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Original research article

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

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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.
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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.

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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,

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