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Does statin therapy influence steroid hormone synthesis?

Beeinflusst die Statin-Therapie die Steroid-Hormon-Synthese?

Zusammenfassung Statine reduzieren die Cholesterin- und Isoprenoid-de-novo-Biosynthese, darüber hinaus die rezeptorvermittelte Aufnahme von Cholesterin für die Steroidhormonsynthese. In der vorgelegten randomisierten, placebo-kontrollierten Studie wurde der Effekt von Pravastatin (40 mg/Tag) auf die Plasmakonzentrationen von Steroidhormonen und Gonadotropinen untersucht. Die Patienten (n = 22; 15 Männer, 7 Frauen) wurden mit Pravastatin 40 mg/Tag oder Placebo behandelt. Die Konzentrationen des Gesamtcholesterins sowie des LDL-Cholesterins und der Steroidhormone Östradiol, Testosteron, Cortisol und Dehydroepiandrosteron-Sulfat (DHEAS) sowie der Gonadotropine FSH und LH wurden untersucht. Pravastatin führte zu einer signifikanten Reduktion der Serumkonzentration des Gesamtcholesterins und des LDL-Cholesterins. Signifikante Veränderungen von Östradiol, Testosteron, Cortisol oder DHEAS wurden nicht beobachtet. Kompensatorische Veränderungen von FSH oder LH fanden sich nicht. Es wird schlussgefolgert, dass die Pravastatin-Therapie, die zu einer signifikanten Reduktion des Gesamtcholesterins und des LDL-Cholesterins führte, in therapeutisch verwendeten Dosierungen keinen Einfluss auf die Steroidhormon-Synthese oder die Freisetzung von Gonadotropinen hat.

Schlüsselwörter Statine – pleiotrope Effekte – Sekundärprävention – Steroidhormone

Summary Statins reduce cholesterol and isoprenoid de novo biosynthesis as well as receptor-mediated uptake of cholesterol for steroidogenesis. The present randomized placebo-controlled trial investigated whether pravastatin (40 mg/day) reduces the plasma concentrations of steroid hormones as well as of gonadotropins. Patients (n = 22; 15 males, 7 females) were treated with pravastatin (40 mg/day) or placebo. Levels of total and LDL cholesterol, the steroid hormones estradiol, testosterone, cortisol and dehydroepiandrosterone sulphate (DHEAS) as well as FSH and LH were studied. Pravastatin led to a significant reduction of total cholesterol and LDL cholesterol. There was no significant change in estradiol, testosterone, cortisol or DHEAS plasma concentrations. There was no compensatory change in FSH or LH. It is concluded that pravastatin does not alter steroid hormones or gonadotropins in a clinically applicable dose, which significantly reduces total and LDL cholesterol.

Key words Statins – pleiotropic effects – secondary prevention – steroid hormones

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Introduction

Inhibition of cholesterol synthesis by inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase (statins) is effective to reduce cardiovascular complications in primary prevention (AFCAPS/TEXCAPS) as well as in secondary prevention (4S, CARE, LIPID). In these trials, statins have shown to improve mortality and morbidity (Sacks et al., 1996; Sacks et al., 2000; Scandinavian Simvastatin Study Group 1994, Shepherd et al., 1995; The **L**ong-term **I**ntervention with **P**ravastatin **I**schaemic **D**isease (LIPID) Study-Group, 1998). There is evidence that statins have effects beyond lipid lowering, so-called pleiotropic effects (Werner et al., 2002 a). In this context, patients on statins have a lower cardiovascular mortality compared to individuals without therapy and similar concentrations of lipoproteins as shown in epidemiological studies (Massy et al.; Sacks et al., 1996; Shepherd et al., 1995). Reduction of LDL is primarily due to hepatic inhibition of cholesterol synthesis leading to an upregulation of LDL receptors which finally enhances the clearance of LDL from the serum (Goldstein and Brown, 1990). However, there is also a direct impact on the vascular system, which is potentially relevant for prevention of atherosclerotic complications. Among these are downregulation of AT1 receptors (Wassmann et al., 2001), improvement of endothelial function (Laufs et al., 2000 a), inhibition of platelet aggregation (Laufs et al., 2000 b), inhibition of vascular inflammation as shown by a decline in high sensitive CRP (Ridker et al., 2001), and an increase of circulating endothelial progenitor cells (Vasa et al., 2001; Werner et al., 2002 b). Many of these effects appear to be mediated by isoprenoid intermediates involved in cholesterol biosynthesis, which regulate cellular distribution and function of small GTPases (Werner et al., 2002 a).

Therefore, it is presumable that statin therapy could also have an effect on adrenal and gonadal steroidogenesis because hormone synthesis requires an efficient intracellular pool of free cholesterol. Impairment of hormone synthesis could be due to the direct inhibition of cholesterol synthesis or could be caused by a reduction of LDL-particle uptake by steroidogenic tissues (Tureck and Strauss, 1982; Bolté et al., 1974). In Watanabe rabbits with defective LDL receptors, simvastatin lowers stimulated progesterone levels. Dogs treated with high doses of statins showed reduction of testicular endocrine function (McDonald et al., 1988; Robins et al., 1994). However, in males with heterozygous hypercholesterolemia or polygenic hypercholesterolemia, pravastatin and simvastatin applied in a non-randomized, non-placebo controlled trial exerted no significant effects on steroidogenesis (Travia et al., 1995). In a more recent study, simvastatin produced a slight but nonsignificant decrease of total testosterone (Dobs et al., 2000). The effect of statins on sex hormones in women has not been investigated. Furthermore, data on steroid hormone plus gonadotropic hormones are not available. Therefore, we performed a double-blind placebo-controlled trial in males and females with hypercholesterolemia with a clinically relevant dose of pravastatin (40 mg/d).

Methods and materials

Estradiol, testosterone and dehydroepiandrosterone sulphate, cortisol and the gonadotropins FSH and LH were determined before and after three months of treatment with pravastatin (40 mg/d). In addition, total cholesterol and LDL cholesterol concentrations were determined. 22 individuals (15 males, 7 females) were treated with pravastatin 40 mg/d or placebo. Hormones as well as lipid concentrations were taken before and after three months of therapy in the placebo and in the pravastatin group. The demographic data are summarized in Table 1. Blood was drawn in the morning from patients fasting and at bedrest.

LH and FSH were determined by sandwich chemiluminescence immunoassays using the ADVIA® Centaur™ analyzer (Bayer Diagnostics, Tarrytown, USA). The ADVIA® Centaur assays for LH and FSH are calibrated against the 2nd international standard 80/552 (WHO), the 2nd international standard 94/632 (WHO) and the 3rd international reference preparation 84/500 (WHO), respectively. The inter-assay imprecision (n = 20) is given for the low level control (CV for LH, FSH and prolactin) as 1.5%, 2.7%, 4.7%, respectively; the intermediate level control as 2.9%, 1.2%, 1.8%, respectively; and the high level control as 2.3%, 1.2%, 4.1%, respectively. The assays for cortisol, testosterone and estradiol are competitive electrochemiluminescence immunoas-

Table 1 Patient characteristics. Data are expressed as mean ± SD. P values for the comparison between groups. *CAD*, coronary artery disease; *NS*, not statistically significant

	Placebo (n = 12)	Statin (n = 10)	*P* value
Age (y)	64.7 ± 8.4	66.3 ± 9.5	NS
Sex (male/female)	9/3	6/4	NS
Diabetes	4	2	NS
Smoker	8	7	NS
Hypertension	9	9	NS
CAD	10	8	NS

Table 2 Effect of pravastatin (40 mg/d) or placebo treatment on blood lipids

Placebo (n = 12)				Statin (n = 10)		
	Baseline	3 months	*p*	Baseline	3 months	*p*
Total cholesterol	194.6 ± 21.3	191.3 ± 24.5	0.70	196.8 ± 24.3	172.6 ± 21	0.02
HDL cholesterol	43 ± 9.2	44.8 ± 10.1	0.38	45.4 ± 12	46.5 ± 10.1	0.64
LDL cholesterol	130.3 ± 19.2	123.8 ± 19.5	0.40	130.7 ± 17.1	111.6 ± 21.2	0.03
Triglycerides	133.0 ± 72.8	138.6 ± 42.4	0.78	114.0 ± 70.9	109.9 ± 53.8	0.80

Mean ± SD

says using the Elecsys 2010 analyzer (Roche, Basel, Switzerland). The inter-assay imprecision (n = 20) is given for the low level control (CV for cortisol, testosterone and estradiol) as 3.3%, 5.8%, 5.5%, respectively; and the high level control as 4.6%, 3.3%, 4.6%, respectively.

DHEAS was determined by competitive chemiluminescence immunoassay on the Immulite analyzer (DPC Biermann, Bad Nauheim, Germany). The inter-assay imprecision (n = 20) is given for the low, intermediate and high level control (CV for DHEAS) as 15%, 13% and 8%, respectively.

Plasma total cholesterol was determined by an enzymatic colorimetric procedure using cholesterol esterase and cholesterol oxidase (Roche, Basel, Switzerland) on the Hitachi 917 analyzer. The inter-assay imprecision (n = 20) is given for the low and high level control (CV for total cholesterol) as 1.6% and 2.3%, respectively. LDL cholesterol was calculated by the Friedewald formula provided that plasma triglycerides were lower than 400 mg/dl. Otherwise the plasma sample was subjected to overnight ultracentrifugation at 244 000 g. After measurement of HDL and total cholesterol in the bottom fraction, LDL cholesterol was calculated.

The ethical committee of the University of the Saarland approved the study.

Statistical analysis

The data were statistically evaluated by the covariance analysis. The p-value of < 0.05 is statistically significant. The data are expressed as the mean ± standard deviation (SD).

Results

Effects on LDL cholesterol

Table 2 shows the effect of pravastatin (40 mg/day) or placebo treatment. The lipid-lowering effect was only observed in the treatment group but not in the placebo group.

Effects on steroidogenesis

Fig. 1 summarizes biochemical pathways leading to the synthesis of steroid hormones including the synthesis of cortisol. The assessed parameters are marked. Steroid hormones were measured in parallel in order to exclude adaptive changes of the activity of the hydroxylases in the biosynthesis pathways. Fig. 2 shows the effect of pravastatin treatment on serum levels of estradiol, testosterone, DHEAS and cortisol in males. There was no significant difference between the statin- and the placebo-treated patients. There was also no significant difference between pre-study values compared to the levels after the three months treatment period. Fig. 3 shows the data for females. There were also no significant changes in women. In particular, the estradiol concentrations were not significantly different before and after treatment as well as between the placebo and pravastatin group.

In order to investigate whether there are changes of the gonadotropic hormones, FSH and LH levels were determined. Similar to steroid hormones, there were no significant changes in males and females (Fig. 4).

Discussion

A double-blind, placebo-controlled trial was performed in males and females investigating the effects of 40 mg pravastatin per day. The treatment with pravastatin reduced cholesterol in males and fe-

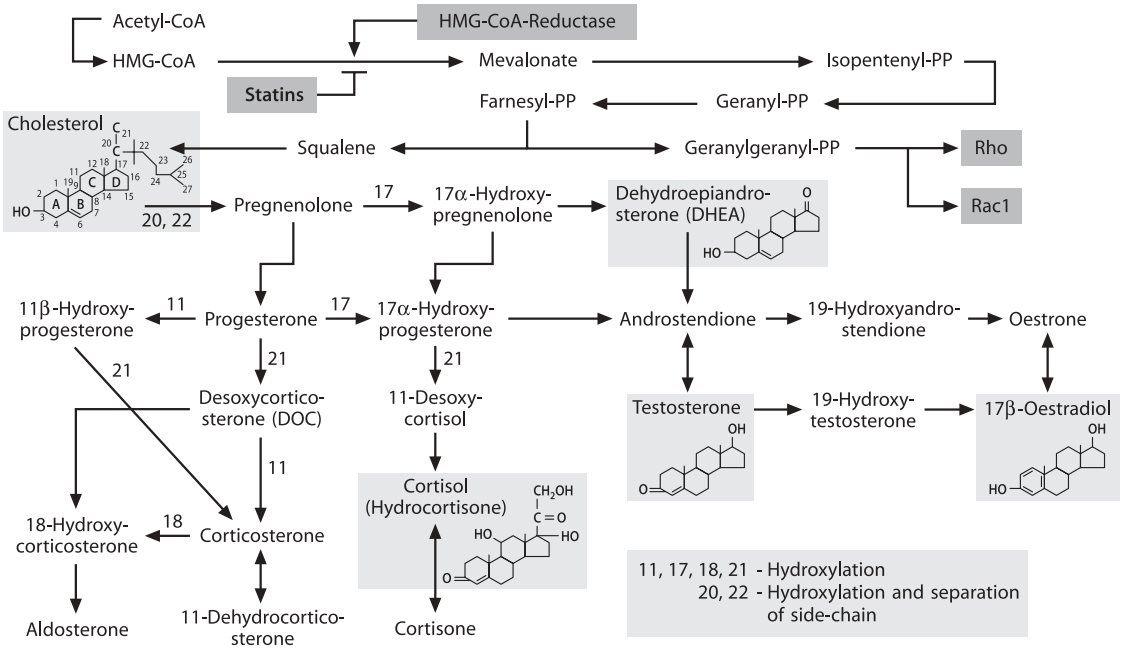

Fig. 1 Biochemical pathways leading to the synthesis of different steroid hormones

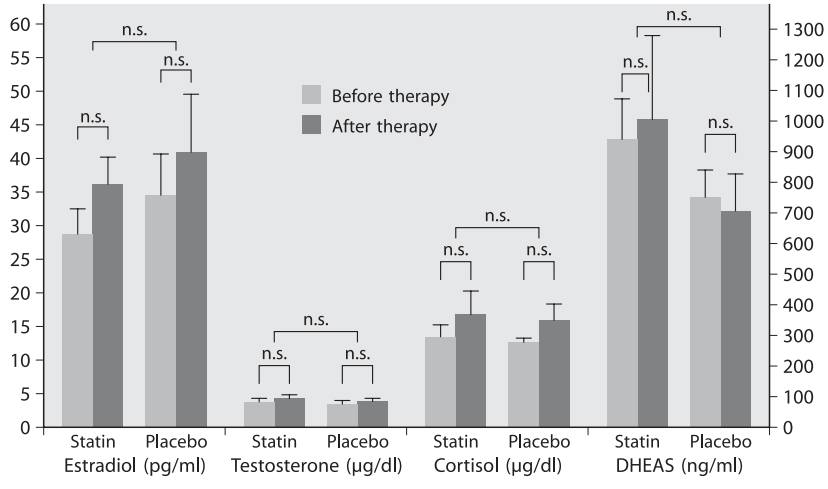

Fig. 2 Effect of pravastatin treatment on estradiol, testosterone, dehydroepiandrosterone (DHEAS) and cortisol concentrations in males. Data are given as mean ± SD

males. There were no significant alterations in steroid hormone or gonadotropin concentrations.

The present data show that extrahepatic effects of statins, which most likely are due to the interference with isoprenoid intermediates, are not relevant for the endocrine function of treated patients. Apparently, cholesterol synthesis is not completely inhibited in peripheral tissues. In contrast, the effects in the liver are more pronounced (Germershausen et al., 1989). Therefore, it is likely that sufficient amounts of cholesterol are available in gonadal and adrenal cells to maintain steroid hormone synthesis. Changes in the activity of 11-hydroxylase or 17-hydroxylase may compensate for a lack of substrate. However, all steroid hormones were measured in parallel, indicating that a selective increase of one hormone did not mask a putative effect of statins on steroid hormone synthesis. In addition, there was no increase of gonadotropins, suggesting that an increase in gonadotropin did not counteract a potential effect on steroid hormone concentrations. These data are in line with a recent study, in which steroid hormones were measured after maximal stimulation with ACTH in patients on simvastatin treatment

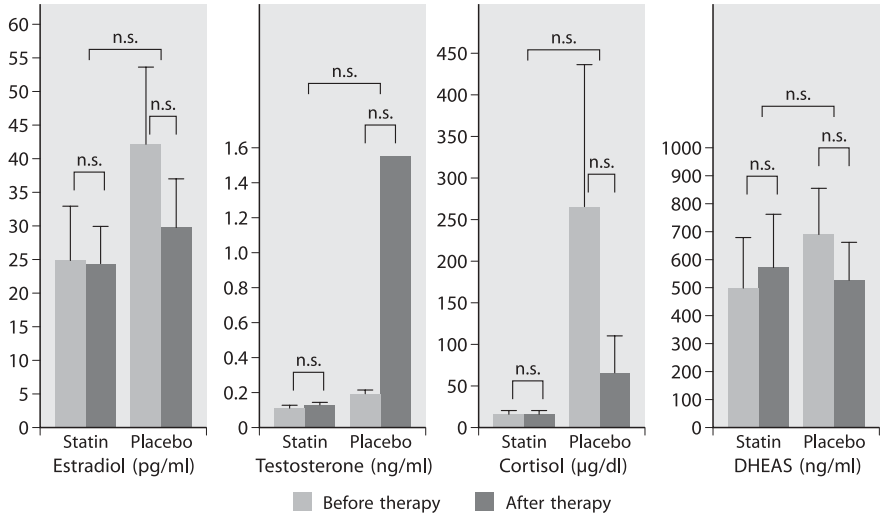

Fig. 3 Effect of pravastatin treatment on estradiol, testosterone, dehydroepiandrosterone (DHEAS) and cortisol concentrations in females. Data are given as mean ± SD

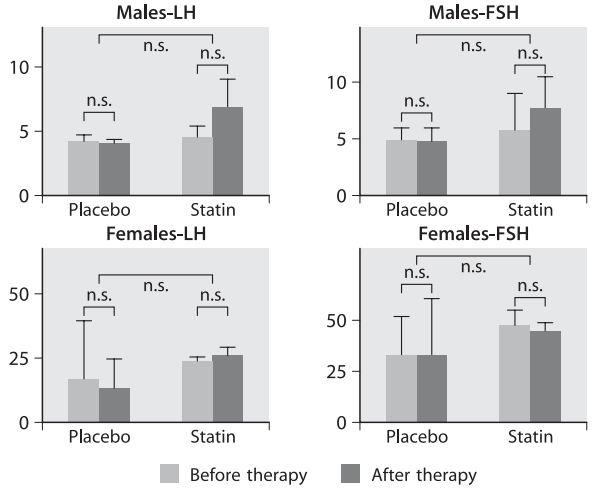

Fig. 4 Effect of pravastatin treatment on FSH and LH levels in males and females. Data are given as mean ± SD

(Dobs et al, 2000). Since the latter study was performed exclusively in men, the present results allow to extend these findings also to females.

In a previous study the application of 40 to 160 mg simvastatin was associated with a significant reduction in serum testosterone levels (Davidson et al., 1997). Since pravastatin is more hydrophilic than simvastatin (Blum, 1994), it cannot be excluded that different pharmacokinetic or physicochemical properties of statins may have had an impact on the investigated parameters. In agreement with the presented findings, a recent study showed no effect of 20 to 40 mg pravastatin on basal or β-HCG-stimulated testosterone (Dobs, 1993). Finally, there were no adverse events on sexual function in approximately 2000 patients treated with simvastatin in the 4S trial (Scandinavian Simvastatin Study Group, 1994).

Taken together, there is no effect of pravastatin therapy on gonadal or adrenal steroidogenesis. A compensatory increase of gonadotropic hormones does not occur, although lipid lowering, as judged by the decline in LDL cholesterol, was present in this placebo-controlled, double-blind trial in males and females.

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