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Gemfibrozil Treatment is Associated with Elevated Adrenal Androgen, Androstanediol Glucuronide and Cortisol Levels in Dyslipidemic Men

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We have investigated the role of steroid hormones as coronary risk factors in the Helsinki Heart Study population of dyslipidemic middle-aged men. We compare here the effects of gemfibrozil and placebo on the serum levels of dehydroepiandrosterone (DHEA), its sulfate (DHEAS), their metabolite androstanediol glucuronide (3α-AdiolG), androstenedione, cortisol, testosterone, and sex-hormone binding globulin (SHBG) in non-smokers. We also examined the associations between steroid and lipoprotein levels in both treatment groups. Compared with placebo gemfibrozil treatment was associated with significant elevations of the mean levels of DHEA 10.2 vs 8.0 nmol/l; $P < 0.005$, of DHEAS 8.0 vs 5.8 μmol/l; $P < 0.001$, of 3αAdiolG 18.3 vs 8.4 nmol/l; $P < 0.001$, of androstenedione 5.7 vs 5.1 nmol/l; $P < 0.02$, and of cortisol 426 vs 358 nmol/l; $P < 0.001$. The mean SHBG levels decreased from 46.4 to 41.7 nmol/l; $P = 0.03$ with gemfibrozil treatment. No difference was found in testosterone levels 17.7 vs 18.8 nmol/l; $P = 0.11$, or the ratio of testosterone/SHBG 0.45 vs 0.43; $P = 0.23$. Positive correlations were found between high density lipoprotein-cholesterol and DHEAS ($r = 0.267$; $P < 0.01$) and DHEA ($r = 0.282$; $P < 0.01$) levels and negative correlations between low density lipoprotein-cholesterol and 3α-AdiolG ($r = -0.400$; $P < 0.001$) and cortisol ($r = -0.281$; $P < 0.01$) levels in the gemfibrozil group. Our results indicate that gemfibrozil treatment increases the production and turnover of adrenal androgens and cortisol, and suggest that activation of the adrenocortical function and increased metabolism of androgens are related to the improved lipoprotein pattern during gemfibrozil treatment.

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INTRODUCTION

Gemfibrozil, a fibric acid derivative, decreases plasma low density lipoprotein (LDL)-cholesterol and triglyceride (TG) and increases high density lipoprotein (HDL)-cholesterol concentrations [1]. Its precise mode of action on lipoprotein metabolism is unknown, although enhanced activity of lipoprotein and hepatic lipases as well as a decrease in hepatic TG synthesis might be of importance [2, 3]. Gemfibrozil reduced the incidence of coronary heart disease (CHD) in middle-aged, dyslipidemic men in the Helsinki Heart Study (HHS) [4]. The present data originates from a nested case-control study on the roles of adrenal cortical steroids, testosterone, and sex-hormone binding globulin (SHBG) as potential risk factors for CHD in the HHS population [5]. We have reported in a preliminary communication that gemfibrozil may increase the production and turnover of adrenal androgens [6]. In this paper we extend the analyses to the effect of gemfibrozil on cortisol, testosterone and SHBG and examine the associations between gemfibrozil induced lipid changes and hormone levels.

SUBJECTS AND METHODS

The study participants were dyslipidemic (non-HDL-cholesterol $\geqslant 5.2$ mmol/l) middle-aged men, free of CHD at the beginning of the 5 year study. Fatal and

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non-fatal myocardial infarction as well as cardiac death were the principal endpoints. For the study of adrenal cortical hormones as CHD risk factors a nested case-control design was used [5]. Cases consisted of subjects with a cardiac end-point during the last 4 years of the HHS. For each case two controls were chosen from participants without coronary events. Because smoking elevated the levels of all hormones measured [7], this paper deals with the effect of gemfibrozil on the non-smoking participants (90 treated with gemfibrozil and 105 with placebo).

Serum samples drawn after an overnight fast at the first annual follow-up visit, e.g. 1 year after initiation of the placebo or gemfibrozil treatment, were used to determine the basal serum levels of steroids. Commercial radioimmunoassay (RIA) kits were used for the determination of cortisol, testosterone, (Farmos Diagnostica, Oulu, Finland), dehydroepiandrosterone-sulfate (DHEAS; Wien Labs, Inc., Succasunna, NJ, U.S.A.), and 5α-androstane-3α,17β-diol glucuronide (androstanediol glucuronide, 3α-AdiolG; Diagnostic Systems Labs, Inc., Webster, TX, U.S.A.). Androstenedione and dehydroepiandrosterone (DHEA) were determined by RIA as described previously [7]. Antisera for androstenedione and DHEA were from Steranti Research Ltd Co. (St Albans, England) and from Radioassay Systems Labs (Carson, CA, U.S.A.), respectively. SHBG was determined by the DELFIA kit from Farmos. The mean SHBG levels of the control samples were 26.4% higher by this method as compared with the immunoradiometric assay (IRMA) we have used previously [8]. Means of duplicate determinations were used in all calculations. Low- and high-value quality controls in duplicate were included in each assay. Samples were re-run, if duplicate values differed more than 10% from their calculated mean. The intra- and interassay coefficients of variation (CV) were 6.4 and 7.0% for cortisol, 6.2 and 7.5% for DHEAS, 6.3 and 7.7% for DHEA, 5.7 and 9.2% for androstenedione, 4.4 and 8.5% for testosterone, and 2.9 and 8.9% for SHBG, respectively. The intra-assay CV of the 3α-AdiolG assay varied between 8.9 and 13.6% (concentration range 1.1–21.8 nmol/l) and the interassay CV between 6.0 and 13.7% (range 1.1–24.7 nmol/l).

The differences between groups in continuous variables were estimated using either the *t*-test or analysis of variance, while the chi-square test was applied for class variables.

RESULTS

Descriptive baseline statistics of the 195 study participants is given in Table 1. There were no significant differences in the baseline levels of any lipids between the gemfibrozil and placebo treated groups. Gemfibrozil treatment reduced serum total cholesterol from 7.62 ± 0.91 to 6.42 ± 1.14 mmol/l; $P < 0.001$, LDL-cholesterol from 5.39 ± 0.90 to 4.55 ± 1.12 mmol/l; $P < 0.005$, and triglycerides from 2.28 ± 2.09 to 1.08 ± 0.64 mmol/l; $P < 0.001$. HDL-cholesterol increased with gemfibrozil from 1.253 ± 0.305 to 1.386 ± 0.341 mmol/l; $P < 0.001$.

Table 1. Baseline statistics of the 195 non-smoking study participants, means (SD) and percentages

Variable	Placebo ($n = 105$)	Gemfibrozil ($n = 90$)	*P* value
Age (years)	48.5 (4.5)	47.9 (4.6)	0.18
Body mass (weight/height^2)	26.8 (3.9)	26 6 (2.4)	0 35
Systolic BP (mmHg)	143.4 (19.0)	146.7 (16.7)	0.10
Diastolic BP (mmHg)	92.6 (10.8)	94.2 (9 0)	0.13
Cholesterol (mmol/l)	7.62 (0.76)	7.62 (0.91)	0.49
HDL-cholesterol (mmol/l)	1.239 (0.289)	1.253 (0.305)	0.36
Triglycerides (mmol/l)	2.36 (1.69)	2.28 (2.09)	0.39*
Alcohol consumption	463 (617)	400 (442)	0.21*
(cl absolute alcohol/year)	$n = 99$	$n = 84$	
Physically active	47.6%	48.9%	0.57

*After logarithmic transformation

Gemfibrozil treatment in this non-smoking population was associated with significantly higher levels of DHEAS, DHEA, androstenedione, 3α-AdiolG, and cortisol when compared with placebo. No difference was found in testosterone levels, while the SHBG levels were significantly lower (Table 2).

The relationship between gemfibrozil induced lipid changes and hormones was studied by comparing the mean hormone levels in the lipid response categories. The responses were calculated as differences between the baseline and 1-year determinations. A direct comparison was possible, because the baseline lipid levels in the response categories were not significantly different. DHEAS in subjects with no gemfibrozil induced HDL-increase was not different from the placebo, while the level was markedly elevated in the medium HDL-response category of 0.01–0.20 mmol/l. However, a response of $\geqslant 0.21$ mmol/l was not associated with any further increment in DHEAS (Table 3). HDL-response was positively associated with

Table 2. Mean (SD) values for steroid determinations in the gemfibrozil and placebo groups in the HHS population

Steroid	Placebo ($n = 105$)	Gemfibrozil ($n = 90$)	*P* value
DHEAS (μmol/l)	5.8 (2.8)	8.0 (5.0)	<0.001
DHEA (nmol/l)	8.0 (4.2)	10.2 (7.3)	0.005
3α-AdiolG (nmol/l)	8.4 (3 1)	18.3 (8.2)	<0.001
Androstenedione (nmol/l)	5.1 (1.3)	5.7 (2.1)	0.015
Cortisol (nmol/l)	358 (110)	426 (140)	<0.001
Testosterone (nmol/l)	18.8 (6.4)	17.7 (5.4)	0.11
SHBG (nmol/l)	46.4 (18.7)	41.7 (14.6)	0.03
Testosterone/SHBG ratio	0.43 (0.12)	0.45 (0.14)	0.23
DHEA/androstenedione ratio	1.55 (0.63)	1.67 (0.84)	0 13
Androstenedione/cortisol ratio (× 1000)	15.3 (5.2)	14.0 (4.3)	0.042

DHEA(S), dehydroepiandrosterone (sulfate); 3α-AdiolG, androstanediol glucuronide; SHBG, sex hormone-binding globulin.

Table 3. Association between gemfibrozil induced HDL-cholesterol changes and the levels of selected hormones in non-smoking study participants, means (SD)

Hormone	Placebo ($n = 105$)	HDL-increase with gemfibrozil (mmol/l) <0.00 ($n = 21$)	0.01–0.20 ($n = 37$)	>0.21 ($n = 31$)	P value*
DHEAS (μmol/l)	5.8 (2.8)	6.2 (3.3)	8.7 (6.2)	8.6 (4.3)	0.16
DHEA (nmol/l)	8.0 (4.2)	9.7 (6.9)	11.5 (8.7)	9.1 (5.5)	0.34
Androstenedione (nmol/l)	5.1 (1.3)	5.6 (1.8)	5.9 (2.6)	5.5 (1.6)	0.77
3α-AdiolG (nmol/l)	8.4 (3.1)	16.1 (7.0)	18.5 (9.6)	19.7 (7.0)	0.30
Cortisol (nmol/l)	358 (111)	440 (134)	438 (160)	405 (123)	0.56

*ANOVA between hormone levels in gemfibrozil induced lipid response categories.
For abbreviations see Table 2.

3α-AdiolG, yet even in the lowest response category the hormone level was 2-fold compared to placebo. There was a positive dose–response association with LDL-decrease and serum 3α-AdiolG and cortisol increase, but the differences were not statistically significant (Table 4).

Pearson's correlations between steroid concentrations and age, body mass index (BMI), and lipoprotein fractions according to the treatment status (placebo or gemfibrozil) are given in Table 5. Age was negatively correlated with DHEAS in both placebo and gemfibrozil groups, with DHEA in the former, and with 3α-AdiolG in the latter group. BMI and cortisol levels tended to be negatively associated, although the correlations were not statistically significant. LDL-cholesterol was positively correlated with DHEA and cortisol in the placebo group, but negatively correlated with 3α-AdiolG and cortisol in the gemfibrozil group. HDL-cholesterol was negatively associated with 3α-AdiolG in the placebo group, but positively associated with DHEAS and DHEA in the gemfibrozil group. TG and cortisol were negatively correlated in the placebo group. However, when the Bonferroni correction for multiple testing was taken into account, only the negative correlation between 3α-AdiolG and LDL-cholesterol remained significant in the matrix ($P = 0.01$). The negative association between 3α-AdiolG and LDL-cholesterol is illustrated in Fig. 1.

Multiple linear regression analyses were also used to examine the contribution of some steroids to the variation of lipoprotein levels. When LDL-cholesterol was used as the dependent variable in the regression models, 3α-AdiolG explained 10.9%, and the combination of gemfibrozil treatment, age, BMI, and 3α-AdiolG 13.9% of the variation in the LDL-cholesterol levels of the whole study group. (Table 6, models 1–3). It should be noted, that gemfibrozil treatment was not a significant predictor of LDL-cholesterol in these models. When only the gemfibrozil group was considered, 3α-AdiolG and cortisol explained 16.0 and 7.9%, respectively, of the variation in the LDL-cholesterol levels independent of age and BMI (Table 6, models 4–6). Although univariate correlations of cortisol and DHEAS with HDL-cholesterol were positive in the whole study group, gemfibrozil treatment and BMI remained the major predictors of the HDL-cholesterol levels in multivariate analyses (Table 7).

DISCUSSION

These results indicate that serum levels of adrenal androgens and cortisol are increased during gemfibrozil treatment, the androgen metabolite 3α-AdiolG levels more than 2-fold. This phenomenon is associated with a decrease of SHBG levels, while testosterone levels remain unaffected. Coincidently, there is an expected

Table 4. Association between gemfibrozil induced LDL-cholesterol changes and the levels of selected hormones in non-smoking study participants, means (SD)

Hormone	Placebo ($n = 105$)	LDL-decrease with gemfibrozil (mmol/l) <0.00 ($n = 22$)	0.01–0.99 ($n = 30$)	>1.0 ($n = 25$)	P value*
DHEAS (μmol/l)	5.8 (2.8)	7.7 (3.7)	8.4 (4.4)	8.3 (6.2)	0.87
DHEA (nmol/l)	8.0 (4.2)	8.6 (6.9)	11.7 (8.1)	10.1 (6.9)	0.33
Androstenedione (nmol/l)	5.1 (1.3)	5.7 (2.4)	5.6 (1.8)	5.7 (2.2)	0.90
3α-AdiolG (nmol/l)	8.4 (3.1)	15.6 (7.9)	19.2 (8.6)	19.6 (7.8)	0.19
Cortisol (nmol/l)	358 (111)	392 (135)	426 (140)	442 (142)	0.36

*ANOVA between hormone levels in gemfibrozil induced lipid response categories.
For abbreviations see Table 2.

Table 5. Pearson's correlations between steroid levels and age, BMI, and lipid fractions in the placebo and gemfibrozil groups in the non-smoking participants of the HHS[a]

Steroid	Age	BMI	LDL-Chol	HDL-Chol	Triglycerides
DHEAS	−0.242*	0.100	−0.135	−0.030	0.181
	(−0.369)***	(0.046)	(−0 082)	(0.267)**	(−0.078)
DHEA	−0.95	0.073	0.200*	−0.015	0.012
	(−0.286)**	(−0.117)	(−0.140)	(0.282)**	(−0.132)
Androstenedione	−0.132	0.118	0.108	−0.049	0.008
	(−0.167)	(−0.046)	(−0.046)	(0.121)	(−0.080)
3α-AdiolG	−0.333***	0.008	−0.122	−0.268**	0.162
	(−0.046)	(−0.067)	(−0.400)***	(0.042)	(0.077)
Cortisol	−0.165	−0.190	0.207*	0.148	−0.221*
	(−0.077)	(−0.182)	(−0.281)**	(0.201)	(−0.195)

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

*, **P = Non-significant, ***P = 0.01 after Bonferroni adjusted probabilities.

[a]Gemfibrozil group in parentheses.

Steroids and triglycerides were logarithmically transformed for calculations.

For abbreviations see Table 2

decrease in triglyceride and LDL-cholesterol and an increase in HDL-cholesterol levels [1, 3].

Fibrates belong to a class of xenobiotic compounds called peroxisome proliferators [9, 10]. Recently a novel member (PPAR, peroxisome proliferator-activated receptor) of a hormone receptor superfamily was cloned, and found to be activated by a group of xenobiotic compounds (typified by clofibrate) [11]. The putative natural ligands of PPAR remain to be identified: recent evidence suggests, however, that fatty acids may activate this receptor, whereby the physiological role of this receptor might be linked to lipid homeostasis [12]. Distinct effects from the receptor activation by peroxisome proliferators are the increased transcription of genes of the cytochrome P-450 superfamily of drug-metabolizing enzymes and also of genes required for the metabolism of long-chain fatty acids in peroxisomes [9].

We can only speculate about the mechanism, whereby gemfibrozil elevates the serum levels of adrenal cortical hormones. By the activation of PPAR, fibrates could act by a mechanism similar to steroid hormones. If so, it is possible that gemfibrozil might activate the pituitary–adrenocortical axis through steroid receptors in the central nervous system, a hypothesis supported by the observed stimulation by fibrates of vasopressin, which can act as a secretagogue for corticotropin [13, 14]. Alternatively, gemfibrozil

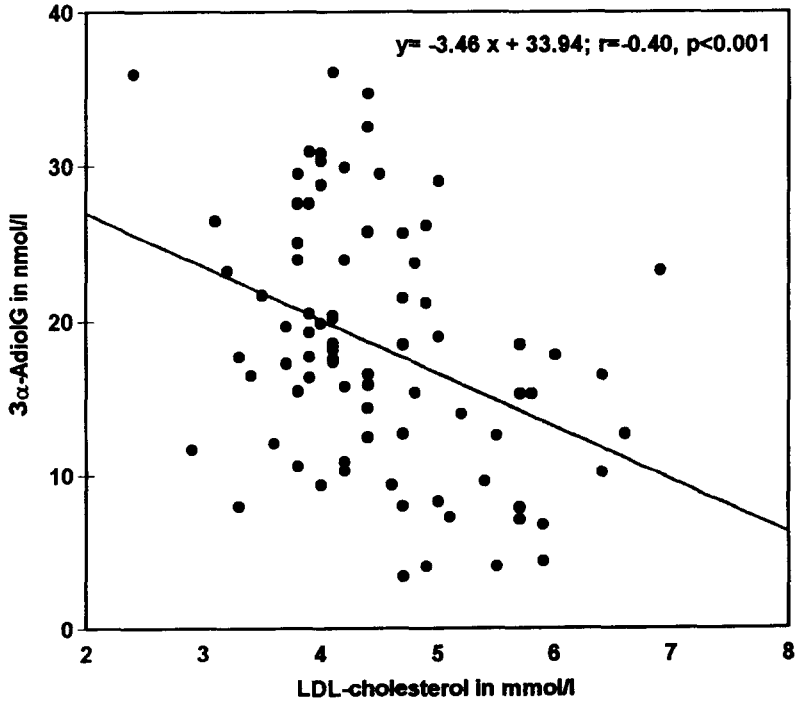

Fig. 1. The relationship between androstanediol glucuronide (3α-AdiolG) and LDL-cholesterol levels in gemfibrozil-treated subjects.

Table 6. Multiple regression models for the prediction of the LDL-cholesterol levels in the study groups[a]

Model[b]	Independent variable(s)	Standardized coefficient of regression	*P*-value (2-tail)	Model R^{2c}
1.	3α-AdiolG	−0.330	<0.001	0.109
2.	Gemfibrozil treatment	0.035	0.698	0.110
	3α-AdiolG[d]	−0.351	<0.001	
3.	Gemfibrozil treatment	0.039	0.655	0.139
	Age	−0.031	0.659	
	BMI	−0.170	0.015	
	3α-AdiolG	−0.366	<0.001	
4.	3α-AdiolG	−0.400	<0.001	0.160
5.	Age	−0.070	0.499	0.167
	BMI	0.058	0.572	
	3α-AdiolG	−0.399	<0.001	
6.	Cortisol	−0.281	0.009	0.079
7.	Age	−0.028	0.794	0.083
	BMI	0.058	0.596	
	Cortisol	−0.272	0.013	

[a] Independent variables in the regression models have been used in groups as shown to predict the LDL-cholesterol levels.

[b] Models 1, 2, and 3 contain all study subjects, whereas models 4, 5, 6, and 7 contain only subjects on gemfibrozil.

[c] R^2 (the square of the multiple regression coefficient) gives the proportion of the total variation in the LDL-cholesterol levels that is explained by the variables in the model.

[d] Androstanediol glucuronide. All steroid concentrations were log transformed for the models.

may activate the steroidogenic adrenocortical enzymes most of which are members of the cytochrome *P*-450 group of oxidases. Some evidence for this notion was provided by the slight but significant decrease of the androstenedione/cortisol ratio by gemfibrozil suggesting increased activity of either 21- or 11β-hydroxylases. Experimental evidence also supports the hypothesis that the cytochrome *P*-450 system may be involved in the mechanism of action of gemfibrozil [15].

Of the steroids measured, the most striking was the increase in 3α-AdiolG levels. The main source of plasma 3α-AdiolG is controversial, but in middle-aged men it appears to be derived from both gonadal and adrenal androgens [16]. In our previous report, we proposed that gemfibrozil may, in addition to an increase in production and turnover of DHEA and DHEAS, stimulate the 5α-reduction of androgens thereby affecting also serum testosterone levels [6]. The present data, however, reveal that testosterone levels remain unaffected, while the SHBG levels decline during gemfibrozil treatment. Although the testoster-

Table 7. Multiple regression models for the prediction of the HDL-cholesterol levels in the study groups[a]

Model[b]	Independent variable(s)	Standardized coefficient of regression	*P*-value (2-tail)	Model R^{2c}
1.	Cortisol	0.231	0.001	0.053
2.	Gemfibrozil treatment	0.233	0.001	0.104
	Cortisol	0.172	0.017	
3.	Gemfibrozil treatment	0.236	0.001	0.149
	Age	−0.035	0.608	
	BMI	−0.214	0.002	
	Cortisol	0.127	0.077	
4.	DHEAS	0.195	0.007	0.038
5.	Gemfibrozil treatment	0.244	0.001	0.094
	DHEAS	0.137	0.057	
6.	Gemfibrozil treatment	0.235	0.001	0.152
	Age	−0.006	0.932	
	BMI	−0.241	0.001	
	DHEAS	0.143	0.054	

[a] See footnote in Table 6. Placebo and gemfibrozil groups combined.

one/SHBG ratio remains unchanged, lower SHBG levels may enhance the metabolic clearance of testosterone, which might contribute to the elevation of 3α-AdiolG levels.

We have not examined the possibility that the elevation of adrenal steroids is an artifact resulting from cross-reactions of gemfibrozil and its metabolites in the steroid assays. This appears to be less probable, because testosterone levels tended to be lower in the gemfibrozil-treated group.

Is the increase of adrenocortical steroids by gemfibrozil treatment related to the change in the lipoprotein pattern? No significant differences were found when the mean steroid levels were compared in various gemfibrozil induced lipid response categories (baseline vs 1-year determinations), in spite of the positive trends between the HDL-increase and DHEAS and DHEA and between the LDL-decrease and 3α-AdiolG and cortisol levels. When univariate comparisons were carried out between lipid and steroid levels determined on samples drawn at the same 1-year visit, the negative correlation between 3α-AdiolG and LDL-cholesterol remained significant even after stringent Bonferroni adjusted probability. Multivariate modeling further demonstrated that 3α-AdiolG was a more important determinant of LDL-cholesterol levels than were age, BMI, and gemfibrozil treatment. Cortisol was also a significant predictor of LDL-cholesterol independent of age and BMI. In contrast, the relationships between HDL-cholesterol, DHEAS, and cortisol were less conclusive in multivariate models, when adjusted for age, BMI, and gemfibrozil treatment.

The fact that lipoprotein cholesterol is the major precursor for adrenal steroid synthesis suggests that the associations found are causal. Nevertheless, considering the cross-sectional nature of this study and the large number of correlations computed fortuitous associations between lipid and steroid levels are possible.

Prior evidence suggests that low DHEA levels might lead to increased cholesterol production as a result of the lack of inhibition by DHEA on glucose-6-dehydrogenase, a key enzyme of the pentose cycle [17–19]. Recent results from this laboratory suggest, however, that several abnormalities in insulin and lipoprotein metabolism may result from the altered function of the pituitary–adrenocortical axis [5, 20, 21]. First, abdominal obesity, hyperinsulinemia, and closely related TG and HDL-cholesterol changes might be associated with a mild hypocortisolism [20]. Our original interpretation regarding the hypothalamic etiology of the latter is probably incorrect, since our recent results suggest that the basic defect underlying the observed alterations in the pituitary–adrenocortical axis in abdominal obesity is partial 21-hydroxylase deficiency (A. Hautanen and H. Adlercreutz, unpublished data). Although the HHS did not specifically address abdominal obesity or insulin levels, cortisol levels in this population also tended to correlate negatively with BMI. Second, smoking inhibits adrenal 21-hydroxylase thereby increasing the secretion of DHEA and androstenedione relative to cortisol, which might also contribute to the insulin resistance and dyslipidemia of smokers [21]. Third, we have found that high DHEAS levels were a risk factor for CHD in the HHS population [5]. Taken together, it appears that not only the correct set point for regulation of hypothalamic–pituitary–adrenal function, but also the DHEA/androstenedione/cortisol balance might affect glucose and lipoprotein metabolism. Increased production of cortisol and metabolism of adrenal androgens and testosterone might lead to decreased androgen activity and improved lipoprotein pattern in gemfibrozil-treated subjects.

In summary, gemfibrozil treatment produces favorable changes in plasma lipoprotein levels, but is also associated with an increase in the levels of adrenocortical androgens, 3α-AdiolG, and cortisol while testosterone levels remain unaffected. These as well as our previous data may suggest that pituitary–adrenocortical function and androgen metabolism are related to the physiological regulation of lipoprotein metabolism.

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