guaranteeing that the changes observed are due to the androgen applied. Other medications, eg, hydrocortisone or levothyroxine, were kept constant throughout the study period. The extremely low levels of serum T before substitution confirm the hypogonadal state. The androgens administered in this study were chosen to examine possible differences between oral and parenteral application modes, and to study possible dose-response effects by achieving different levels of T and DHT with the different androgen preparations. The dosages were based on standard treatment regimens.

Despite achieving considerably different levels of serum T and using aromatizable and nonaromatizable androgens, we

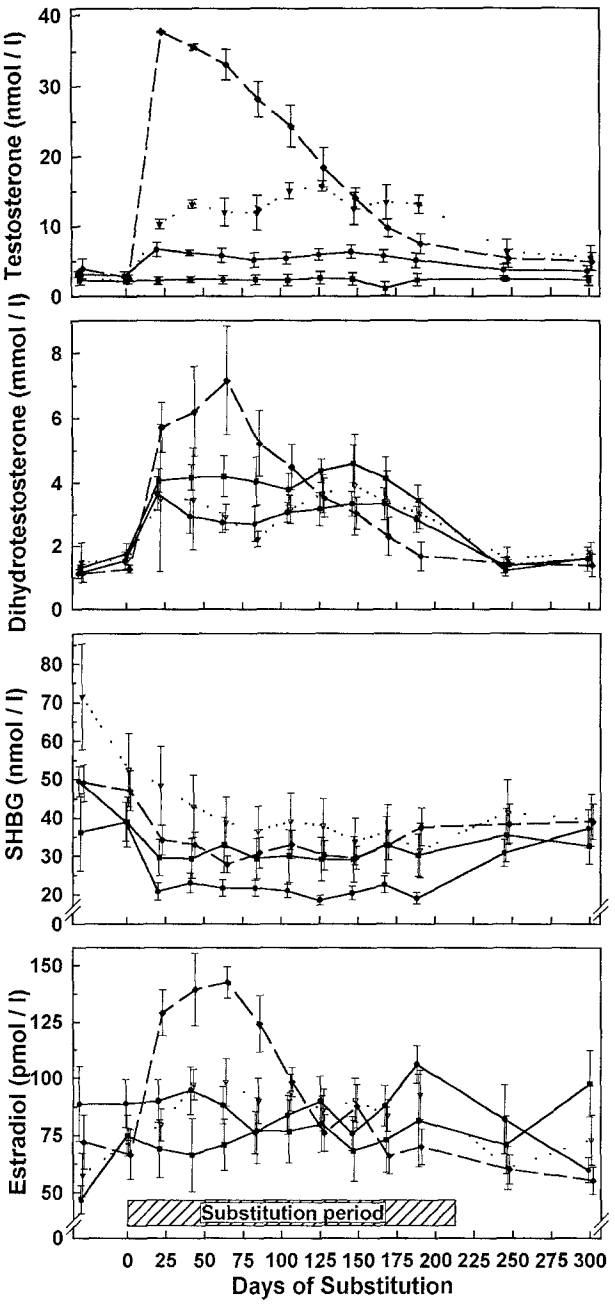

Fig 1. Serum T, DHT, estradiol, and SHBG (mean ± SEM). ●, TU; ■, MES; ▼, TE; ◆, TPEL.

observed a uniform change of serum lipids and lipoproteins. Serum HDL-C decreased and LDL-C increased in all groups significantly, thereby considerably and unfavorably changing the ratio of LDL-C/HDL-C.

Most studies investigating the impact of androgen therapy in healthy men were performed with bodybuilders.[13-18] All showed a decrease of HDL-C in response to androgen therapy, mostly in the range between −10% and −40% and significant in the majority of the studies. Also, the majority of the studies report an increase of LDL-C in the range of +2% to +31%, significant in three of the studies.[14-16] The prevailing influence of endogenous T and the use of synthetic anabolic steroids not comparable to T devalues these studies for the assessment of the true effect of T on lipid metabolism.

In hypogonadal men, substitution of T always reduces serum HDL-C and increases LDL-C.[19-23] with the sole exception of one study investigating transdermal T in eight men.[24] This is in agreement with the results observed in the present study. However, the current investigation shows the most pronounced impact of T on serum lipids and lipoproteins. This may be due to the fact that, unlike all the other studies, only men without any other disease except hypogonadism, particularly without preex-

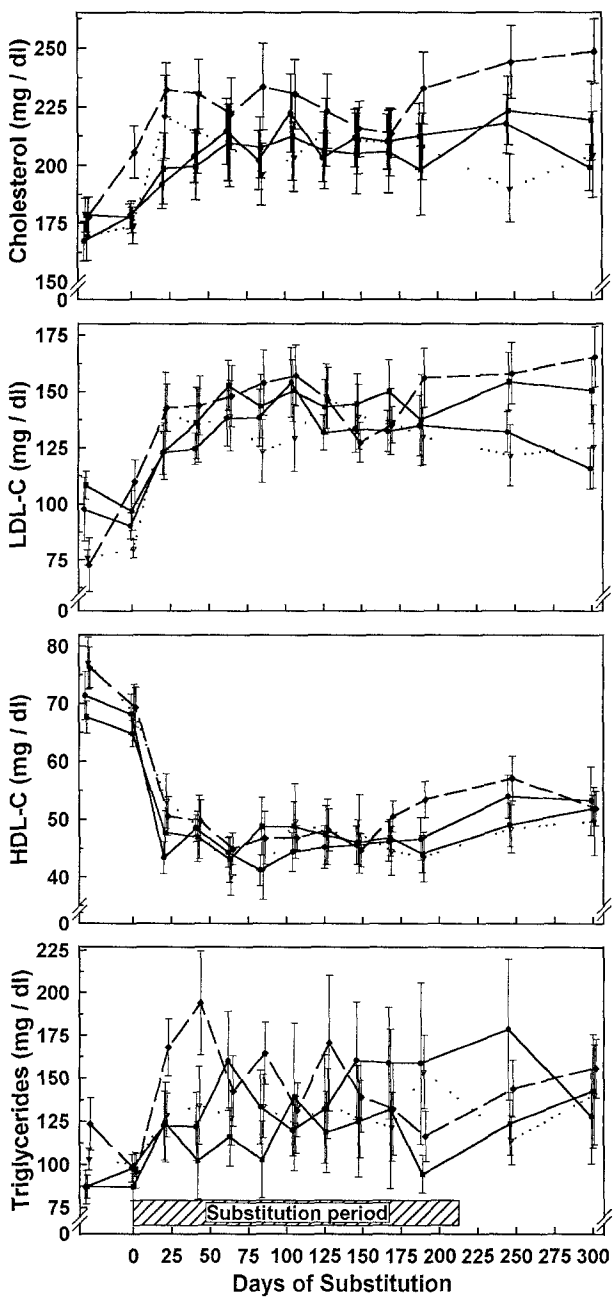

Fig 2. Serum TC, LDL-C, HDL-C, and TG (mean ± SEM). ●, TU; ■, MES; ▼, TE; ◆, TPEL.

Table 3. Change in Lipid and Lipoprotein Parameters During the Substitution Period (mean ± SEM) Compared With the Screening Period

Parameter (%)	TU	MES	TE	TPEL
TC	+14.4 ± 3.0	+18.8 ± 2.5	+20.4 ± 3.0*	+20.2 ± 2.6*
LDL-C	+34.3 ± 5.5†	+46.4 ± 4.1	+65.2 ± 5.7†	+47.5 ± 4.3
HDL-C	−30.9 ± 2.8	−34.9 ± 2.5	−35.7 ± 2.6	−32.5 ± 3.5
TG	+37.3 ± 11.3	+46.4 ± 10.3	+29.4 ± 6.5‡	+22.9 ± 6.7‡

*$P < .05$ *v* TU.
†$P < .02$ *v* all other groups.
‡$P < .05$ *v* TU and MES.

isting hyperlipidemia, were allowed to participate in the present investigation, resulting in a metabolically healthy study population. Furthermore, in this study, previous androgen substitution was suspended for an extended period to allow serum lipids to recover from any previous androgen effect. This is underscored by the high levels of SHBG and low concentrations of derived free T at the start of the study. Other investigations discontinued androgen substitution for an insufficient period of 0 to 6 weeks before the study or included men with only slightly reduced endogenous T, not true hypogonadism.[19,21-24] Therefore, this study more clearly shows the impact of androgens on serum lipids, which thus far has been underestimated considerably. Female weight lifters with male serum T levels due to anabolic androgen abuse have HDL-C levels that are 39% lower and LDL-C levels that are 38% higher than the levels in matched controls not using androgens.[25] This confirms the present study with regard to the extent of the androgen effect on HDL-C.

In the present investigation, serum lipids and lipoproteins did not return to baseline during follow-up study. Possibly, the persistent elevation of serum T and derived free T in the treatment groups receiving TU, TE, or TPEL may have prevented the decrease of serum lipids. In view of the persistently elevated androgens, slightly suppressed SHBG, and reduced estrogens, we must concede that during follow-up study, an androgenic milieu still exists, explaining the persistence of elevated lipids and lipoproteins in these treatment groups.

However, this does not explain the failure of lipids to return to baseline in the MES group, as this is the only treatment group in which serum androgens and SHBG were not different from baseline levels during follow-up study. It is speculated that the high levels of serum DHT induce enzymes and metabolic pathways due to genomic action. This induction may persist for an extended period, independent of ongoing androgenic action and the half-life of the androgen administered, and may wane only slowly. There is no evidence for this speculation, but we know from clinical experience that in hypogonadal men with T substitution, withdrawal of the androgens does not cause an abrupt cessation of androgen-dependent effects. For example, erectile potency and libido very slowly and gradually decrease, as does beard growth.

The general opinion[26] that aromatizable and oral androgens

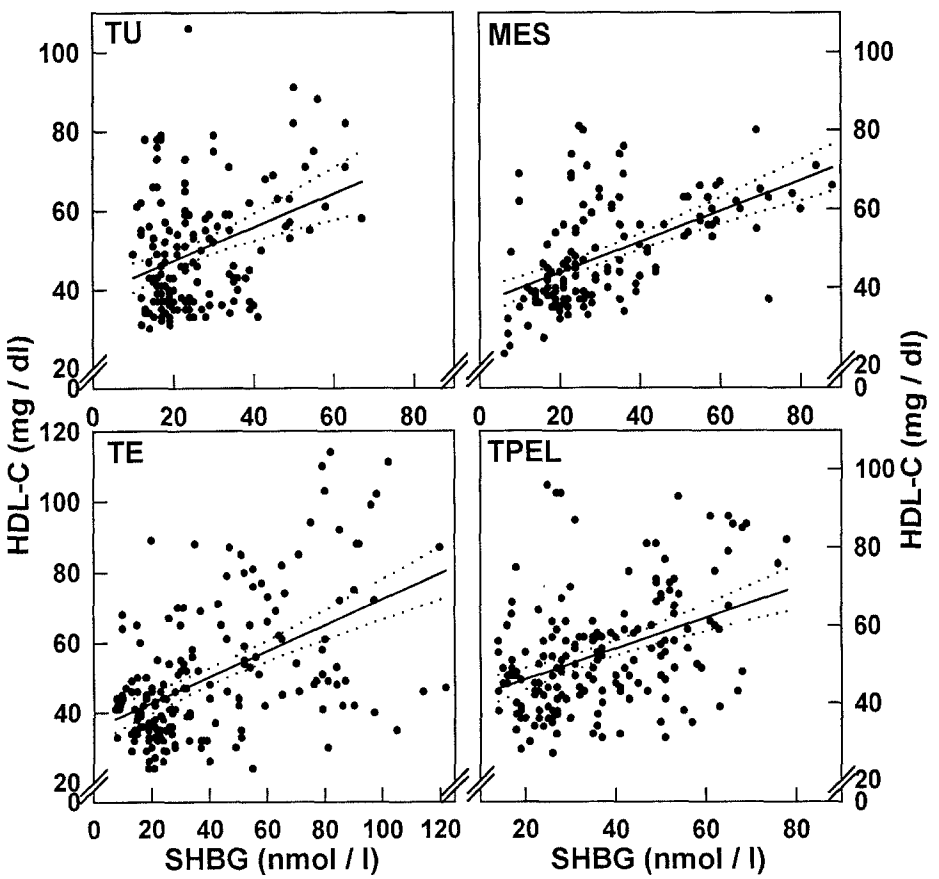

Fig 3. Correlation of serum HDL-C with serum SHBG. Coefficients of correlation: TU, $r = .42$; MES, $r = .53$; TE, $r = .50$; TPEL, $r = .41$ ($P < .001$ for all groups). (—) Linear regression line; (· · ·) corresponding 95% confidence interval.

have less detrimental effects on serum lipids than nonaromatizable or parenteral androgens is based on two studies in bodybuilders,[14,16,27] and was not confirmed in the present investigation of hypogonadal men. The oral nonaromatizable MES had effects similar to the other androgens, despite producing lower T levels. MES is metabolized to DHT, which has a higher androgenic potency than T. Accordingly, the MES group demonstrated an increase of serum DHT but not serum T and estradiol. Since T and DHT act by binding to the same androgen receptor, we assume that the changes of lipids and lipoproteins induced by MES are due to its metabolism to DHT. This allows the conclusion that DHT is the androgen influencing serum lipids. A divergent responsiveness of the target tissues for T and DHT has been described in patients who lack DHT due to 5α-reductase deficiency and is well accepted.

Serum estradiol levels appear to have no detectable effect on serum lipids and lipoproteins. The nonaromatizable MES did not increase serum estradiol, whereas in the treatment groups receiving TE or TPEL, serum estradiol increased significantly during the substitution period. Nevertheless, all androgens induced changes in serum lipids to a similar extent. Possibly, in the presence of high DHT serum levels, estradiol cannot ameliorate the androgenic effects on lipid metabolism. However, we must acknowledge that in the TE and TPEL groups, serum estradiol increased by about 50% over baseline and derived free T increased 10-fold to 15-fold, thereby considerably increasing the androgen to estrogen ratio. Still, we cannot rule out the possibility that higher serum levels of estradiol, eg, above the physiological range, may counteract the androgenic effects.

Androgens induced an increase of TG, in agreement with previous studies[13,17,21,24,28,29] and the pubertal increase of TG observed in boys but not in girls.[4] Due to the influence of diet, all studies, including the present investigation, show a large variation of serum TG, limiting the conclusions. In a placebo-controlled study, T reduced the uptake of TG by fat tissue 34% and postheparin lipoprotein lipase activity 48%,[30] with the latter also reduced in bodybuilders using anabolic-androgenic steroids.[31] Androgens stimulate the activity of hepatic TG lipase, thereby increasing the clearance of HDL-C.[31,32] The influence of androgens on LDL receptor expression has not been evaluated, but the assumption of an antagonistic action to estrogens, which stimulate LDL receptor expression, is tempting. This action could be mediated by androgen receptors, which are present in hepatocytes.[33]

As in other studies,[34-36] we observed a highly significant correlation between SHBG and HDL-C. The lack of correlation between serum androgens and SHBG and the similar suppression of SHBG by all four androgens administered in this investigation support the concept of a low hepatic threshold for androgenic effects. We propose that the already-low levels of serum androgens—above the normal female range but well below the normal male range—can induce a "male-type" serum lipid profile. The lack of a dose-dependent influence of T on serum lipids in this study is in agreement with the observation that women with hyperandrogenemia exhibit serum lipid changes comparable to the changes observed in this study and have an increased risk for cardiovascular disease.[37-41] The hypothesis of a low threshold for establishing a male lipid profile also explains the lack of relevant effects of androgen therapy on serum lipids in elderly men. In these studies, baseline serum T levels were above the threshold, and therefore, no additional effect on serum lipids was observed.[42] In accordance with this hypothesis, in pubertal boys, HDL-C begins to decline long before adult serum T levels are achieved.[2-4] Increasing androgens above the normal male range, eg, with androgen abuse or androgen-based male contraceptive regimens, will then exert further effects and induce a greater increase of LDL-C and decrease of HDL-C.[14-16,43,44]

In summary, this randomized investigation of severely hypogonadal but metabolically healthy men shows that androgen substitution induces a considerable increase of TC, LDL-C, and TG and a significant suppression of HDL-C independently of the dose, aromatizability, and route of administration. This unfavorable change in the lipid profile may be associated with an increased risk for cardiovascular disease[45] and may contribute to the elevated morbidity and mortality of men compared with women. Oral androgen substitution offers no advantage over parenteral androgen substitution. These results indicate that the lipid profile of hypogonadal men on T substitution must be monitored. Furthermore, high-dose T for male contraception needs to be carefully evaluated with regard to its influence on lipid metabolism.

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