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The effect of testosterone on cardiometabolic risk factors in atorvastatin-treated men with late-onset hypogonadism

Robert Krysiak [a,*], Wojciech Gilowski [a,b], Bogusław Okopień [a]

[a] Department of Internal Medicine and Clinical Pharmacology, Medical University of Silesia, Katowice, Poland
[b] Cardiology Department, Chrzanow District Hospital, Chrzanów, Poland

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ABSTRACT

Background: By reducing LDL cholesterol levels, statins may decrease androgen production. This study was aimed at investigating whether testosterone treatment has an impact on cardiometabolic risk factors in statin-treated men with late-onset hypogonadism (LOH).
Methods: The study included 31 men with LOH who had been treated for at least 6 months with atorvastatin (20–40 mg daily). On the basis of patient preference, atorvastatin-treated patients were divided into two matched groups of patients: receiving intramuscular testosterone enanthate (100 mg weekly, $n = 16$) and not treated with this hormone ($n = 15$). Plasma lipids, glucose homeostasis markers, as well as plasma levels of androgens, uric acid, high-sensitivity C-reactive protein (hsCRP), homocysteine, and fibrinogen were assessed before and after 4 months of therapy.
Results: Compared with the control age-, weight, and lipid-matched statin-naïve subjects with LOH ($n = 12$), atorvastatin-treated patients were characterized by decreased levels of testosterone, hsCRP, and homocysteine. In patients not receiving testosterone therapy, plasma lipids, glucose homeostasis markers, as well as plasma levels of the investigated risk factors remained at the similar levels throughout the whole period of atorvastatin treatment. In atorvastatin-naïve patients, testosterone increased its plasma levels and decreased HDL cholesterol. Apart from an increase in testosterone levels, if administered to atorvastatin-treated subjects with LOH, testosterone reduced plasma levels of LDL cholesterol, uric acid, hsCRP, homocysteine, and fibrinogen, as well as improved insulin sensitivity.
Conclusions: Our study may suggest the clinical benefits associated with combination therapy with a statin and testosterone in elderly men with LOH.

Introduction

In opposition to the abrupt cessation of ovarian estrogen production, the decline in testicular endocrine function begins slowly around the age of 40 years [1]. In men aged between 40 and 70 years, total testosterone level falls by about 1.6% per year, while free and bioavailable testosterone by about 2–3% per year [2]. The slow nature of testosterone decline in the elderly causes that clinical symptoms are less expressed than in young hypogonadal men and the clinical manifestation of testosterone deficiency is characterized by great individual variability [3]. Some middle-aged and elderly men may develop late-onset hypogonadism (LOH), also known under the names of androgen deficiency in the aging male, partial androgen deficiency in the aging male or andropause, and defined as a clinical and biochemical syndrome associated with advancing age, characterized by typical symptoms, and deficiency in serum testosterone levels [4]. Low testosterone levels in aging men is accompanied by a decrease in muscle mass and strength, osteopenia or osteoporosis, increased adiposity, decreased insulin sensitivity, impaired sexual function, cognitive disturbances, and impaired quality of life [5–7]. In the light of recent clinical studies, low plasma testosterone levels are associated with increased cardiovascular morbidity and mortality [8,9]. The decrease in serum testosterone in more pronounced in men with hypertension,

Abbreviations: DHEA-S, dehydroepiandrosterone sulphate; HDL, high-density lipoprotein; HOMA1-IR, the homeostatic model assessment 1 of insulin resistance ratio; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LOH, late-onset hypogonadism; SD, standard deviation.

* Corresponding author.
E-mail address: r.krysiak@interia.pl (R. Krysiak).

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obesity, hyperlipidemias, type 2 diabetes, cardiovascular disease, and chronic obstructive pulmonary disease [3,7,10]. It is unclear whether low testosterone levels are primarily associated with normal aging *per se* or with age-related changes in general health and lifestyle [11].

Unlike hypogonadism in younger patients, testosterone treatment of LOH is a much more controversial issue because testosterone levels are often borderline or slightly reduced, the symptoms are usually mild and unspecific, while low testosterone and high symptom score often do not coincide [3]. Therefore, testosterone therapy is suggested to be considered on an individualized basis to older men with low testosterone levels on more than one occasion and significant symptoms of androgen deficiency, after appropriate discussion of the uncertainties of the risks and benefits of testosterone therapy in older men [12]. In some studies, testosterone administered to patients with LOH was found to improve libido, sexual functions, glycometabolic control, mood, and muscle strength [13,14].

Because of a decrease in cardiovascular morbidity and mortality [15], 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins) are often used in elderly patients at high risk of cardiovascular events [16]. By limiting the amount of cholesterol for steroidogenesis [17], these agents may, however, theoretically impair adrenal cortex and/or gonadal function. A recent meta-analysis of randomized controlled studies carried out by Schooling et al. [18], as well as the results of our recent study [19] suggest that statin may reduce plasma testosterone levels in men. Although this reduction is relatively small, it may be relevant in patients with low testosterone levels. To the best of our knowledge, no previous study has investigated the effect of combined treatment with a statin and exogenous testosterone. Therefore, in the present study we have decided to assess whether the currently recommended dose of intramuscular testosterone enanthate added to atorvastatin is superior to the treatment with only atorvastatin in affecting cardiovascular risk factors in men with LOH.

Materials and methods

This research study included males (55–79 years old) who, because of elevated LDL cholesterol levels, were treated with atorvastatin (20–40 mg daily) and followed a lipid-lowering diet for at least 6 months before the beginning of the study. To be admitted to the study, they had to meet the inclusion criteria of LOH: total testosterone level below 3.0 ng/mL on two different occasions and the presence of the following symptoms: decreased frequency of morning erection, erectile dysfunction, and decreased frequency of sexual thoughts. We excluded patients with prostate cancer, severe lower urinary tract symptoms (the American Urological Association International Prostate Symptom Score exceeding 19), baseline prostate-specific antigen $>$ 4 ng/mL (or $>$3 ng/mL in men at high risk of prostate cancer), breast cancer, myocardial infarction, acute coronary event, unstable angina, coronary revascularization procedure or stroke within 6 months preceding the study, heart failure (classes II–IV according to the New York Heart Association Functional Classification), hematocrit exceeding 50%, untreated obstructive sleep aspnea, diabetes mellitus, and with poor compliance. We also excluded patients treated with other drugs known either to affect plasma lipid and steroid hormone levels or known to interact with statins and testosterone. The study complied with the principles of the Declaration of Helsinki and its protocol was approved by the Bioethical Committee of the Medical University of Silesia. All included patients (n = 31) gave their written informed consent to participate in the study. The participants were informed about the benefits and harms of androgen therapy. On the basis of patient preference, the participants were then allocated to one of two groups treated for 120 days with intramuscular testosterone enanthate (100 mg weekly, n = 16) and not receiving androgen therapy (n = 15). Throughout the entire study period, the participants continued treatment with the same daily dose of atorvastatin as before the study and complied with dietary recommendations. These patients were compared with 12 age- and plasma-lipid-matched men with LOH not receiving statin therapy. Compliance assessment was performed during each visit by tablet counts and was considered satisfactory when the number of tablets taken by a patient ranged from 90 to 100%.

Blood samples for laboratory assays were obtained at approximately 8:00 a.m. following at least a 12-h overnight fasting before and after 4 months of testosterone treatment. All tests were carried out by a person blinded to individuals' identity and all clinical details. Plasma lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), fasting glucose, plasma uric acid, and plasma insulin were assayed by routine laboratory techniques (Roche Diagnostics, Basel, Switzerland). LDL-cholesterol levels were measured directly. Plasma insulin, total testosterone, and dehydroepiandrosterone sulphate (DHEA-S) were determined by enzyme-linked immunosorbent assay (DRG Instruments GmbH, Marburg, Germany). The homeostatic model assessment one of insulin resistance ratio (HOMA1-IR), being an index of insulin sensitivity, was calculated by the formula: [fasting insulinemia (mU/L) x glycemia (mg/dL)]/405. Plasma levels of C-reactive protein were measured using a high-sensitivity monoclonal antibody assay (hsCRP) (MP Biomedicals, Orangeburg, NY, USA). Plasma levels of homocysteine were measured with commercial enzyme immunoassay kits obtained from Diazyme (San Diego, California, USA). Plasma fibrinogen levels were determined by the Clauss method with a semi-automated blood coagulation analyzer OPTION 2 Plus using reagents obtained from bioMerieux (Marcy l'Etoile, France). The intra- and interassay coefficients of variation for the assessed variables were less than 6.4 and 8.8%, respectively.

The normality of the quantitative variables was verified using the Kolmogorov–Smirnov test. Variables with non-normal distribution (triglycerides, HOMA1-IR, hsCRP homocysteine, fibrinogen, and hormones) were log-transformed to fit a normal distribution curve. Comparisons between the groups were performed using analysis of covariance followed by Bonferroni *post hoc* tests after consideration of age, smoking, body mass index, waist–hip ratio, blood pressure, duration of atorvastatin treatment, and atorvastatin dose as potential confounders. The differences between baseline and post-treatment values within the same treatment group were compared with the Student's paired t-test. Correlations were assessed using Kendall's tau test. The level of significance was set at $p < 0.05$.

Results

The characteristics of the included patients are summarized in Tables 1 and 2. There were no significant differences between all study groups in demographic data (age, smoking, and body mass index), as well as between both groups of atorvastatin-treated patients in baseline laboratory results. Compared with statin-naïve subjects, atorvastatin-treated patients were characterized by lower levels of testosterone, hsCRP, and homocysteine.

The treatment was well tolerated and all but one patient completed the study protocol. This patient, receiving atorvastatin and testosterone enanthate, was withdrawn because of erythrocytosis.

In patients not receiving testosterone therapy, plasma lipids, glucose homestasis markers, as well as plasma levels of the investigated risk factors remained at the similar levels throughout the whole period of atorvastatin treatment. After 4 months,

Table 1
Baseline characteristics of participants.*

Variable	Atorvastatin	Combination therapy	Testosterone
Number of patients	15	15	12
Age [years; mean (SD)]	68 (4)	65 (5)	67 (4)
Body mass index [kg/m^2; mean (SD)]	28.5 (2.8)	28.9 (2.3)	29.0 (2.4)
Atorvastatin dose [mg; mean (SD)]	32[a]	30[a]	0
Waist circumference [cm; mean (SD)]	97 (5)	99 (4)	99 (5)
Smokers [%]	27	27	25

* Only data of patients who completed the study were included in the final analyses.
[a] $p < 0.001$ vs. atorvastatin-naïve patients (treated in the study with testosterone)

Table 2
The effect of testosterone on steroid hormones, plasma lipids, glucose homeostasis markers and the investigated cardiometabolic risk factors in atorvastatin-treated, and atorvastatin-naïve patients with late-onset hypogonadism.*

Variable	Atorvastatin	Combination therapy	Testosterone
Total testosterone [ng/mL; mean (SD)]			
Baseline	2.0 (0.3)[a]	1.9 (0.3)[a]	2.4 (0.3)
After 4 months	2.1 (0.4)[c]	3.8 (0.4)[e,h]	4.0 (0.5)[e]
DHEA-S [μg/dL; mean (SD)]			
Baseline	124 (31)	115 (27)	138 (34)
After 4 months	118 (22)	125 (29)	142 (40)
Total cholesterol [mg/dL; mean (SD)]			
Baseline	225 (29)	221 (35)	234 (38)
After 4 months	220 (24)	213 (28)	226 (31)
LDL-cholesterol [mg/dL; mean (SD)]			
Baseline	137 (14)	132 (15)	143 (16)
After 4 months	141 (15)	115 (14)[d,g]	135 (21)
HDL-cholesterol [mg/dL; mean (SD)]			
Baseline	43 (4)	45 (4)	46 (4)
After 4 months	42 (5)	46 (4)[a,f]	41 (5)[d]
Triglycerides [mg/dL; mean (SD)]			
Baseline	195 (41)	203 (39)	212 (49)
After 4 months	205 (38)	194 (28)	202 (39)
Glucose [mg/dL; mean (SD)]			
Baseline	99 (5)	98 (5)	95 (6)
After 4 months	100 (7)	95 (6)	94 (5)
HOMA1-IR			
Baseline	3.5 (0.5)	3.4 (0.6)	3.0 (0.7)
After 4 months	3.7 (0.7)[c]	2.8 (0.5)[d,g]	2.5 (0.5)
Uric acid [μmol/L; mean (SD)]			
Baseline	324 (60)	340 (56)	407 (67)
After 4 months	341 (53)[b]	283 (51)[c,d,f]	399 (59)
hsCRP [mg/L; mean (SD)]			
Baseline	2.4 (0.4)[c]	2.6 (0.4)[c]	3.9 (0.6)
After 4 months	2.5 (0.5)[c]	1.6 (0.3)[c,e,h]	3.4 (0.4)
Homocysteine [μmol/L; mean (SD)]			
Baseline	29 (8)[b]	31 (7)[b]	42 (11)
After 4 months	30 (7)[a]	23 (5)[c,d,f]	40 (10)
Fibrinogen [mg/dL; mean (SD)]			
Baseline	360 (52)	356 (61)	329 (47)
After 4 months	349 (49)	283 (60)[a,d,f]	344 (56)

* Only data of men who completed the study were included in the final analyses.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$ vs. atorvastatin-naïve patients (treated in the study with testosterone).
[d] $p < 0.05$.
[e] $p < 0.001$ vs. baseline value.
[f] $p < 0.05$.
[g] $p < 0.01$.
[h] $p < 0.001$ vs. atorvastatin-treated patients not receiving testosterone.

atorvastatin-testosterone combination therapy increased plasma testosterone by 50% ($p < 0.001$), as well as reduced LDL cholesterol by 13% ($p < 0.05$), HOMA1-IR by 18% ($p < 0.05$), uric acid by 17% ($p < 0.05$), hsCRP by 38% ($p < 0.001$), homocysteine by 26% ($p < 0.05$), and fibrinogen by 21% ($p < 0.05$). However, the combination therapy produced no effect on circulating levels of DHEA-S, total cholesterol, HDL cholesterol, triglycerides, and glucose (Table 2). Testosterone enanthate administered to atorvastatin-naïve patients increased plasma testosterone by 40% ($p < 0.001$), decreased plasma HDL cholesterol by 11% ($p < 0.05$), as well as tended to reduce hsCRP (−13%, $p = 0.065$) and HOMA1-IR (−17%, $p = 0.095$). In this group of patients, testosterone did not affect DHEA-S, total and LDL cholesterol, triglycerides, glucose, uric acid, homocysteine, and fibrinogen.

Between-group comparisons showed that in atorvastatin-treated patients, post-treatment circulating levels of testosterone, and HDL cholesterol were higher, while plasma levels of LDL cholesterol, uric acid, hsCRP, homocysteine, and fibrinogen, as well as HOMA1-IR were lower in the group treated additionally with testosterone enanthate than in patients not receiving androgen therapy (Table 2). At the end of the study, plasma levels of total testosterone, uric acid, hsCRP, and homocysteine were lower, while HOMA1-IR was higher in atorvastatin-treated patients not receiving testosterone than in atorvastatin-naïve testosterone-treated patients. Post-treatment levels of HDL cholesterol were higher, while post-treatment levels of uric acid, hsCRP, homocysteine, and fibrinogen were lower in testosterone-treated patients receiving atorvastatin than in atorvastatin-naïve subjects.

At entry, hsCRP, uric acid, homocysteine, and fibrinogen did not correlate with plasma lipids. However, they correlated weakly with HOMA1-IR (r values between 0.29 [$p < 0.05$] and 0.35 [$p < 0.001$]) and plasma testosterone (r values between −0.31 [$p < 0.05$] and −0.39 [$p < 0.001$]). The impact of testosterone on plasma levels of hsCRP, homocysteine, and fibrinogen correlated with its effect on HOMA1-IR (r values between 0.37 [$p < 0.01$] and 0.56 [$p < 0.001$]), but was unrelated to the action on plasma lipids. Treatment-induced changes in hsCRP, uric acid, homocysteine, and fibrinogen inversely correlated with baseline testosterone levels (atorvastatin-treated patients: r values between −0.42 [$p < 0.001$] and −0.53 [$p < 0.001$]; atorvastatin-naïve patients: r values between -0.34 [$p < 0.05$] and -0.46 [$p < 0.001$]). Moreover, the effect of testosterone treatment on hsCRP, homocysteine, and fibrinogen in atorvastatin-treated and atorvastatin-naïve patients correlated with their baseline values (atorvastatin-treated patients: r values between −0.35 [$p < 0.01$] and −0.51 [$p < 0.001$]; atorvastatin-naïve patients: r values between −0.30 [$p < 0.05$] and −0.47 [$p < 0.001$]). No other correlations were found in both baseline conditions and after treatment.

Discussion

Apart from lowering lipid levels, HMG-CoA reductase inhibitors exhibit multiderectional pleiotropic effects, such as

endothelial-protective effects, regulation of smooth muscle cell proliferation and migration, anti-inflammatory and antioxidative actions, as well as beneficial effects on coagulation, fibrinolysis, and platelet activities [20–23]. This explains lower baseline levels of hsCRP, homocysteine, fibrinogen, and uric acid in atorvastatin-treated patients than in men with LOH previously untreated with a statin, despite similar levels of plasma lipids in both groups of patients.

Despite using relatively moderate doses, patients receiving atorvastatin were characterized by slightly lower levels of testosterone than patients not receiving statin therapy. This finding seems to support our previous hypothesis [19] that although the effect of statins on testosterone is probably unimportant in patients with baseline undisturbed adrenal and gonadal steroidogenesis, it should be taken into consideration in subjects with subclinical dysfunction of steroid hormone-producing organs. Both adrenocortical and gonadal hormones are produced from cholesterol and LDL particles are considered the most important source of cholesterol for steroidogenesis [17]. Therefore, it cannot be excluded that the effect of HMG-CoA reductase inhibitors on plasma testosterone levels in patients with LOH may be more pronounced in the case of more aggressive statin treatment resulting in much lower levels of LDL cholesterol than in our study. Interestingly, no differences were observed in DHEA-S levels, which is line with our observation that the impact of statins on steroidogenesis is stronger in the testis than in the adrenals [19].

However, the major finding of the study is that testosterone exerted a multidirectional effect on plasma levels of the investigated cardiovascular risk factors in statin-treated patients, while in subjects non receiving HMG-CoA reductase inhibitors this effect was much weaker. Although pleiotropic effects of statins was found to increase with time [24,25], this explanation cannot account for our results because no differences in the assessed markers were observed in atorvastatin-treated subjects not receiving testosterone at the beginning and at the end of the study. Taking into account a direct involvement of the assessed variables in the initiation and progression of atherosclerosis, as well as the fact that even small differences in their levels are associated with a various cardiovascular risk and a various grade of insulin resistance in the general population [21,26–29], the additive effect of both drugs on the assessed variables may, in our opinion, bring some cardiometabolic benefits to the studied population or at least may reflect these benefits.

As a meta-analysis of randomized trials shows testosterone use in men with low testosterone levels reduces plasma levels of total, LDL and HDL cholesterol, and triglycerides [30]. Our study showed for the first time that statin use may prevent a testosterone-induced decrease in HDL cholesterol levels, considered to have a protective effect against coronary heart disease [31]. Another benefit of statin-testosterone combination therapy is an additive effect on LDL cholesterol, which may be of particular importance in aging men with severe and treatment-resistant hypercholesterolemia, as well as in men in whom high-dose hypolipidemic therapy is either contraindicated or results in adverse effects.

Interestingly, post-treatment testosterone levels did not differ between atorvastatin-treated and atorvastatin naïve patients. Therefore, its use in a statin-treated patients may minimize this unwanted effect associated with statin therapy and enable their use at higher doses. Unlike plasma testosterone, exogenous hormone does not seem to affect adrenal androgens. Irrespectively of whether patients received atorvastatin, testosterone did not change plasma levels of DHEA-S.

The addition of testosterone enanthate to atorvastatin was well tolerated and associated with favorable changes in glucose homeostasis. Taking into account that both statin-treated [32,33] and elderly subjects [34] are more prone to the development of type 2 diabetes, our findings are an additional argument for statin-testosterone combination therapy of patients with LOH. Interestingly, baseline plasma glucose and HOMA1-IR did not differ between patients receiving and not receiving atorvastatin. This suggests that atorvastatin administered to patients with LOH either does not increase the risk of worsening glycemic control or its deteriorating effect on glucose metabolism is only minimal.

The presence of a correlation between testosterone- ad combination therapy-induced changes in the investigated risk factors and the changes in HOMA1-IR suggests that the impact of intramuscular testosterone on hsCRP, uric acid, homocysteine, and fibrinogen seems to be, in part, a consequence of the improvement in insulin sensitivity and may be associated with an increase in muscle mass, and strength, as well as with a reduction in body mass index and a reduction in abdominal obesity observed by other authors [13,14].

Some limitations of this study need to be mentioned. The major ones are a small sample size and some differences in the baseline characteristics of the study groups. Theoretically, baseline differences between atorvastatin-treated patients and men not receiving a HMG-CoA reductase inhibitor could not have resulted from statin therapy. Moreover, all patients were treated with atorvastatin and therefore, the obtained results need to be confirmed in further studies with the use of other HMG-CoA reductase inhibitors. Finally, because our study included patients with mild hypercholesterolemia (in part because of statin therapy), it is not certain whether testosterone produces a similar effect on cardiometabolic risk markers in patients with markedly elevated LDL cholesterol levels.

In conclusion, our study has shown that intramuscular testosterone enanthate produces a multidirectional beneficial effect on cardiovascular risk particularly in patients already treated with atorvastatin. This effect of testosterone-statin combination therapy may play a role in the prevention and treatment of atherosclerosis and its complications, as well as glucose metabolism abnormalities in elderly patients with LOH.

Conflict of interest statement

The authors declare no financial interests.

Author contributions

R.K. conceived of the study, participated in its design, performed the statistical analysis as well as drafted and edited the manuscript. W.G. conducted the literature search and carried out the assays. B.O. participated in its design and coordination, and provided critical input during manuscript preparations. All authors read and approved the final manuscript.

Institutional approval

The study was approved by the Bioethical Committee of the Medical University of Silesia.

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