DOI: https://doi.org/10.17816/uroved623777

Androgenic condition and statins: contradictions in modern literature

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ABSTRACT

Pathological age-related involution of the male reproductive system is characterized by combined clinical manifestations, which are designated by the terms age-related androgen deficiency syndrome, andropause, and male menopause. In modern foreign literature, the term “late hypogonadism” is more often used; in domestic literature, “age-related androgen deficiency” is utilized. The problem of late hypogonadism has gone beyond the scope of endocrinology and sexopathology. Currently, it has acquired an interdisciplinary character and gained attention from gerontologists, cardiologists, diabetologists, andrologists, and other specialists. The medical and social significance of age-related androgen deficiency syndrome is determined by the fact that it worsens the quality of life and is a risk factor for death, primarily from cardiovascular diseases. The review article presents modern ideas regarding the effect of statins on the androgen status of men with cardiac pathology and hypercholesterolemia.

Keywords: statin; cardiovascular diseases; androgen deficiency; erectile dysfunction; hypercholesterolemia.

To cite this article
Osipov AV, Derevyanko TI, Agranovich NV, Frantsev RS, Babasheva GG, Aleksandrova OA. Androgenic condition and statins: contradictions in modern literature. *Urology reports (St. Petersburg)*. 2024;14(2):175–185. DOI: https://doi.org/10.17816/uroved623777

Received: 24.11.2023 **Accepted:** 25.05.2024 **Published online:** 28.06.2024

DOI: https://doi.org/10.17816/uroved623777

Андрогенный статус и статины: противоречия в современной литературе

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АННОТАЦИЯ

Патологическая возрастная инволюция мужской репродуктивной системы характеризуется сочетанием клинических проявлений, которые обозначаются терминами «синдром возрастного дефицита андрогенов», «андропауза», «мужской климакс». В современной зарубежной литературе чаще используют термин «поздний гипогонадизм», в отечественной — «возрастной андрогенодефицит». Проблема позднего гипогонадизма уже давно вышла за рамки эндокринологии и сексопатологии. В настоящее время она приобрела междисциплинарный характер и является предметом интереса геронтологов, кардиологов, диабетологов, андрологов и других специалистов. Медико-социальное значение синдрома возрастного андрогенодефицита определяется тем, что он не только ухудшает качество жизни, но и признается как фактор риска смерти, прежде всего от сердечно-сосудистых заболеваний. В обзорной статье авторы приводят современные представления влияния статинов на андрогенный статус мужчин с кардиологической патологией и гиперхолестеринемией.

Ключевые слова: статины; сердечно-сосудистые заболевания; андрогенный дефицит; эректильная дисфункция; гиперхолистеринемия.

Как цитировать

Осипов А.В., Деревянко Т.И., Агранович Н.В., Францев Р.С., Бабашева Г.Г., Александрова О.А. Андрогенный статус и статины: противоречия в современной литературе // Урологические ведомости. 2024. Т. 14. № 2. С. 175–185. DOI: https://doi.org/10.17816/uroved623777

Рукопись получена: 24.11.2023 **Рукопись одобрена:** 25.05.2024 **Опубликована online:** 28.06.2024

INTRODUCTION

In Russia, androgen deficiency is underdiagnosed in men, and the frequency of prescribing replacement therapy for detected testosterone deficiency in men is 5%–10% [1]. Owing to low awareness of patients and doctors and challenges in diagnosing androgen deficiency, such pathology often remains hidden for a long time, which leads to the development of cardiovascular diseases and other pathological conditions at a younger age than in men without androgen deficiency [2].

Undiagnosed testosterone deficiency, because of the universality of physiologic effects of androgens, can worsen the prognosis of any somatic disease in men, including cardiovascular disease. Androgenic deficiency reduces the efficiency of glucose utilization by myocytes and hepatocytes and can result in deficiency of muscle mass and its replacement with adipose tissue, which actively secretes leptin and inflammatory factors, and thus, in hyperglycemia and hyperinsulinemia [3–5], and eventually, insulin resistance may develop, which is the main component of the metabolic syndrome [6].

Testosterone is involved in several vital functions in the male body, inducing androgenic, reproductive, psychophysiologic, anabolic, hematopoietic, and antigonadotropic effects. In men, after age 30–40 years, testosterone levels in the blood decrease by an average of 1%–1.5% per year. Low-onset hypogonadism (LOH) develops when the level of total testosterone is <10–12 nmol/l [7, 8] (according to other data, <8 nmol/l) and free testosterone is <220 pmol/l [9]. These indicators were recorded in 5%–7% of men aged 40–49 years, 10% of those aged 50–59 years, 20% of those aged 60–69 years, 30% of those aged 70–79 years, and almost half of the surveyed men aged ⩾80 years [10, 11].

The main substrate for the synthesis of testosterone and of all steroids in the male body is cholesterol, which can be synthesized from acetate and serum lipoproteins, possibly from the fraction of low-density lipoproteins (LDL) [12]. In the synthesis of this androgen, cholesterol acts as a precursor. Testosterone and cholesterol have a close relationship. The main source of testosterone in the male body is the Leydig cells of the testicles, wherein testosterone is formed from cholesterol by successive enzymatic reactions. Cholesterol can be synthesized from acetate or extracted from LDL in the blood. When lipids in the male body are insufficient or when taking cholesterol-lowering drugs, symptoms of hypogonadism are observed [13], including decreased libido and erectile dysfunction (ED) [14–16].

Androgen deficiency can be considered as a risk factor of atherosclerosis in young men [17]. The significant role of androgen deficiency in atherogenesis has been confirmed by several studies, wherein it was determined that male patients with coronary heart disease (CHD) manifest low levels of free testosterone [18]. Activation of systemic inflammation processes may be a universal pathological reaction combining atherogenesis with manifestations of androgen deficiency [5].

CLINICAL OBSERVATIONS AND STUDIES

Literature and clinical practice data indicate that the problem of age-related androgen deficiency (AAD) in CHD is crucial owing to the continuing relevance of CHD as the main cause of mortality worldwide [19–21]. Vlachopoulus et al. [22] concluded that low testosterone levels in older men with hypertension can be an additional criterion for cardiovascular risk. This opinion is shared by other authors [23, 24]. In addition, to the vasodilating effect of testosterone [25], this hormone has a protective effect on the development of vascular inflammation and insulin resistance, which are key factors of atherogenesis [26, 27].

Over the past 15 years, a direct correlation between endogenous testosterone levels and antiatherogenic high-density lipoprotein (HDL) levels and an inverse correlation with plasma levels of total cholesterol and LDL have been found [28]. Thus, AAD can be considered a predictor of systemic atherosclerosis and related diseases [28] and is associated with atherogenic dyslipidemia and early development of atherosclerosis [29]. To date, adequate information has indicated that the atherosclerotic process exhibit signs of chronic inflammation. Cells responsible for inflammation and high levels of pro-inflammatory cytokines were found in atheromatous plaques [30]. Moreover, in the most vulnerable plaques, which are the cause of acute arterial thrombosis, inflammation is most pronounced [31, 32].

Lowering the levels of cholesterol and LDL using lipid-lowering therapy provides significant reduction in cardiovascular risk. Notably, the mechanism of atherogenesis is a complex process involving various complicated interacting factors of the internal and external environment.

Statins should be used in the treatment of primary and secondary prevention of diseases associated with atherosclerosis. The treatment of atherosclerosis has become possible owing to the discoveries in recent decades, the main of which is the receptor theory of lipid metabolism and the therapy based on it using 3-hydroxy3-methylglutaryl coenzyme (HMG-CoA reductase) inhibitors, namely, statins. Statins were discovered by Japanese scientists led by Akira Endo in the early 1970s [33]. The first statin (i.e., compactin, later renamed to mevastatin) was used to treat a homozygous form of familial hypercholesterolemia.

The hypocholesterolemic effect of statins is based on their ability to inhibit the activity of the enzyme HMG-CoA reductase, which is a key enzyme in endogenous

cholesterol synthesis [33]. Currently available statins can be divided into two groups: enzyme-derived statins (e.g., simvastatin and pravastatin) and synthetic statins (e.g., atorvastatin, cerivastatin, fluvastatin, pitavastatin, lovastatin, and rosuvastatin). Currently, eight statins have been studied: lovastatin, pravastatin, fluvastatin, simvastatin, cerivastatin (withdrawn from the pharmaceutical market), atorvastatin, rosuvastatin, and pitavastatin (clinical trials are ongoing). Statins have different lipid-lowering activity — from moderate (fluvastatin and pravastatin) to very high (atorvastatin and rosuvastatin).

The clinical results of statin treatment are elucidated by its hypocholesterolemic effect and other beneficial effects called pleiotropic. These effects of statins are obtained through regulation of endothelial function and restoration of endothelium-dependent vasodilation and NO metabolism. By a complex effect, including by activating protein kinase B directly in endothelial cells, phosphorylation of endothelial NO synthase (eNOS) under the influence of statins causes an increase in NO production [34, 35]. The lipid-lowering effect differs when using different statins. Numerous studies have shown that rosuvastatin is the most effective statin in reducing LDL levels, significantly increasing HDL levels and slowing the progression of the atherosclerotic process, which the main cause of CVD [36].

The hypoandrogenic effects of statins can be observed in the inhibition of the mevalonate pathway, resulting in decreased synthesis and availability of cholesterol, which is a substrate for androgen production. The mechanism of action of statins on hypothalamic/pituitary function is unclear and requires further study. The statin-induced decrease in androgen levels may be associated with an effect on the function of the hypothalamic/pituitary system [37].

The results of studies on the assessment of the effect of statins on erectile function are contradictory. Chou et al. [38] found that the use of statins in men aged 40–79 years was associated with a reduced risk of ED. These data can be explained by the conjugation of the main mechanism of action of statins, the presence of pleiotropic and metabolic effects, and factors that form ED [39]. In a double-blind randomized controlled trial, Trivedi et al. [40] showed that in men with ED aged 40 years, the use of simvastatin at a dose of 40 mg for 6 months significantly improved erectile function and quality of life in general [40]. However, other studies presented a different opinion about the effect of statins on the erectile function of men. Cai et al. [41] and Kostis et al. [42] reported that therapy with statins can reduce testosterone levels and aggravate ED symptoms.

The main lipid-lowering effect of statins is to reduce the level of total cholesterol by reducing its most atherogenic fraction, namely, LDL [43, 44]. The administration of statins can lead to testicular discomfort, ED, changes in sperm parameters, and impaired steroid hormone production [45]. Reports on the adverse effects of statins on the male reproductive system are contradictory. Apparently, the negative effects of statins are associated with an unbalanced or reduced level of steroid hormones, which are crucial for normal spermatogenesis and sexual function. However, the positive effects are associated with the anti-inflammatory and cardioprotective properties of the statins. These contradictory results are partly due to the different age of patients, concentration of statins, type and duration of treatment, and underlying disease and/or concomitant nosologies [45].

Kocum et al. [46] evaluated androgen and gonadotropin levels in 77 men with CHD initially and after 12 weeks of treatment with different doses of atorvastatin (40–80 mg per day) with target serum LDL level <70 mg/dL and compared them with 83 patients with CHD who were regularly receiving doses of atorvastatin (10–20 mg per day) with target serum LDL level <100 mg/dL. The study results showed that the average LDL levels in the groups taking higher and regular doses of atorvastatin were 77 ± 9 and 98 ± 10 mg/dL, respectively. After 12 weeks of treatment, no significant changes were noted in the blood serum levels of total and free testosterone, sex hormone-binding globulin (SHBG), and luteinizing and follicle-stimulating hormones in patients of both groups. Thus, a higher dose of atorvastatin to achieve serum LDL levels of 70 mg/dl appear to be as safe as the usual dose to achieve serum LDL levels of 100 mg/dl from the point of view of gonadal steroidogenesis in men with CHD [46]. In their meta-analysis of placebo-controlled randomized trials, de Keyser et al. [15] showed that current statin intake for 1–6 months was accompanied by lower levels of total testosterone compared to those patients who did not take statins. Moreover, current statin use for 1–6 months has been associated with significantly lower levels of non-SHBG testosterone. Testosterone levels tended to decrease with higher doses of statins for both total and non-SHBG testosterone. No association was found between statin use in the past and testosterone levels [15]. However, the analysis of several sufficiently comprehensive and representative randomized trials by Grundy et al. [47] demonstrated that statins induce a minimal effect on steroidogenesis in men, and such an effect is not clinically significant [47]. Drugs of this group can slightly lower the level of testosterone in blood plasma, but do not cause hypogonadism [48, 49], and their effect on erectile function is favorable and may be beneficial [50]. There is no direct evidence that statins cause ED [51–53].

Furthermore, experimental studies on the effect of statins (simvastatin and rosuvastatin) on the level of sex hormones in male rats demonstrated a significant

decrease in testosterone, estradiol, and progesterone levels while reducing total cholesterol [54–56]. Klinefelter et al. [57] measured 18-hour testosterone production *in vitro* using highly purified Leydig rat cells exposed to atorvastatin, mevastatin, or simvastatin. Statins had no effect on testosterone production when cultured without the luteinizing hormone. However, at a level of 10 ng/mL, testosterone production was 12-fold or even higher and markedly inhibited (–40%) at ⩾0.3 μM of any of the statins used. In contrast, an experimental study of the effect of atorvastatin on the erectile function of rats with induced diabetes mellitus demonstrated an improvement in the erectile response of animal penile tissue [58].

Clinical studies have shown a negative effect of statins on the erectile function of men with hyperlipidemia after a 6-month treatment [59–62]. It has been reported that in patients with type 2 diabetes mellitus, the use of rosuvastatin for 6 months reduces the level of free testosterone but does not affect sexual function [63]. Böhm et al. obtained similar results in their study of pravastatin on the hormonal profile in men [64].

A meta-analysis of five placebo-controlled randomized trials involving 501 middle-aged men with hypercholesterolemia showed that statins significantly reduced testosterone levels by 0.66 nmol/l (95% confidence interval, from –0.14 to –1.18) [65]. A study comparing simvastatin at doses of 80 and 40 mg/day among 640 men after 48 weeks of treatment demonstrated a 10.3% and 7.5% decrease in total testosterone levels, respectively [66], which is consistent with a 3.4% decrease among men taking simvastatin at a dose of 20 mg/day. These findings indicate the dose-dependent effect of statins on testosterone levels. Dobs et al. [67] found that after 12 weeks of simvastatin treatment, the levels of total testosterone and free testosterone decreased by 13.6% and 6.3%, respectively [67].

In vitro studies conducted by Smals et al. [68] showed that in concentrations exceeding *in vivo* concentrations, simvastatin suppresses the synthesis of androgens androstenediol and testosterone in human testicular homogenates. Simvastatin, in addition to its known inhibitory effect on HMG-CoA reductase activity, has been demonstrated to affect the later stages of steroidogenesis in the testicles by selectively inhibiting the 17-ketosteroid oxidoreductase-catalyzed conversion of dehydroepiandrosterone and androstenedione to androstenediol and testosterone, respectively. At doses commonly used in the treatment of hypercholesterolemia, simvastatin does not affect steroidogenesis in the testicles; however, at higher doses, especially when inadvertently administered in early pregnancy, adverse effects on normal testosterone biosynthesis and, consequently, on fetal development should be considered [42, 68–74].

CONCLUSIONS

1. Late hypogonadism, or LOH, is a critical medical problem that has now acquired an interdisciplinary character. It is the subject of study not only by endocrinologists and sex therapists but also by gerontologists, cardiologists, diabetologists, andrologists, and other specialists, which indicates its high clinical significance.

2. Pathological age-related involution of the male reproductive system characterized by AAD syndrome, andropause, or male menopause leads to clinical manifestations that significantly worsen the quality of life of patients.

3. AAD syndrome worsens the quality of life of patients and is a risk factor for death, primarily from cardiovascular diseases. This highlights the medical and social significance of the problem and the need for timely diagnosis and treatment.

4. The contradictions revealed in the existing literature, reflecting different views on the mechanisms of development and treatment of late hypogonadism (statin therapy), indicate the relevance of further research and development of a unified methodology for the diagnosis and treatment of this syndrome.

5. Other key aspects of the problem of late hypogonadism are drug treatment and lifestyle correction of patients, which emphasizes the need for an integrated approach to solving this problem.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: A.V. Osipov — search and analysis of literary data, writing the text of the manuscript; T.I. Derevyanko, N.V. Agranovich — concept of the study, analysis of literary data, editing the text of the manuscript; R.S. Frantsev, G.G. Babasheva, O.A. Aleksandrova — search and analysis of literary data, editing the text of the manuscript

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Личный вклад каждого автора: А.В. Осипов — поиск и анализ литературных данных, написание текста рукописи; Т.И. Деревянко, Н.В. Агранович — концепция исследования,

анализ литературных данных, редактирование текста рукописи; Р.С. Францев, Г.Г. Бабашева, О.А. Александрова — поиск и анализ литературных данных, редактирование текста рукописи.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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