Effect of Statins on Total Testosterone Levels in Male Veterans

Muhammad Jawad Sethi, MD; and William P. Newman, MD

When patients present with decreased serum testosterone levels, these researchers recommend considering statin use as a potential contributing factor.

The conversion of cholesterol to pregnenolone is the rate-limiting step in steroidogenesis. Statins act by inhibiting HMG CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. On this basis, statins could potentially decrease serum testosterone levels by reducing the availability of cholesterol for androgen biosynthesis.[1-3]

The libido and sexual life of a man is initiated and maintained by testosterone and its interaction with the sex hormone-binding globulin (SHBG). Lower testosterone levels are associated with erectile dysfunction (ED).[4] Risk factors for male hypogonadism include diabetes, hypertension (HTN), heart disease, psychological stress, inflammatory illness, chronic obstructive pulmonary disease (COPD), chronic pain with opioid use, and obesity.[4] Men with proven coronary atherosclerosis have lower levels of testosterone and SHBG, which has had a negative correlation with very low-density lipoprotein cholesterol, triglycerides, body mass index (BMI), and body fat. Thus, in men, endogenous sex steroids are thought to impart beneficial effects on the heart.[4]

Dr. Sethi is a resident physician at the University of North Dakota School of Medicine and Health Sciences in Grand Forks and Fargo, North Dakota. **Dr. Newman** is chief of endocrinology at the Fargo VA Health Care System in Fargo, North Dakota, and professor of medicine in the Department of Internal Medicine at the University of North Dakota School of Medicine and Health Sciences.

A review of the literature reveals that the prevalence of hypogonadism among male veterans has been found to be as high as 38.7%.[5] In one study, low testosterone was associated with increased mortality in male veterans.[6] In another study in a veteran population looking at the association between statins and cancer incidence, there was a very high percentage of patients who were on statins.[7] Emerging evidence suggests that statin use is a significant contributor to decreased serum testosterone levels.[1,3,8-10] We undertook this retrospective analysis to find the impact of statin use on serum testosterone levels among male veterans.

RESEARCH DESIGN AND STUDY METHODS

This cross-sectional study was conducted at the Fargo VA Health Care System in Fargo, North Dakota. We looked at the profiles of 1,049 veterans who presented to the medical center and had a serum total testosterone level obtained. We looked at total testosterone levels and identified the prevalence of low testosterone in these patients. Mild low testosterone was defined as a total testosterone level of < 350 ng/dL, and very low testosterone was defined as < 230 ng/dL.[3] We compared testosterone levels in veterans on various types of statins, including atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Furthermore, the relationship between testosterone levels and the dosage and duration of various statins was investigated.

We searched the Fargo VA laboratory database from January 1, 2004, to May 31, 2010. We included all patients who had testosterone levels checked and stratified them by patients who were on statin therapy during the interval. Each testosterone level per subject was regarded as a discrete instance, if separated from a prior testosterone level by at least 6 months. Multiple results obtained within 6 months were averaged.

EXCLUSION CRITERIA

We excluded patients with acute systemic illness at the time of testosterone levels ± 1 month, including burn injury, stroke, traumatic brain injury, myocardial infarction, respiratory illness, sepsis, surgical stress, patients with chronic systemic illness, cancer, chronic renal failure, chronic liver disease, rheumatoid arthritis, human immunodeficiency virus (HIV), COPD, and androgen deprivation therapy (ADT).

Statistical analysis was done by paired T test for continuous variables, Wilcoxon rank sum test for variables with a "nonnormal" distribution, and the Fisher exact test for categorical variables. The Chi square test for trend was used to assess hypogonadism by statin dose. SAS version 9.2 software was used for all calculations.

RESULTS

We screened 1,100 patients who pre-

Table 1. Demographics (patient characteristics)

Variable	Total	Nonstatin use	Statin use	*P* value (statin use vs nonstatin use)
Patients (n)	1,049	553	496	-
Age (mean and SD)	60.9 (11.6)	58.6 (12.4)	63.4 (10.0)	< .001
BMI (mean and SD)	30.9 (5.9)	30.7 (5.8)	31.1 (5.8)	= .26
Testosterone level (ng/dL)	373 (204)	388 (204)	357 (204)	= .015
DM (%)	30.3	20.1	41.7	< .001
Opioid use (%)	10.7	9.2	12.3	= .11
HTN (%)	73.2	64.7	82.7	< .001
CAD (%)	30	15.6	46.2	< .001
Dyslipidemia (%)	77	58.6	97.6	< .001

BMI = body mass index; CAD = coronary artery disease; DM = diabetes mellitus; HTN = hypertension.

sented to the Fargo VA medical center from January 1, 2004, to May 31, 2010. Out of these 1,100 patients, 51 were on ADT and were excluded from the study. Of the remaining 1,049 patients, 553 patients were not on statins, while 496 patients were on various types of statins (Table 1). Of these 496 patients on statins, 369 were on simvastatin, 52 were on atorvastatin, 32 on lovastatin, 28 on rosuvastatin, 13 on pravastatin, and only 2 on fluvastatin. There was no statistically significant demographic difference between the simvastatin and the nonsimvastatin groups except for duration of statin use (Table 2).

The nonstatin group was younger than the statin users ($P < .001$). There was no statistically significant difference in BMI between the 2 study populations. Diabetes mellitus (DM) was prevalent among 30.3% of the study population. In the nonstatin group, 20.1% of the patients had DM vs 41.7% in the statin group ($P < .001$). There was no statistically significant difference in opioid use between the 2 study populations. In the statin group, 46.2% had coronary artery disease (CAD), while 15.6% in the nonstatin group had CAD ($P < .001$). The prevalence of HTN in the statin group and nonstatin group was 82.7% and 64.7%, respectively ($P < .001$). In the statin group, 97.6% had dyslipidemia vs 58.6% among the nonstatin users ($P < .001$).

The prevalence of low testosterone (< 350 ng/dL) was 49.2% and 57.5% in the nonstatin and statin groups, respectively ($P < .007$) (Table 3). The prevalence of low testosterone in the simvastatin group was 58.8%, and it was 53.5% among the nonsimvastatin users ($P = .3$). Prevalence of very low serum testosterone levels (< 230 ng/dL) was 27.4% in the statin group, while the prevalence was 19.2% among the nonstatin users ($P < .002$). Among the simvastatin users, 28.7% had very low serum testosterone levels, and 22.8% had very low serum testosterone levels in the nonsimvastatin group ($P = .2$).

Regression analysis demonstrates that testosterone level declines slightly with statin use duration ($R^2 = 0.014$; $P < .01$). Statin dose assessment is complicated by the varying potency of statins; thus, statin dose was stratified by quartiles of maximum dose. There is a difference between no statin use and the highest dosage quartile using this approach ($P < .05$). A logistic regression model with low testosterone as the dependent variable and CAD, HTN, age, dyslipidemia, opioid use, and statin use as potential predictors was determined. In this model, BMI, diabetes, and statin use are significant predictors. (Odds ratio for statin use is 1.4, $P = .03$).

DISCUSSION

The question of whether statin use significantly lowers serum testosterone level remains unresolved. Previous studies have demonstrated that statin therapy might induce overt primary hypogonadism and should be considered as a possible confounding factor for the evaluation of low testosterone levels in patients with ED.[1,3,8-10] In a study evaluating the effects of lipid-lowering treatment on steroid synthesis in patients with type 2 diabetes, 80 mg of atorvastatin decreased gonadal steroids.[11] On the contrary, another study showed that high-dose atorvastatin seemed to be safe in terms of gonadal steroidogenesis.[12] Another study done concluded that decreased libido was a probable adverse effect of statins.[1] Our study is most consistent with those studies that have documented a small, but

significant, decrease in serum testosterone level with statins.

Our study shows that statin users have a lower average serum total testosterone level than nonusers. They have a higher frequency of "low" (< 350 ng/dL) serum testosterone levels. Statin users have a lower frequency of "very low testosterone levels" (< 230 ng/dL).

There is a trend for high-dose statin users to have a greater frequency of "very low" serum testosterone levels. Serum testosterone level declines by statin dose and duration. This implies that clinicians need to be cautious while initiating statin therapy in patients who already have borderline or low serum testosterone levels. Initiating statin therapy, especially high-dose statin therapy, in this group of patients may cause their serum testosterone levels to decline further to very low levels.

Simvastatin does not seem to have a significant disproportionate effect on serum testosterone levels or frequency of "low" and "very low" testosterone compared with other statins.

Statin users are older and have a higher prevalence of DM, CAD, and HTN than nonusers. Statin use persists as a significant factor when controlling for BMI, DM, CAD, HTN, age, dyslipidemia, and opioid use.

Thus, in obese patients and patients with diabetes who are predisposed to severe hypogonadism, high-dose statin use may exacerbate the disorder.

CONCLUSION

Our data indicate that statin use may be a significant factor contributing to male hypogonadism. Men who experience hypogonadal symptoms following initiation of or during statin use should have their statin use considered as a potential factor in

Table 2. Individual statin comparisons

Variable	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin	Statins other than simvastatin	*P* value (simvastatin vs other statins)
Patients (n)	52	2	32	13	28	369	127	–
Age (mean and SD)	59.8 (10.0)	56.5 (10.6)	69.4 (10.1)	61.8 (8.8)	63.5 (10.0)	31.2 (5.8)	63.2 (10.5)	= .78
BMI (mean and SD)	33.1 (6.3)	30.1 (2.4)	29.4 (5.2)	29.1 (4.6)	29.4 (5.4)	20 (20)	31.0 (5.9)	= .71
Statin dose (mg) (median and IQR)	40 (40)	40 (0)	20 (20)	20 (30)	10 (10)	37 (50)	20 (30)	= .10
Statin duration (months) (median and IQR)	28.5 (47)	13 (16)	26 (34)	12 (17)	11.5 (16.5)	37 (50)	19.0 (28)	< .001
DM (%)	44.2	50	34.4	30.8	39.3	43.1	39.4	= .53
Opioid use (%)	9.6	0	9.4	7.7	17.9	12.2	11	= .87
HTN (%)	90.4	50	62.5	84.6	85.7	82.9	81.1	= .68
CAD (%)	59.6	50	56.3	23.1	42.9	43.9	51.2	= .18

BMI = body mass index; CAD = coronary artery disease; DM = diabetes mellitus; HTN = hypertension; IQR = interquartile range.

Table 3. Hypogonadism by statin use and simvastatin use vs other statins

Hypogonadism (laboratory level)	Nonstatin use (%)	Statin use (%)	*P* value	Nonsimvastatin use (%)	Simvastatin use (%)	*P* value
Low testosterone (< 350 ng/dL)	49.2	57.5	< .007	53.5	58.8	= .30
Very low testosterone (< 230 ng/dL)	19.2	27.4	< .002	22.8	28.7	= .20

the often multifactorial process. Furthermore, serum testosterone levels decline by statin dose and duration. Initiating statins, especially in high doses, in patients who already have borderline or low serum testosterone levels may cause their serum testosterone levels to decline to very low levels. ●

Acknowledgements

This material is the result of work supported with resources and use of facilities at the Fargo VA Health Care System.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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