Postmenopausal Hormone Replacement Therapy with Tibolone Decreases Serum Lipoprotein(a)

By *W. Haenggi*[1], *W. Riesen*[2] and *M. H. Birkhaeuser*[1]

[1] *Abteilung für gynäkologische Endokrinologie, Universitäts-Frauenklinik Bern, Switzerland*
[2] *Institut für Klinische Chemie und Hämatologie, Kantonsspital St. Gallen, Switzerland*

Summary: Lipoprotein(a) is a cholesterol-rich plasma lipoprotein consisting of LDL and apolipoprotein(a). Apolipoprotein(a) shows structural similarity with plasminogen and thus may interfere with thrombogenesis. Lipoprotein(a) has been shown to be a strong independent risk factor for coronary heart disease.

So far no drug or diet is known to have prominent effects on the serum levels of lipoprotein(a).

In the present study we found a highly significant decrease (in the order of 26%) of lipoprotein(a) in 28 women treated for 6 months with Tibolone, compared with an age-matched healthy control group.

Tibolone is a synthetic steroid with gestagenic and weak androgenic and oestrogenic properties, which shows no stimulation of the endometrium. Tibolone also produced a decrease in HDL-cholesterol of 23% ($p < 0.001$), a decrease in apolipoprotein A-I of 14% ($p < 0.001$) and an increase in apolipoprotein B of 17% ($p < 0.001$), whereas the control group showed no significant changes in these quantities.

Tibolone in a daily dose of 2.5 mg is at present the only complete postmenopausal hormone replacement therapy that shows a significant inhibiting influence on serum levels of lipoprotein(a). Its effect on lipoprotein(a) might counterbalance, at least to some extent, the theoretical adverse effect on the other lipoprotein risk factors.

Introduction

Lipoprotein(a) is a cholesterol-rich plasma lipoprotein consisting of one particle of low density lipoprotein and one molecule of apolipoprotein(a) (1). Apolipoprotein(a) shows a close structural similarity to plasminogen and may compete with plasminogen in fibrinolysis (2). Due to an amino acid substitution at the site of action of the tissue plasminogen activator, apolipoprotein(a), however, may not be split into an active plasmin-like fragment (3).

Lipoprotein(a) has been shown to be a genetically determined independent risk factor for coronary heart disease (1, 4) and stroke (5) and its metabolism is independent of that of low density lipoprotein.

Plasma concentrations of lipoprotein(a) vary over a wide range between individuals but they are remarkably constant in any given individual (6).

This study was initiated to get more insight into the different effects of sex steroids on lipoprotein(a), since it is known that lipoproteins are strongly influenced by sex hormones. Low density lipoprotein is known to increase in post menopausal women, probably accounting for the increased cardiovascular risk. Post menopausal hormone replacement therapy with oestrogen has been shown to reduce low density lipoprotein and increase high density lipoprotein levels, with a 40—50% decrease in the risk of cardiovascular death (7). Little is known, however, about the effects

of hormone replacement therapy on lipoprotein(a). We therefore looked at changes in plasma lipoproteins (low density lipoprotein-cholesterol, total high density lipoprotein-cholesterol and subfractions, apolipoprotein A-I, apolipoprotein A-II, apolipoprotein B) and lipoprotein(a) in a group of 28 post menopausal women treated for 6 months with Tibolone (Livial®; Organon International) and in a control group of untreated volunteers. Tibolone is a synthetic steroid, $(7\alpha,17\alpha)$-17-hydroxy-7-methyl-19-nor-pregn-5(10)-en-20-yn-3-one, structurally related to the progestogens, norethynodrel and norethisterone (fig. 1). It shows
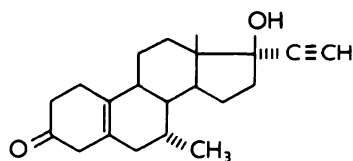

Fig. 1. Chemical structure of Tibolone [Org OD 14: $(7\alpha,17\alpha)$-17-hydroxy-7-methyl-19-nor-pregn-5(10)-en-20-yn-3-one].

weak progestogenic, oestrogenic and androgenic actions in animal tests (8). Tibolone has been shown to be effective in the relief of climacteric symptoms (9—11) and in preventing post menopausal bone loss (12). Tibolone is also effective in the treatment of established postmenopausal osteoporosis (13). A further advantage of Tibolone is the absence of endometrial stimulation (14, 15). Thus, in non-hysterectomized women no withdrawal bleeding occurs, an otherwise leading cause for discontinuation of hormone replacement therapy.

Patients and Methods

Patients

In 28 apparently healthy, early post menopausal women, serum lipids, lipoprotein(a), low density lipoprotein- and high density lipoprotein-cholesterol, and the apolipoproteins A-I, A-II and B were measured before and after 6 months of hormone substitution with Tibolone 2.5 mg daily. The results were compared with a control group of 28 age-matched postmenopausal volunteers not wishing to receive hormonal substitution therapy. All women participating in the study were recruited among patients consulting our endocrinological outpatient consultation for climacteric symptoms. None of the women had taken oestrogen gestagen medication during at least 2 months prior to the first examination, and none took lipid-lowering or any other type of drug. They were advised not to change their diet and smoking habits.

The major characteristics of the study population are given in table 1. The two groups did not differ statistically. Menopause was ascertained by serum follitropin values above 30 U/l.

All patients gave their informed consent to participation in the study. The study protocol was approved by the ethical committee of the women's hospital of the University of Berne.

Tab. 1. Characteristics of study population. Data are presented as mean ± SEM. Body-Mass-Index: weight in kg/(height in cm)^2 × 10 000.
There was no significant difference between the two groups (Student's t test: p > 0.05).

	Controls	Tibolone
Number of patients	28	28
Age (a)	51.9 ± 0.6	52.9 ± 0.7
Duration of menopause (a)	3.1 ± 0.4	3.5 ± 0.4
Weight (kg)	64.1 ± 1.7	68.8 ± 2.1
Height (cm)	164.3 ± 1.1	163.2 ± 1.1
Body-Mass-Index	23.8 ± 0.6	24.8 ± 0.6
Systolic blood pressure (mmHg)	124.5 ± 3.2	126.1 ± 3.5
Diastolic blood pressure (mmHg)	78.0 ± 1.8	79.3 ± 1.8
Hysterectomized	9	11
Bilateral ovarectomized	2	1
Smoker	5	5
Previous hormonal replacement therapy	7	9

Methods

Fasting blood samples were obtained from all subjects before enrolment in the study and after 6 months. All sera were stored at −20 °C until analysed. Total cholesterol and triacylglycerols were measured by enzymatic methods (Boehringer Mannheim), high density lipoprotein-cholesterol was determined after precipitation with phosphotungstate Mg^{2+} (Boehringer Mannheim), and low density lipoprotein-cholesterol was measured after precipitation with an amphiphilic polymer (Bio Mérieux, Lyon) in the washed and re-dissolved precipitate. The high density lipoprotein$_2$/high density lipoprotein$_3$ (HDL_2/HDL_3)-ratio was measured by precipitation with polyethylene glycol according to Kostner (16). Apolipoproteins A-I, A-II and B were measured by immunonephelometry on a Behring Nephelometer Analyser (Behringwerke Marburg). The between-run coefficient of variation for apolipoprotein-A-I was 4.6% at 1.7 g/l and the within-run coefficient of variation was 1.8%. The between-run coefficient of variation for apolipoprotein B was 3.3% at 1.22 g/l and the within-run coefficient of variation was 1.9%. Apolipoprotein values were standardised with reference material from Behring-Werke which is proposed as the WHO standard.

Lipoprotein(a) was measured by immunoradiometric assay (Pharmacia Uppsala). This method was shown not to be affected by storage of samples in the frozen state. The between-run coefficient of variation for lipoprotein(a) was 9.7% at 93 mg/l.

Statistical analysis

The comparison of initial values, treatment differences within groups after 6 months and comparison of treatment changes between groups were statistically analysed with Student's test. For lipoprotein(a), which is known for its skewed distribution, logarithmic transformation was performed before testing. Testing was performed two-sided. All p-values below 0.05 were considered to be significant.

Results

Initial lipid and lipoprotein values did not differ between the two groups of volunteers (tab. 2). Lipoprotein(a) concentrations showed the typical skewed var-

iation among individuals. At the start of the study, 8 of the 28 women in the control group and 4 of the 28 women in the treated group had lipoprotein(a) values above the norm of 300 mg/l, this difference was statistically not significant (Fisher's exact test).

After 6 months of treatment with Tibolone, significant changes were found in the values for high density lipoprotein-cholesterol, the high density lipoprotein$_2$/ high density lipoprotein$_3$-ratio, apolipoprotein A-I and apolipoprotein B, whereas no significant alterations occurred in total cholesterol, triacylglycerols, low density lipoprotein-cholesterol, very low density lipoprotein-cholesterol and apolipoprotein A-II. High density lipoprotein-cholesterol and apolipoprotein A-I concentrations significantly decreased after Tibolone treatment, whereas apolipoprotein B showed a statistically significant increase (tab. 2). Within the non-substituted group only the high density lipoprotein$_2$/high density lipoprotein$_3$ ratio showed a significant decrease after 6 months. In contrast to apolipoprotein B, lipoprotein(a) showed a decrease of 26.1% in the treated group, while within the control group an insignificant change of only 1.7% was observed (tab. 2). When compared between the two groups, the decrease of lipoprotein(a) after 6 months under Tibolone treatment is highly significant (p < 0.0002).

Twenty-four of the 28 lipoprotein(a) values showed a decrease after treatment with Tibolone, the largest decreases occurring in the 7 patients with the highest pre-treatment values.

The mean change of lipoprotein(a) as a percentage of the initial value in the 7 patients with highest initial values (upper quartile) was 0.7% in the controls and −42.9% in the treated group, this difference between the two groups being highly significant (p < 0.004).

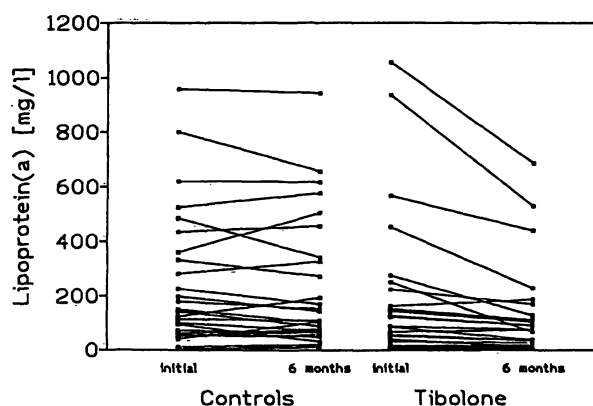The individual changes in lipoprotein(a) levels are illustrated in figure 2.

Fig. 2. Individual changes of serum levels of lipoprotein(a) during 6 months in control and treatment groups.

Tab. 2. Changes in serum lipids after six months in controls and in patients treated with 2.5 mg of Tibolone daily. Data are presented as mean and 95% confidence limits. Significance of changes within groups: initial values versus values after 6 months therapy, according to paired Student's t test.
* p < 0.05, *** p < 0.001

| | Controls | | | Tibolone | | | Probability of differences between groups |
	Initial	Difference after 6 months	Change in %	Initial	Difference after 6 months	Change in %	p
Total cholesterol (mmol/l)	6.2 (5.8, 6.7)	−0.15 (−0.32, 0.03)	− 2.4	6.2 (5.9, 6.5)	−0.07 (−0.37, 0.23)	− 1.1	ns
Triacylglycerols (mmol/l)	1.4 (0.9, 1.3)	−0.07 (−0.20, 0.06)	− 6.4	1.2 (0.9, 1.4)	−0.05 (−0.2, 0.09)	− 4.2	ns
HDL cholesterol (mmol/l)	1.9 (1.7, 2)	−0.07 (−0.16, 0.02)	− 2.7	1.7 (1.6, 1.9)	−0.39 (−0.5, −0.28)	−22.9***	0.00001
HDL$_2$/HDL$_3$-ratio	0.3 (0.3, 0.4)	−0.05 (−0.1, 0)	−16.7*	0.28 (0.2, 0.3)	0.05 (0, 0.1)	+17.9*	0.003
LDL cholesterol (mmol/l)	4.0 (3.6, 4.4)	−0.03 (−0.21, 0.15)	− 0.8	4.0 (3.8, 4.3)	0.22 (−0.06, 0.5)	+ 5.5	ns
VLDL cholesterol (mmol/l)	0.4 (0.3, 0.6)	−0.04 (−0.18, 0.1)	−10	0.5 (0.3, 0.6)	0.07 (−0.08, 0.22)	+ 1.4	ns
Apolipoprotein A-I (g/l)	1.9 (1.8, 2)	−0.04 (−0.09, 0.01)	− 2.1	1.8 (1.7, 1.9)	−0.26 (−3.36, −0.17)	−14.4***	0.0001
Apolipoprotein A-II (g/l)	0.49 (0.47, 0.52)	0.01 (−0.03, 0.04)	+ 2	0.49 (0.46, 0.51)	−0.02 (−0.05, 0)	− 4.1	ns
Apolipoprotein B (g/l)	1.2 (1.1, 1.3)	0.05 (−0.03, 0.1)	+ 4.2	1.4 (1.2, 1.4)	0.24 (0.15, 0.33)	+17.1***	0.0028
Lipoprotein(a) (mg/l)[1]	176.7 [46.5; 671.7]	179.7 [55.6; 580.6]	+1.7	107.6 [25.5; 454.8]	79.5 [20.2; 312.6]	−26.1***	0.0002

[1] Values of Lp(a) are derived from logarithmic transformation and are expressed as mean [−SD, +SD].

Discussion

It is well established that oestrogens and progestins have different effects on lipoproteins. Oestrogens are associated with a decrease in the atherogenic low density lipoprotein fraction and with an increase in the concentration of high density lipoprotein, shown to be negatively associated with coronary heart disease. Tibolone, which was used in the present study, is a synthetic steroid with oestrogenic, progestogenic and weak androgenic activity. We confirmed an already known significant decrease in high density lipo-protein-cholesterol (17) and its major apolipoprotein A-I of 22.9% and 14.4%, respectively, in the treatment group, probably due to the progestagenic and androgenic properties of Tibolone. Concomitant with the decrease in high density lipoprotein, there was also a significant increase of the high density lipoprotein$_2$/high density lipoprotein$_3$ (HDL$_2$/HDL$_3$) ratio in the order of 17.9%, indicating that high density lipoprotein$_3$ is decreased to a greater extent than high density lipoprotein$_2$. The high density lipoprotein$_2$ subfraction is regarded as the antiathero-genic fraction of high density lipoprotein-cholesterol (18). Furthermore, Klosterboer et al. demonstrated that after treatment for 3 years, high density lipo-protein-cholesterol returned to pretreatment concentrations (17). However, in view of the important decrease of total high density lipoprotein, an increase of the coronary risk has to be postulated.

On the other hand, recent data from experiments in Cynomolgus monkeys showed that the extent of coronary atherosclerosis was lessened by oestrogen gestagen combination, despite the fact that serum concentrations of high density lipoprotein-cholesterol were lowered (19).

In our treatment group no significant alteration was observed for total cholesterol, triacylclycerols and low density lipoprotein-cholesterol, while apolipoprotein B showed a highly significant increase of 17.1%. Elevated serum concentrations of apolipoprotein B are significantly correlated with a higher risk for cardiovascular disease in women (20). In both groups we found no significant influence on triacylglycerol serum concentrations, but there was a slight decrease of 4% (Tibolone) and 6% (controls), compared with the initial values. These results are not in accord with earlier findings (17, 21) of a significant decrease (20%) of triacylglycerol after Tibolone treatment. Elevated concentrations of triacylglycerols are considered to be associated with a higher risk for cardiovascular disease (22, 23).

The main focus of our study, however, was the response of lipoprotein(a), (an independent risk factor for coronary heart disease) to Tibolone treatment. It is difficult to influence the level of lipoprotein(a). Conventional hormone replacement therapy with oral oestrogens only marginally decreased serum concentrations of lipoprotein(a), probably due to a minor influence on its hepatic synthesis (24). A decrease of lipoprotein(a) in the order of 50%, due to combined postmenopausal hormone replacement therapy with 1.25 mg conjugated oestrogens daily plus 10 mg medroxyprogesterone acetate for 10 days a month as described by Soma et al. (25) in 10 patients treated for one year, was not confirmed by the data of Meusing et al. (26). Further indications for an influence of sex steroids on lipoprotein(a) levels are provided by the results of Kuhl et al. (27) who found a transitory decrease of lipoprotein(a) in 19 premenopausal women taking an oral contraceptive containing ethinyloestradiol and desogestrel. Lipoprotein(a) decreased during the 3rd month and reached initial values after 6 months. Two other publications deal with the influence of oestradiol therapy on lipoprotein(a) in men treated for prostatic cancer. Lipoprotein(a) decreased to 50% after 6 months in 15 men treated with oral ethinyloestradiol 150 µg daily (28), whereas the case report of a 67 year old man with familial hypercholesterolaemia treated with 200 mg diethylstilboestrol per day showed a decrease of lipoprotein(a) of more than 80% after 4 weeks of treatment (29).

Conventional lipid lowering drugs also have little effect on this lipoprotein. The same holds true for diet (30, 31). So far, decreases of lipoprotein(a) have been obtained only with niacin and combination of niacin and neomycin (32, 33), and by low density lipoprotein apheresis (34).

Statistical analysis of plasma lipoprotein(a) levels is difficult because of their extremely skewed distribution in the white race. In a non-selected population, values above a cut-off-point of 300 mg/l, which are thought to be associated with increased risk for coronary heart disease, are observed in about 20% of healthy volunteers (W. Riesen: MONICA-Switzerland, unpublished data). In our study group of 56 post menopausal women, lipoprotein(a) concentrations above 300 mg/l were observed in 21%.

In the group of 28 women treated with Tibolone there was a highly significant decrease in the concentrations of lipoprotein(a). The mean decrease was 26.1%, while in the untreated group a mean increase of 1.7%

was observed. Compared with lipid lowering drug treatment, where effects in the order of a 30% decrease are only seen with very potent lipid regulating agents, the change of lipoprotein(a) with Tibolone treatment is certainly remarkable. These findings are consistent with the results of a pilot study by *Farish* et al. (35) who demonstrated a significant decrease of the median serum lipoprotein(a) values of 47% in 9 women treated with 10 mg norethisterone daily for 2 months. Tibolone shows a close structural similarity to norethisterone. These data are compatible with an unexpected constellation of a theoretically unfavourable fall of high density lipoprotein and a favourable change of lipoprotein(a) values.

In conclusion, Tibolone is so far the only complete post menopausal hormone replacement therapy that shows a significant decrease of serum concentration of lipoprotein(a) after an oral intake of 2.5 mg daily. Its effort on lipoprotein(a) concentrations, however, might counterbalance, at least to some extent, the adverse effect of Tibolone on other lipoprotein risk factors such as the important decrease of high density lipoprotein-cholesterol and the significant increase in apolipoprotein B. The clinical long-term effect of Tibolone on the risk of coronary heart disease, known to be elevated in unsubstituted post menopausal women, has to be evaluated in prospective long term studies.

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Dr. med. Willy Haenggi
Oberarzt
Universitäts-Frauenklinik Bern
Schanzeneckstraße 1
CH-3012 Bern
Switzerland