DOES STATIN TREATMENT ALTER STEROID HORMONE LEVELS?

(Statin Tedavisi Steroid Hormon Seviyelerini Değiştirir mi?)

Süleyman Ahbab[*], Esra Ataoğlu[*], Mustafa Yenigün[**], Tunga Turker[*], Levent Ümit Temiz[*],
Tayyibe Saler[*], Faik Çetin[*], Zuhal Sağlam[*], Fuat Şar[*]

Summary

Statins blockade cholesterol synthesis by inhibition of HMG CoA (hydroksy methyl glutaryl coenzyme A) reductase. It is an important part of therapy in cardiovascular diseases to hold cholesterol levels in normal ranges for reducing risks of mortality and morbidity. Beyond the proven benefits of inhibition of HMG CoA reductase, the possible effects to steroid hormone synthesis should also be considered. Because steroid hormones are derived from cholesterol. This trial is performed to evaluate the effects of statin administration on steroid hormone synthesis.

Key words: Statin, steroid hormone

Özet

Statinler, HMG CoA (hidroksi metil glutaril koenzim A) redüktaz enzimini inhibe ederek, kolesterol sentezini engellerler. Kardiovasküler hastalıklarda, serum kolesterol düzeylerinin tespit edilen normal sınırlarda tutulması, mortalite ve morbidite riskinin azaltılması açısından, tedavinin önemli bir parçasıdır. HMG CoA redüktazın inhibisyonunun kanıtlanmış faydalarının ötesinde, steroid hormon sentezi üzerine etkisi düşünülebilir. Çünkü steroid hormon sentezi, kolesterole bağlı olarak gerçekleşmektedir. Bu çalışma, statin kullanımının steroid hormon sentezi üzerine etkisi olup olmadığını değerlendirmek amacı ile yapılmıştır.

Anahtar kelimeler: *Statin, steroid hormon*

** Haseki Training and Research Hospital, 4th Internal Medicine Clinic, MD*
*** Haseki Training and Research Hospital, 4th Internal Medicine Clinic, Clinic Chief*

INTRODUCTION

Drug therapy takes an important role in hyperlipidemia treatment. This therapy inhibits progression of atherosclerosis, improves lipid profile and cardiovascular prognosis. At present, usually statins are used to reach this goals. Statins have life saving potential in properly selected patients, particularly those with established coronary heart disease and others at high risk for developing heart disease. Lovastatin is the first discovered molecule of statins group and after that, pravastatin, fluvastatin, simvastatin and atorvastatin have been added in. Statins may be natural or synthetic.

Stains are structural analogues of 3 hydroxy 3 methyl glutaryl Co-enzyme A and they inhibit Hydroxy Methyl Glutaryl Co-enzyme A (HMG CoA) reductase. HMG CoA reductase, takes role in the first step and reaction dependent phase of cholesterol synthesis [(1)]. Inhibition of cholesterol synthesis by statins, is resulted in a decrease in liver cholesterol content and enhanced LDL receptor expression [(2)]. The major planned effect of statins is to lower LDL cholesterol level. It is important to prevent atherosclerosis and indirectly, its complications. By this, the mortality and morbidity related to coronary heart disease declines.

Statins are tolerated well. But, there are few side effects. Increase of liver transaminases (ALT, AST), myopathy and rarely rhabdomyolisis can be seen [(2)]. HMG CoA reductase inhibitors are metabolized in liver by cytocrom P-450 enzyme systems. For that reason, this type of drugs, are not used in cholestatic and chronic liver diseases.

MATERIAL and METHOD

This trial is performed to evaluate the influence of statin treatment on blood levels of steroid hormones. 39 male hypercholesterolemic patients have been followed up for 3 months, under atorvastatin (10 mg/day) treatment. Female patients were not taken in this trial. Because of the menstrual cyclus, it was hard to asses the changes of steroid hormones. Biochemical (glucose, BUN, creatinin, total cholesterol, LDL, electrolytes, fibrinogen, transaminases, creatin kinase) and hormonal (LH, FSH, prolactin, estrogen, progesteron, cortisol, testosteron) tests were performed. These measurements were repeated for three times in trial, before the treatment (basal), under therapy the first month and the third month. To measure the biochemical parameters, Abbot Aeroset auto analisator systems with colorimetric method and for the hormonal parameters, Abbot Architech analisator systems were applied. Results were evaluated with Wilcoxon t test. Our study included 39 male hypercholesterolemic patients either with diabetes or estabileshed ischemic heart disease. Risk categories, detection and treatment of hypercholesterolemia in these patients were evaluated in regard of Adult Treatment Panel III guidelines. (Table - 1, Table - 2 [(3)])

Table 1. ATP III Classification of LDL, Total and HDL Cholesterol (mg/dl) (3)

LDL Cholesterol:		Total Cholesterol:	
<100	optimal	< 200	desirable
100 - 129	near or above optimal	200-239	border line high
130 - 159	borderline high	>240	high
160 - 189	high		
>190	very high		

HDL Cholesterol:	
< 40	low
> 60	high

RESULTS

We administered statin therapy following ATP (Adult Treatment Panel) III guideline to lower total cholesterol under 200 mg/dl and LDL under 100 mg/dl [(3)]. Our study group consisted of hypercholesterolemic patients with diabetic and ischemic heart disease. In our study group of 39 male patients mean age was 61.75 ± 7.39. At the commence of the trial, mean total cholesterol was 208,70 ± 24,98 mg/dl, mean LDL was 139 ± 22,08 mg/dl. After the treatment (in third month), mean total cholesterol dropped to 179,38 ± 31,31 mg/dl, mean LDL declined to 117,23 ± 24,87 mg/dl.It was statistically meaningful, ($p < 0,05$). Fibrinogen levels showed a decrease from starting of the trial untill the third month (from 419,49 ± 94,87 mg/dl to 334,25 ± 87,10 mg/dl, $p < 0,05$). Other biochemical parameters (BUN, creatinin, AST, ALT, creatin kinase, total protein) did not change statistically throughout the trial ($p > 0,05$). No side effects originating from atorvastatin was seen.

There were no change in cortisol, estradiol, FSH, LH, testosterone and prolactin plasma concentrations during the study. Progesterone levels pointed out an appearent reduction (onset mean progesterone level 0,50±0,16 ng/ml, after 3 months downed to 0,19± 0,22 ng/ml). It was a statistically significant decrease ($p < 0,05$).

The values of our study are mean ± SD.

Results of Statin Treatment:

	Onset (mean values)	After 3 months (mean)	P value
Total Cholesterol	208,70 ± 24,98 mg/dl	179,38 ± 31,31 mg/dl	< 0,05
LDL Cholesterol	139,85 ± 22,08 mg/dl	117,23 ± 24,87 mg/dl	< 0,05
Fibrinogen	419,49 ± 94,87 mg/dl	334,25 ± 87,10 mg/dl	< 0,05
Progesterone	0,50 ± 0,16 ng/ml	0,19 ± 0,22 ng/ml	< 0,05
LH	6,06 ± 5,17 mIU/ml	6,66 ± 5,52 mIU/ml	> 0,05
FSH	10,68 ± 12,66mIU/ml	6,79 ± 2,67 mIU/ml	> 0,05
Prolactin	9,70 ± 9,29 ng/ml	8,77 ± 8,44 ng/ml	> 0,05
Estradiol	45,42 ± 18,21 pg/ml	37,17 ± 19,25 pg/ml	> 0,05
Testosterone	415,77 ± 132,20ng/dl	423,08 ± 126,33ng/dl	> 0,05
Cortisol	11,55 ± 1,70 µg/dl	12,45 ± 1,92 µg/dl	> 0,05

DISCUSSION

Plasma lipoproteins are major source of cholesterol for steroid hormone synthesis. HMG CoA reductase inhibitors, which reduce both intracelluler cholesterol synthesis and serum cholesterol levels, thus have a potential negative impact on steroidogenesis [4]. For that reason, we have performed this trial to asses statins impact with atorvastatin. Atorvastatin (10 mg/day) has been given orally to 39 male patients for three months and followed. During statin treatment serum total cholesterol and LDL cholesterol levels were lowered by about 14% and 16%, respectively. Fibrinogen levels decreased in the trial. Fibrinogen is one of the molecules of acute phase reactants. It can rise in inflammatory processes. Reduction in the fibrinogen levels with statin treatment indicates antiinflammatory impact of statins.

Steroid hormone levels, were not statistically changed under atorvastatin treatment, except for progesterone. For the last 8 years, few trials have been performed with other statins. Travia et all.,in 1995, have carried out in 26 patients, pravastatin (12 patients) and simvastatin (14 patients) therapy for 6 months, both at maximum therapeutic dosage of 40 mg/day. Results of study indicated that statin treatment has no negative impact on hormone synthesis [5]. In another study, Bernini et all. have treated 8 male patients with pravastatin (20 mg/day) and followed for 6 months and then, there was not any influence on serum hormone levels and synthesis of statin treatment [4].

In 2003, Böhm et all. have performed placebo controlled statin trial in 29 patients and administered pravastatin treatment (40 mg/day). As a result of this trial, there was not any reduction in steroid hormone levels [6]. According to these results, we did not find any reason to explain the reduction in progesterone levels. Statins may not be responsible for the decrease on progesterone which we spotted in our study. There are no major studies made regarding this relationship between statins and progesteron levels. To prove a link between statins and the decrease of progesteron levels further investigations ought to be carried out.

REFERENCES

1. Murray RK, Mayes PA, Granner KD, Rodwell VW. Harper's Illustrated Bichemistry, Mc Graw Hill, 2003, 26th edition, page 219-221

2. Grundy MS. Etiology and Treatment of Hyperlipidemia, 1996, Mosby-Wolfe Medical Com, page 55-57

3. Expert Panel On Detection, Evaluation and Treatment High Blood Cholesterol in Adults, Executive summary of the third report of the National Cholesterol Education Program (NCEP), Adult Treatment Panel (ATP) III, JAMA 2001; 285:2486

4. Travia D, Tosi F, Negri CJ. ***Clin Endocrinol Metab*** 1995 Mar; 80 (3): 836-40

5. Bernini GP, Brogi G, Argenio GF. ***J Endocrinol Invest*** 1998 May; 21 (5): 310-7

6. Böhm M, Herrmann W, Wassmann S, Laufs U. Zeitscrift für Kardiologie, Januar 2004, band 93, nummer 1, seiten 43-48