Established risk factors for coronary heart disease are unrelated to androgen-induced baldness in female-to-male transsexuals

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Abstract

A high scalp sensitivity to androgens is part of the pathophysiology of male-pattern baldness (MPB). Androgens affect established risk factors for coronary heart disease (CHD), and a supposedly heightened impact on these risk factors is hypothesized to explain the epidemiological association between MPB and CHD. In this retrospective, observational study we studied 81 female-to-male transsexual (F→M) subjects, mean age 36·7 years (range 21–61), treated with testosterone esters (n=61; 250 mg i.m./2 weeks) or testosterone undecanoate (n=20; 160–240 mg/day orally). The degree of MPB was self-assessed using a 5-point scale (i.e. type I (no hair loss) to type V (complete hair loss)). Body mass index, blood pressure and levels of lipid and insulin were retrospectively assessed at the start of testosterone administration (0·5–24 years before) and between 3 and 4 months of follow-up. We found that 31 of 81 (38·3%) F→M transsexuals had MPB type II–V. Thinning of hair was related to the duration of androgen administration and present in about 50% of F→M transsexuals after 13 years. None of the CHD risk factors at follow-up, nor proportional changes, was associated with the degree MPB, except that there was an unexpected tendency of lower fasting glucose levels in balding subjects. Therefore, our findings do not support the idea that MPB serves as an indicator of increased CHD risk through androgenic effects on classic CHD risk factors.

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Introduction

Several cohort (Herrera *et al.* 1995, Schnohr *et al.* 1995, Ford *et al.* 1996, Lotufo *et al.* 2000, Matilainen *et al.* 2001) and a case-control study (Lesko *et al.* 1993) have shown an association between the degree of male-pattern baldness (MPB) and myocardial infarction, coronary heart disease (CHD) events and CHD mortality. Established CHD risk factors are typically found in the metabolic syndrome and the common endocrine disorder of polycystic ovary syndrome (PCOS) (Laws & Reaven 1993, Dunaif 1997), including hyperinsulinemia, glucose intolerance, high fasting triglycerides, low high-density lipoprotein (HDL)-cholesterol, hypertension and obesity (Dunaif 1997). Androgenic alopecia has also been associated with PCOS in some (Ferriman & Purdie 1979, Dunaif 1997) but not all studies (Legro *et al.* 2002).

While cohort and case-control studies are useful instruments in finding associations, they cannot explain the association between MPB and CHD. It has been hypothesized that high androgen levels or activity may explain this association. Androgens can induce MPB in genetically susceptible men and women (Price 1999, Signorello *et al.* 1999), and can also alter lipid profiles (Glazer 1991) and other established CHD risk factors (Asscheman *et al.* 1994, Elbers *et al.* 2003). Three previous studies found support for a possible association between MPB and a higher serum cholesterol and blood pressure (Trevisan *et al.* 1993, Lotufo *et al.* 2000) or disorders clustered in the metabolic syndrome (Matilainen *et al.* 2000). Another study, however, found no evidence for an intermediate role of established CHD risk factors (Ellis *et al.* 2001). These studies cannot reveal whether androgens form the link between MPB with CHD risk factors. We were able to study the effects of androgen administration in female-to-male (F→M) transsexuals, who requested hormonal induction of secondary sex characteristics of the opposite sex (Giltay & Gooren 2000). We have related androgen-induced changes in CHD risk factors in the first 3 months of treatment with MPB which occurred years later. During these first months of treatment the main changes in CHD risk factors occur, yielding more statistical power. Thus, we analyzed (i) the temporal effects of exogenous androgens on MPB in biological women, and (ii) the association between androgen-induced MPB and (changes in) established CHD risk factors to investigate whether MPB is associated with CHD risk factors.

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Subjects and Methods

All consecutive F→M transsexuals were approached for this study between January and July 2002. The degree of MPB was assessed by way of a self-assessment questionnaire using a 5-point scale (i.e. type I (no loss) to type V (complete hair loss at the crown); Fig. 1) (Lotufo *et al.* 2000), based on the scale by Norwood (1975). The questionnaire was filled in by 81 Caucasian F→M transsexuals with a mean age of 36·7 years (range 21–61). F→M transsexuals were treated either with 250 mg/2 weeks of testosterone esters i.m. ($n=61$) (Sustanon; Organon, Oss, The Netherlands) or with 160–240 mg/day oral testosterone undecanoate ($n=20$) (Andriol; Organon) following the patient's preference. For diagnosis and treatment, guidelines of the Harry Benjamin International Gender Dysphoria Association were followed (Walker *et al.* 1985). Testosterone administration aimed to reach serum testosterone levels within the normal range for men. We assumed that no MPB occurred prior to treatment and that any MPB was caused by androgen treatment. Androgen treatment started between 1977 and 2001 at our department and had a median duration of 8 years (range 0·5–24 years). None of the subjects was taking lipid-lowering therapy. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters and was a mean of 23·0 kg/m^2 (S.D. 4·6; range 15·6–41·0) at baseline. Systolic (SBP) and diastolic blood pressure (DBP) were taken and the mean arterial pressure (MAP; i.e. DBP+(SBP − DBP)/3) was calculated.

Retrospectively, we gathered baseline (i.e. before the start of androgen administration) as well as 3–4 month values of all parameters. We only used these values, because in our previous studies the strongest androgen-induced changes were found during the first months (Elbers *et al.* 2003), which consequently provides the strongest discriminating power to detect individual androgen-induced changes in CHD risk factors. In fasting blood samples we assessed levels of glucose (hexokinase method; Boehringer Mannheim), insulin (IRMA; Biosource Diagnostics, Fleurus, Belgium), HDL-cholesterol, low-density lipoprotein (LDL)-cholesterol, total cholesterol and triglycerides (enzymatic colorimetric method; Boehringer Mannheim), testosterone (Coat-A-Count; Diagnostics Products Corporation, Los Angeles, CA, USA), 17β-estradiol (Sorin Biomedica, Saluggia, Italy), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Amerlite Immunometric Luminescence Assay; Amersham). Complete laboratory values were available in 56 subjects. Measurements were performed within the scope of several studies, all of which had been approved by the Ethics Review Board of the Vrije University Medical Center in Amsterdam, and all subjects gave their informed consent to the present study.

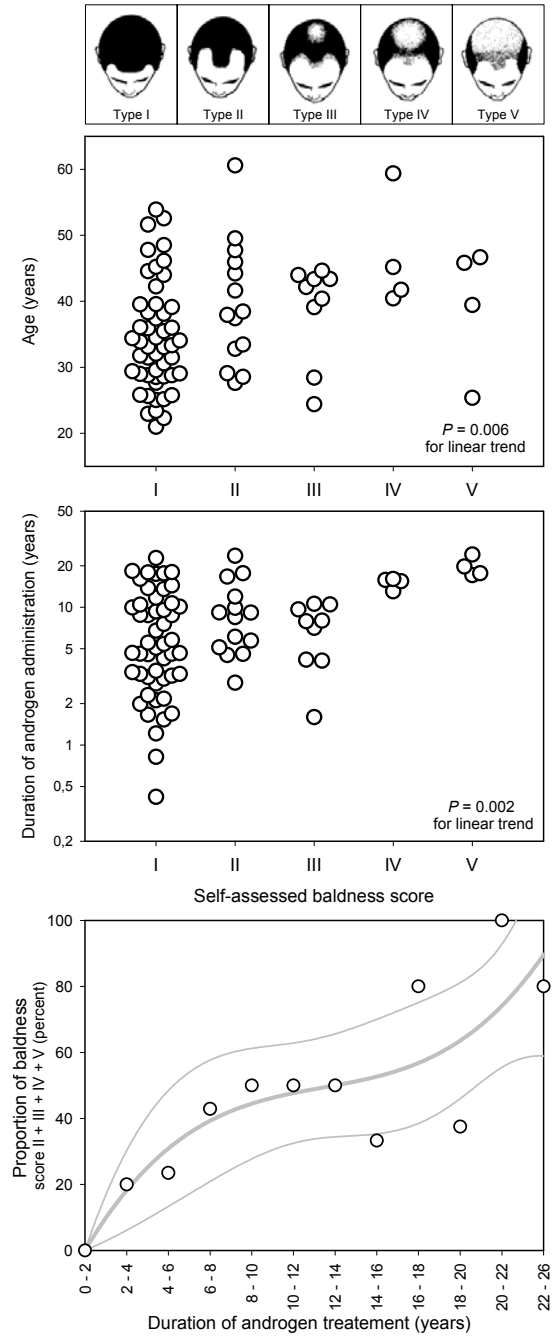

Figure 1 The two upper plots show the positive association of baldness with increasing age and duration of treatment. The spline plot (with 95% confidence intervals) shows the association of duration of treatment and MPB, which suggests that after about 13 years of androgen administration 50% of M→F transsexuals have developed thinning of the hair (baldness score II–V).

Variables with right-skewed distributions (i.e. testosterone, 17β-estradiol, LH, FSH, triglycerides and insulin) were logarithmically transformed before analysis. ANOVA

Table 1 Characteristics of F→M transsexuals before and upon testosterone administration. Testosterone, 17β-estradiol, LH, FSH, triglycerides and insulin were logarithmically transformed before analyses. Data are either means ± S.D. or, for logarithmically transformed values, medians (25 and 75 percentiles)

	Baseline	3–4 months of follow-up	*P*-value*
Variable			
Testosterone (nmol/l)	1·2 (0·5–1·8)	30·0 (16·0–42·5)	<0·001
17β-Estradiol (pmol/l)	167 (102–265)	139 (106–163)	0·044
LH (U/l)	3·7 (2·3–5·5)	1·8 (0·6–3·6)	<0·001
FSH (U/l)	4·4 (3·5–6·1)	3·4 (1·4–4·9)	0·002
BMI (kg/m^2)	22·89 ± 4·53	24·46 ± 3·85	<0·001
SBP (mmHg)	126·62 ± 13·14	122·02 ± 10·75	0·005
DBP (mmHg)	79·80 ± 8·00	77·72 ± 6·81	0·032
MAP (mmHg)	142·11 ± 15·70	136·74 ± 12·85	0·006
Total cholesterol (mmol/l)	4·57 ± 0·87	4·53 ± 1·12	0·656
HDL-cholesterol (mmol/l)	1·41 ± 0·43	1·14 ± 0·29	<0·001
LDL-cholesterol (mmol/l)	2·72 ± 0·86	3·03 ± 1·14	0·002
HDL/LDL ratio	0·59 ± 0·31	0·42 ± 0·18	<0·001
Triglycerides (mmol/l)	0·70 (0·55–1·20)	0·80 (0·60–1·05)	0·766
Glucose (mmol/l)	5·22 ± 1·26	4·90 ± 0·67	0·002
Insulin (pmol/l)	47·0 (32·0–73·0)	42·0 (30·3–52·0)	0·055

**P*-values by the *t*-test for paired samples.

trend analyses were used to seek for linear trends between the degree of baldness and risk factors for CHD. Independent-sample *t*-tests, paired-sample *t*-tests, ANOVA and a multivariate general linear model were used as appropriate. Proportional changes were calculated as the ratio of the 3-month value over the baseline value (× 100%). If measurements appeared to be below the lower limit of detection, the value of that lower limit divided by 2 was used for statistical analyses. Analyses were performed with SPSS 8·0.

Results

Table 1 shows the changes upon testosterone administration. Serum levels of testosterone increased significantly, whereas 17β-estradiol, LH and FSH decreased significantly. BMI increased and the SBP, DBP and MAP decreased. Both insulin and glucose levels decreased. HDL-cholesterol levels decreased by 17%, whereas LDL-cholesterol levels increased by 13%, leading to a 22% decrease in the ratio of HDL to LDL. No statistically significant changes were found for total cholesterol and triglyceride levels.

The 81 F→M transsexuals classified themselves as MPB type I (n=50; 61·7%), II (n=14; 17·3%), III (n=9; 11·1%), IV (n=4; 4·9%) and V (n=4; 4·9%). There were no baseline differences between subjects who later developed MPB type I vs MPB type II–V for any of the measurements (i.e. testosterone, 17β-estradiol, LH, FSH, BMI, SBP, DBP, MAP, total-, HDL- and LDL-cholesterol, HDL/LDL ratio, triglycerides, glucose or insulin). As expected, MPB was significantly related to age and the duration of treatment (Fig. 1). Spline plots showed that after 13 years of androgen administration, hair loss (type II–V) had started in about 50% of F→M transsexuals (Fig. 1). A more severe MPB type III–V was present in 50% of F→M transsexuals only after 24 years of androgen administration. The 61 F→M transsexuals treated with parenteral testosterone had a similar degree of hair loss as compared with the 20 F→M transsexuals treated with oral testosterone undecanoate (P=0·28).

Because of the low number of subjects with class II, III and IV type of baldness, these three classes were collapsed in further analyses. None of the CHD risk factors (i.e. blood pressure, BMI, levels of lipids and insulin) at 3–4 months was associated with the degree of hair loss, except for lower fasting glucose levels in more severely balding subjects (Table 2), a finding that contrasts with our hypothesis. In particular, the strong and consistent change in the ratio of HDL- over LDL-cholesterol was not related to the degree of hair loss. The proportional changes during the first 3–4 months of treatment were neither related to the degree of hair loss (data not shown). Adjusting for treatment duration, age and the route of administration (oral or parenteral) had no influence (data not shown).

Discussion

It has been hypothesized that androgens link MPB and established CHD risk factors, and consequently explain the higher rate of CHD in balding men (Lesko *et al.* 1993, Herrera *et al.* 1995, Schnohr *et al.* 1995, Ford *et al.* 1996,

Table 2 Comparing established CHD risk factors at 3–4 months of androgen administration in 81 F→M transsexuals between different categories of MPB (i.e. androgenic alopecia). Testosterone, 17β-estradiol, LH, FSH, triglycerides and insulin were logarithmically transformed before analyses. Data are either means ± S.D. or, for logarithmically transformed values, medians (25 and 75 percentiles)

	Non-balding (type I) (n=50)	**Balding (type II)** (n=14)	**Balding (type III+IV+V)** (n=17)	***P*-value***	***P*-value****
Variable					
Testosterone (nmol/l)	30·2 (15·7–39·7)	33·3 (21·8–60·5)	20·5 (5·4–46·9)	0·77	0·51
17β-Estradiol (pmol/l)	144 (111–175)	129 (95–150)	127 (107–188)	0·48	0·55
LH (U/l)	2·0 (0·6–3·6)	2·1 (1·1–5·4)	1·1 (0·4–2·3)	0·44	0·26
FSH (U/l)	3·2 (1·0–5·1)	4·4 (3·1–5·5)	2·7 (1·5–3·7)	0·39	0·12
BMI (kg/m^2)	24·1 ± 3·0	25·7 ± 3·7	25·4 ± 5·1	0·12	0·21
SBP (mmHg)	122·2 ± 10·5	123·8 ± 11·2	120·1 ± 10·3	0·59	0·63
DBP (mmHg)	77·0 ± 7·5	79·4 ± 6·8	78·2 ± 5·5	0·43	0·53
MAP (mmHg)	137·3 ± 12·5	138·5 ± 13·0	134·0 ± 12·5	0·45	0·67
Total cholesterol (mmol/l)	4·4 ± 0·8	5·1 ± 1·7	4·5 ± 1·2	0·39	0·12
HDL-cholesterol (mmol/l)	1·10 ± 0·24	1·24 ± 0·29	1·14 ± 0·38	0·42	0·34
LDL-cholesterol (mmol/l)	2·91 ± 0·90	3·47 ± 1·55	3·04 ± 1·22	0·44	0·33
HDL/LDL ratio	0·41 ± 0·16	0·43 ± 0·23	0·42 ± 0·19	0·88	0·98
Triglycerides (mmol/l)	0·82 (0·65–1·04)	0·65 (0·60–1·55)	0·90 (0·52–1·12)	0·82	0·97
Glucose (mmol/l)	5·01 ± 0·74	4·67 ± 0·33	4·47 ± 0·60	0·02	0·06
Insulin (pmol/l)	43·2 (34·1–53·2)	36·5 (28·0–58·5)	34·0 (21·0–55·5)	0·09	0·22

**P*-values by the weighted linear term in an ANOVA.
***P*-values corrected for the duration of treatment in a multivariate general linear model.

Lotufo *et al.* 2000, Matilainen *et al.* 2001). Our findings, however, do not support the idea that androgen-induced changes in established CHD risk factors explain the epidemiological association between MPB and CHD. What may explain our null-finding? First, the degree of MPB and established CHD risk factors may be unrelated, as was found in a study among 1219 males (Ellis *et al.* 2001). Yet the lack of association between MPB and CHD risk factors contrasts with findings of two cohort studies (Trevisan *et al.* 1993, Lotufo *et al.* 2000) and a case-control study (Matilainen *et al.* 2000) that found associations between MPB and CHD risk factors. We found that levels of fasting glucose and insulin were somewhat lower in balding subjects, which contrasts with the positive associations found between disorders clustered in the metabolic syndrome and MPB (Matilainen *et al.* 2000). The discrepancy may be the consequence of our study group of F→M transsexuals in whom endogenous androgens were naturally low at baseline, and in whom androgen administration induced both MPB and strong changes in serum lipids and body weight but not in blood pressure. Secondly, it could be that androgens do not link MPB with established CHD risk factors. Although sensitivity of the scalp to androgens is the important component of the pathophysiology of MPB, it may be unrelated to the epidemiological association between MPB and CHD. Moreover, androgen excess is not always present in men with MPB nor in women with androgenic alopecia (Futterweit *et al.* 1988, Vexiau *et al.* 2000), and among subjects in whom androgens have induced MPB CHD morbidity and mortality are not necessarily increased (e.g. 293 F→M transsexuals during the 2418 person-years of androgen treatment (van Kesteren *et al.* 1997) and 319 women with PCOS followed for 31 years (Wild *et al.* 2000)).

Thirdly, some CHD risk factor not studied may be the intermediate. In that case, androgen metabolism and sensitivity is still directly involved, but through a pathway other than classic CHD risk factors. It could be hypothesized that heightened androgen action (Horton *et al.* 1993, Hibberts *et al.* 1998, Vierhapper *et al.* 2001) is present in the balding scalp as well as in endothelium, macrophages and vascular smooth muscle cells, which contain sex steroid receptors (McGill *et al.* 1980, Hodges *et al.* 1999). Androgens may negatively affect smooth muscle cell proliferation and endothelial and macrophage function, and consequently relate MPB to CHD. Further, insulin-like growth factor I (IGF-I) is a regulator of skin 5α-reductase activity increasing dihydrotestosterone formation (Horton *et al.* 1993, Signorello *et al.* 1999). High levels of IGF-I have also been related to an increased risk of vertex baldness (Signorello *et al.* 1999).

Our study has some potential limitations. MPB evaluation was self-assessed, F→M transsexuals were unfamiliar with the classification system, and the questionnaire was not internally validated, providing a source of misclassification. The effects of testosterone in humans also depend on the endocrine environment already determined by the sex and age of the studied subjects, and therefore we do not know whether the results would be similar in biological men receiving androgens. Moreover, our study may have been statistically underpowered, since we included only a relatively small group of subjects due to the nature of the treatment indication. Yet this study

provided a unique and attractive model of F→M transsexuals in whom androgens induced MPB as well as changes in CHD risk factors.

Changes in several CHD risk factors were rather quick and established within months, while the onset of hair loss appeared only after about 13 years in 50% of F→M transsexuals. This is in accord with the observation that in either sex thinning of the hair begins between the ages of 12 and 40 years and that approximately 50% of Caucasian men have some degree of MPB before the age of 50 (Price 1999). As expected, we found that MPB increased in prevalence and severity with age and duration of androgen administration. Apparently, biological women are as similarly prone to MPB as biological men, when their androgen receptors are exposed to testosterone and its 5α-reduced metabolite dihydrotestosterone. Dihydrotestosterone is the important mediator of MPB, as illustrated by the effectiveness of finasteride in stopping MPB (Price 1999) and high production rates in men with MPB (Horton *et al.* 1993, Hibberts *et al.* 1998, Vierhapper *et al.* 2001). In summary, our findings do not support the idea that MPB serves as an indicator of increased CHD risk through androgenic effects on classic CHD risk factors.

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