The effect of estroprogestagen therapy on lipid status in menopause depending on the drug administration route

Uticaj terapije estroprogestagenima na lipidni status u menopauzi zavisno od načina primene leka

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Abstract

Background/Aim. In menopausal women lipid and lipo-protein values are important predictors of development of cardiovascular diseases (CVD). The use of estrogens reduces levels of low density lipoprotein cholesterol (LDL-C) and lipoprotein A [Lp(a)], and increases levels of triglycerides (TG) and high density lipoprotein cholesterol (HDL-C) depending on the dose and route of admi-nistration. Simultaneous administration of progesterone, depending on the type, can have different effects on lipids. The aim of the study was to examine the effect of estroprogestagen therapy on the lipid metabolism of women in menopause, depending on the administration route. **Methods.** A study was conducted as prospective clinical interventional study with controlled parallel groups. It included 64 women in menopause, divided into three groups: the group 1 (n = 22) on oral therapy with estro-progestagens, the group 2 (n = 17) on transdermal patch therapy with estroprogestagens and the group 3 (n = 25) treated with estroprogestagens given intramuscularly. The following biochemical parameters in the serum were determined: total cholesterol (TC), HDL-C, LDL-C, TG, Lp(a), apoprotein A (Apo-A), apoprotein B (Apo-B), fo-llicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, testosterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-SO$_4$), prolactin and thyroid-stimulating hormone (TSH), prior to administration of the menopausal hormonal therapy (MHT), as well as after sixth months and 2–5 years from the beginning of the therapy. The statistical signi-ficance of the difference in values obtained was examined independently and depending on the route of MHT application. **Results.** MHT, regardless of the administration route, led to a statistically significant continuous decrease of TC, LDL-C and Apo-B levels and the continuous increase of HDL-C and Apo-A levels. Serum levels of TC, LDL-C, HDL-C, Lp(a), Apo-A and Apo-B did not show a statistically significant differences among groups of women given MHT by different routes. It was found that the serum level of Apo-A increased significantly with the rise of estradiol, and the values of LDL and Apo-B decreased re-gardless of the route of the MHT application. **Conclusion.** MHT introduced in time, regardless of the route of administration, has beneficial effects on the lipid status of menopausal women and consequently might prevent numerous cardiovascular diseases that are the leading cause of mortality.

Key words:
hormone replacement therapy; cardiovascular diseases; lipids; menopause.

Apstrakt

Uvod/Cilj. Kod žena u menopauzi, vrednosti lipida i lipoproteina su značajni prediktori razvoja kardiovaskularnih bolesti (KVB). Primena estrogena smanjuje serumske nivoe LDL holesterola (LDL-C) i lipoproteina A [Lp(a)], uz povećanje novoa triglicerida (TG) i HDL holesterola (HDL-C), što zavisi od doze i puta primene leka. Istovremena primena progesterona, zavisno od vrste, može imati različite efekte na novo lipida u serumu. Cilj rada je bio ispitivanje uticaja terapije estroprogestagenima na metabolizam lipida žena u menopauzi, zavisno od puta primene leka. **Metode.** Istraživanje je sprovedeno po tipu prospektivne kliničke interventne, kontrolisane studije sa paralelnim grupama.

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Njime su bile obuhvaćene 64 žene u menopauzi, podeljene u tri grupe: grupa 1 (n = 22), na oralnoj terapiji estro-progestagenima, grupa 2 (n = 17) na terapiji transdermalnim flasterima i grupa 3 (n = 25) koja je estroprogestagene primala intramuskularno. U serumu se bili određivani nivoi: ukupnog holesterola (TC), LDL-C, HDL-C, TG, Lp(a), apolipoproteina A (Apo-A) i apolipoproteina B (Apo-B), folikulosti-mulirajućeg hormona (FSH), luteinizirajućeg hormona (LH), estradiola, progesterona, testosterona, *sex hormone-binding globulin* (SHBG), dehidroepiandrosteron sulfata (DHEA-S04), prolaktina i tiroid-stimulišućeg hormona (TSH), i to pre primene hormonske terapije u menopauzi (HTM), kao i posle šest meseci i 2–5 godina od početka terapije. Statistička značajnost razlika u doim vrednostima ispitivana je nezavisno i zavisno od puta primene HTM. **Rezultati.** HTM, bez obzira na put primene, dovela je do statistički značajnog kontinuiranog sniženja serumskih nivoa TC, LDL-C i Apo-B i kontinuiranog porasta nivoa HDL-C i Apo-A. Vrednosti TC, LDL-C, HDL-C, Lp(a), Apo-A i Apo-B nisu se statistički značajno razlikovale između grupa žena tretiranih HTM, primenjenom na različite načine. Uvrđeno je da s porastom nivoa estradiola u serumu stastički značajno rastu i serumski novoi Apo-A, dok su serumski nivoi LDL-C i Apo-B bili sniženi bez obzira na put primene HTM. **Zaključak.** HTM, uvedena na vreme, bez obzira na put primene, ima povoljne efekte na lipidni status žena u menopauzi i posledično mogla bi sprečiti brojne kardiovaskularne bolesti koje su vodeći uzrok smrtnosti.

Ključne reči:
hormoni, supstituciona terapija; kardiovaskularne bolesti; lipidi; menopauza.

Introduction

In menopausal women, lipid and lipoprotein levels in the serum are significant predictors of atherosclerosis development and risk factors for cardiovascular diseases (CVD). Significant increase or decrease in serum levels of some lipids and lipoproteins significantly increases the risk of CVD [1–3]. In menopause, due to decrease in estradiol concentrations, there are higher concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), apolipoprotein B (Apo-B) and lipoprotein (a) [Lp(a)], and lower concentrations of high-density lipoprotein cholesterol (HDL-C) compared to values in women in reproductive period [4, 5]. During this period small, thick LDL particles dominate, prone to modifications, more precisely oxidation, glycosylation and acetylation, which all together additionally increase the risk of atherogenesis and the development of CVD [6, 7].

A study in Denmark has shown that the introduction of menopausal hormonal therapy (MHT), immediately after menopause, significantly reduces the risk of myocardial infarction or cardiac insufficiency, because TG, TC and LDL-C are growing after 6 months of the last menstrual period [8–10].

Analysis of randomized controlled trials (RCTs) from the Cochrane Base in 2015 showed that MHT, applied within 10 years of the last menstruation, reduced the risk of coronary disease [11]. Relationship between centripetal obesity and lipid status disorders, i.e. increased risk for CVD is known. The North American Menopause Society (NAMS) states that MHT can help in reducing abdominal accumulation of adipose tissue and preventing body mass gain [12].

Estrogen therapy reduces LDL-C and Lp(a), increases TG and HDL-C, depending on the drug dose and the route of its administration. Simultaneous administration of progesterone, depending on the type, may have different effects on lipids [13].

The aim of the study was to examine the influence of estroprogestagen therapy on the metabolism of lipids in menopausal women depending on the route of drug administration.

Methods

The research was carried out at the Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia in Belgrade, from 1996 to 2010, as a prospective clinical interventional controlled study with parallel groups. The study included 64 women in menopause divided into three groups: the group 1 (n = 22) – women in menopause on estroprogestagen oral therapy (2 mg of estradiol in the form of estradiol hemihydrate; 2 mg of estradiol and 1 mg of norethisterone acetate; 1 mg estradiol), the group 2 (n = 17) – menopausal women treated with transdermal estroprogestagen patch (50 μg of 17-β estradiol and 250 μg of norethidron acetate daily) and the group 3 (n = 25) – menopausal women treated with estroprogestagene (4 mg of estradiol valerate and 200 mg of prasterone) given intramuscularly.

Exclusion criteria were: bleeding from the uterus of unknown etiology in the last 2 years; previous, existing or suspected breast cancer; the malignancy of any localization in the past 5 years; endometrial thickness > 5 mm; existing liver dysfunction or liver disease; an earlier or existing thromboembolic process; application of hormone substitution therapy in the last 12 months; body mass index (BMI) > 30 kg/m^2; poor motivation.

According to the study protocol, the following patient's data were taken: age of menarche and menopause, period from last menstruation to beginning of MHT and the age when MHT began.

To assess the metabolic profile, we determined: TC (mmol/L), HDL-C (mmol/L), LDL-C (mmol/L), TG (mmol/L), Lp(a) (g/L), apolipoprotein (Apo-A) (g/L), Apo-B (g/L). Lp(a), Apo-A, and Apo-B were determined by the method of nephelometry (Nephelometer BN/100, Behring, Germany). TC, LDL-C, HDL-C and TG were determined by chromatography (Boeringher Mannheim accessories).

The hormone status was defined according to serum levels of following hormones: follicle-stimulating hormone (FSH) (IU/L), luteinizing hormone (LH) (IU/L), estradiol (E2) (pmol/L), progesterone (P) (nmol/L), testosterone (T)

(nmol/L), sex hormone-binding globulin (SHBG) (nmol/L), dehydroepiandrosterone sulfate (DHEA-S04 (µmol/L), prolactin (PRL) (mIU/L) and thyroid-stimulating hormone (TSH) (mIU/L). The radioimmunoassay (RIA) method was used to determine serum concentrations of these hormones. The reference values of these parameters are given by the appropriate analytical method. Lipid and hormonal status were assessed prior to administration of MHT (initially), after sixth month (first control) and after 2–5 years from the MHT beginning (second control). All procedures were approved by the local Ethic Committee and conducted in accordance with the Helsinki Declaration.

Results were present as mean ± standard deviation (SD). Differences between groups were assessed by two-way analysis of variance (ANOVA) with Bonferroni post hoc analysis for continuous variables. Correlations between parameters were analyzed with Parson's test. Differences were considered statistically significant at $p < 0.05$. SPSS 18.0 software was used for the statistical analysis.

Results

The study included 64 women in menopause, aged between 34 and 59 years. Respondents had their first menstruation at an average age of 14 (13.35 ± 1.53), and their last menstruation at an average age of 47 (46.72 ± 4.27). The average period, from the last menstruation to the beginning of the MHT, was 2.5 years (2.48 ± 2.47), and the MHT started in 50s (49.19 ± 4.62). No statistically significant difference was found among patient groups, depending on the route of MHT administration, for any of the mentioned parameters ($p > 0.05$), that is the groups were homogeneous.

During the monitoring of MHT administration, a statistically significant continuous decrease of TC, LDL-C and Apo-B serum levels was observed. Only after 2–5 years of the MHT, a significant reduction in TC level occurred, whereas statistically significant decrease of LDL-C and Apo-B was observed after 6th month from the MHT beginning and this tendency continued for following 2–5 years of the MHT administration. Statistically significant increase of HDL-C and Apo-A was recorded. While significant increase of HDL-C level was recorded only after 2–5 years of continuous MHT, an increase of Apo-A level was recorded after 6 months from the MHT beginning and it was maintained during following 2–5 years of monitoring. TG and Lp(a) levels had an insignificant tendency to decrease during the MHT (Table 1).

The results of hormonal analyses during the MHT, regardless of the route of administration of estroprogestagen, are shown in Table 2. During the MHT, a continuous decline in the serum levels of FSH, LH, DHEA-SO4 and progesterone was observed, and this decline was statistically significant. FSH and LH levels had statistically significant decline over 6 months from the MHT beginning and this decline continued during 2–5 years of the MHT application. A statistically significant reduction in DHEA-SO4 and

progesterone levels were noted after 2–5 years of the MHT application. On the other hand, serum levels of estradiol and SHBG had a statistically significant continuous growth throughout the entire period of the MHT administration. Statistically significant increase in both estradiol and SHBG levels was recorded after 6 months from the MHT beginning and it was maintained in following 2–5 years of the MHT. Serum level of testosterone was decreased during MHT compared to the period prior to the therapy beginning, but this decrease was not maintained during 2–5 years of the MHT administration.

For TG levels, a statistically significant difference was found only after 2–5 years of the MHT administration. It was found that in women on transdermal MHT there were a statistically significantly lower TG levels comparing to those in women on oral MHT; this difference was noted only after 2–5 years of the MHT (TG: oral route 1.71 ± 0.75 mmol/L, transdermal 1.11 ± 0.57 mmol/L, intramuscular 1.39 ± 0.649 mmol/L; $p < 0.05$). Serum levels of TC, LDL-C, HDL-C, Lp(a), Apo-A and Apo-B had no statistically significant differences among groups of women given MHT by different route, in any period of monitoring (Table 3).

The results of hormonal analyses during the MHT, depending on the route of administration of estroprogestagen, are shown in Table 4. After 6 months from the MHT beginning, statistically significantly lower FSH and LH levels were found in intramuscularly treated women compared to those given MHT orally or transdermally. During 2–5 years of MHT, lowest FSH levels were noticed in women given MHT by the oral route. On the other hand, there were no differences in LH serum levels regardless of the MHT administration route.

There were statistically significantly higher levels of SHBG in women on oral MHT compared to the other two groups of women after 6 months, as well as after 2–5 years of continuous MHT.

Although TSH levels were in the normal range during the entire monitoring period, regardless of the MHT administration route, in intramuscularly treated women, compared with those treated orally, statistically significantly lower levels were recorded after 2–5 years of the treatment.

Serum levels of estradiol had constant increase in all three groups of women regardless of the MHT administration route, without statistically significant differences among them in any of the period monitored.

Also, there were no statistically significant differences in serum levels of progesterone, testosterone, prolactin and DHEA-SO4 among three groups of women given MHT by different route in any of the period monitored.

There was a positive correlation of serum levels of FSH and LH with LDL-C level, as well as positive, statistically significant correlation of serum levels of estradiol with Apo-A levels and negative with LDL-C and Apo-B levels, which suggests favorable influence of MHT on the reduction of cardiovascular risk.

Table 1

Lipid status during menopausal hormonal therapy (MHT) regardless of the route of administration

Lipids	Initially	First control	Second control	*p*
TC (mmol/L)	6.33 ± 1.30	5.89 ± 0.93	5.80 ± 0.80	< 0.01
LDL-C (mmol/L)	4.30 ± 1.10	3.87 ± 0.84	3.72 ± 0.81	< 0.01
HDL-C (mmol/L)	1.33 ± 0.40	1.39 ± 0.28	1.48 ± 0.32	< 0.05
TG (mmol/L)	1.75 ± 0.98	1.57 ± 0.069	1.43 ± 0.69	ns
Lp (a) (g/L)	0.28 ± 0.36	0.24 ± 0.32	0.22 ± 0.30	ns
Apo-A (g/L)	1.56 ± 0.28	1.64 ± 0.25	1.79 ± 0.26	< 0.001
Apo-B (g/L)	1.36 ± 0.32	1.23 ± 0.28	1.08 ± 0.27	< 0.001

ns – not statistically significant; initially – prior to MHT; first control – after sixth month of MHT; second control – after 2–5 years of MHT; TC – total cholesterol; LDL-C – low density lipoprotein cholesterol; HDL-C – high density lipoprotein cholesterol; TG – triglicerides; Lp(a) – lipoprotein a; Apo-A – apolipoprotein A; Apo-B – apolipoprotein B.

Table 2

Hormone status during menopausal hormonal therapy (MHT) regardless of the route of administration

Hormones	Initially	First control	Second control	*p*
FSH (IU/L)	74.2 ± 21.2	32.1 ± 13.9	27.6 ± 12.5	< 0.001
LH (IU/L)	32.9 ± 19.3	18.9 ± 11.45	16.3 ± 10.9	< 0.001
Estradiol (pmol/L)	12.8 ± 7.3	79.1 ± 55.2	101.3 ± 50.3	< 0.001
Progesterone (nmol/L)	3.21 ± 0.70	2.91 ± 0.75	2.77 ± 0.87	< 0.001
Testosterone (nmol/L)	1.14 ± 0.60	0.92 ± 0.46	1.10 ± 0.71	< 0.01
DHEA-SO4 (μmol/L)	2.80 ± 1.53	2.27 ± 1.13	1.90 ± 0.94	< 0.001
SHBG (nmol/L)	45.4 ± 17.0	62.0 ± 22.9	71.8 ± 31.3	< 0.001
Prolactin (mIU/L)	233.4 ± 83.8	248.7 ± 120.8	225.8 ± 84.8	ns
TSH (mIU/L)	2.23 ± 0.74	2.27 ± 0.74	2.11 ± 0.70	ns

ns – no statistical significance; initially – prior to MHT; first control – after sixth month of MHT; second control – after 2–5 years of MHT; FSH – follicle stimulating hormone; LH – luteinizing hormone; DHEA-SO4 – dehydroepiandrosterone sulfate; TSH – thyroid-stimulating hormone.

Table 3

Lipid status during menopausal hormonal therapy (MHT) depending on the route of administration

Lipids	Time of analysis	Oral	Transdermal	Intramuscular	*p*
TC (mmol/L)	Initially	6.27 ± 1.35	6.11 ± 0.93	6.54 ± 1.47	ns
	First control	5.98 ± 0.92	5.81 ± 0.83	5.85 ± 1.03	ns
	Second control	5.68 ± 0.73	5.69 ± 0.73	5.99 ± 0.88	ns
LDL-C (mmol/L)	Initially	4.26 ± 1.04	3.98 ± 0.83	4.55 ± 1.28	ns
	First control	3.92 ± 0.80	3.67 ± 0.71	3.96 ± 0.97	ns
	Second control	3.63 ± 0.66	3.57 ± 0.75	3.90 ± 0.95	ns
HDL-C (mmol/L)	Initially	1.26 ± 0.40	1.41 ± 0.35	1.33 ± 0.44	ns
	First control	1.36 ± 0.27	1.42 ± 0.30	1.41 ± 0.27	ns
	Second control	1.57 ± 0.31	1.40 ± 0.27	1.44 ± 0.36	ns
TG (mmol/L)	Initially	1.80 ± 0.68	1.73 ± 1.24	1.72 ± 1.04	ns
	First control	1.71 ± 0.63	1.43 ± 0.79	1.54 ± 0.67	ns
	Second control	1.71 ± 0.75	1.11 ± 0.57	1.39 ± 0.64	< 0.05
Lp(a) (g/L)	Initially	0.16 ± 0.20	0.31 ± 0.38	0.37 ± 0.45	ns
	First control	0.15 ± 0.18	0.22 ± 0.20	0.35 ± 0.44	ns
	Second control	0.13 ± 0.16	0.20 ± 0.19	0.33 ± 0.43	ns
Apo-A (g/L)	Initially	1.53 ± 0.32	1.59 ± 0.21	1.55 ± 0.30	ns
	First control	1.67 ± 0.25	1.64 ± 0.24	1.61 ± 0.27	ns
	Second control	1.82 ± 0.25	1.74 ± 0.24	1.80 ± 0.28	ns
Apo-B (g/L)	Initially	1.36 ± 0.34	1.38 ± 0.31	1.34 ± 0.32	ns
	First control	1.23 ± 0.31	1.19 ± 0.27	1.25 ± 0.27	ns
	Second control	1.09 ± 0.26	1.06 ± 0.33	1.08 ± 0.27	ns

ns – not statistically significant; initially – prior to MHT; first control – after sixth month of MHT; second control – after 2–5 years of MHT; TC – cholesterol; LDL – low density lipoproteins; HDL – high density lipoproteins; TG – triglycerides; Lp(a) – lipoprotein a; Apo-A – apolipoprotein A; Apo-B – apolipoprotein B.

Table 4
Hormone status during menopausal hormonal therapy (MHT) depending on the route of administration

Hormones	Time of analysis	Oral	Trandermal	Intramuscular	p
FSH (IU/L)	Initially	73.1 ± 26.0	78.5 ± 20.4	72.2 ± 17.1	ns
	First control	33.1 ± 16.3	38.3 ± 8.4	27.1 ± 13.1	< 0.05
	Second control	23.1 ± 11.3	33.9 ± 14.6	27.4 ± 10.5	< 0.05
LH (IU/L)	Initially	35.2 ± 28.6	33.6 ± 10.7	30.2 ± 13.3	ns
	First control	18.1 ± 11.8	24.8 ± 12.1	15.7 ± 9.3	< 0.05
	Second control	13.9 ± 8.9	18.4 ± 10.3	16.9 ± 12.9	ns
Estradiol (pmol/L)	Initially	15,8 ± 8.3	11.6 ± 6.2	11.1 ± 6.5	ns
	First control	94.8 ± 85.6	70.1 ± 20.9	71.5 ± 30.8	ns
	Second control	114.1 ± 68.2	96.7 ± 42.7	93.1 ± 33.4	ns
Progesterone (nmol/L)	Initially	3.35 ± 0.88	3.15 ± 0.54	3.10 ± 0.59	ns
	First control	3.00 ± 0.90	2.95 ± 0.64	2.80 ± 0.69	ns
	Second control	2.65 ± 0.91	2.53 ± 0.78	3.05 ± 0.84	ns
Testosterone (nmol/L)	Initially	1.11 ± 0.40	1.27 ± 0.70	1.09 ± 0.69	ns
	First control	0.88 ± 0.40	0.94 ± 0.50	0.95 ± 0.49	ns
	Second control	0.99 ± 0.47	1.05 ± 0.60	1.24 ± 0.94	ns
DHEA-SO4(μmo/L)	Initially	3.31 ± 1.72	2.80 ± 1.72	2.36 ± 1.08	ns
	First control	2.52 ± 1.38	2.24 ± 1.01	2.08 ± 0.97	ns
	Second control	1.93 ± 1.10	1.97 ± 0.90	1.83 ± 0.86	ns
SHBG (nmol/L)	Initially	43.8 ± 18.2	46.6 ± 15.3	46.0 ± 17.6	ns
	First control	71.5 ± 24.1	52.8 ± 18.2	59.9 ± 22.3	< 0.05
	Second control	97.0 ± 31.0	52.2 ± 20.9	62.9 ± 22.3	< 0.001
Prolactin (mIU/L)	Initially	210.0 ± 93.3	228.2 ± 91.1	257.6 ± 64.3	ns
	First control	225.1 ± 98.7	260.1 ± 117.8	260.7 ± 140.9	ns
	Second control	223.0 ± 84.6	204.5 ± 73.1	242.3 ± 91.9	ns
TSH (mIU/L)	Initially	2.40 ± 0.77	2.18 ± 0.77	2.13 ± 0.70	ns
	First control	2.47 ± 0.75	2.30 ± 0.69	2.09 ± 0.75	ns
	Second control	2.43 ± 0.42	2.09 ± 0.53	1.88 ± 0.87	< 0.05

Ns – not statistically significant; initially – prior to MHT; first control – after sixth month of MHT; second control – after 2–5 years of MHT; FSH – follicle-stimulating hormone; LH – luteinizing hormone; DHEA-SO4 – dehydroepiandrosterone sulfate; SHBG – sex hormone-binding globulin; TSH – thyroid-stimulating hormone.

Discussion

In the reproductive period the serum estradiol concentration is in the range from 40 to 400 pg/mL while in menopause it is decreased to 5–20 pg/mL. The main source of estrogen in menopause is the peripheral conversion of androstenedione from the adrenal glands to estrone, owing to the activity of the aromatase complex in the fat tissue, muscles, skin and liver which does not provide sufficient estrogen, as we demonstrated in our study. Estradiol deficiency leads to a number of symptoms and signs [14], the redistribution of fat deposits and the increase in visceral deposits [15]. Menopause leads to the development of central obesity, the atherogenic lipid profile increase and increase in the prevalence of metabolic syndrome (MS) regardless of the age and other factors [16].

A significant number of papers have been published so far, suggesting that hormone therapy in the menopause reduces the risk of coronary artery disease in healthy mopausal women [17, 18].

Omodei et al. [19] reported that estradiol valerate in a dose of 2 mg, administered during the period of 1–21 days, and ciproterone acetate, given in a dose of 1 mg during the period of 12–21 days, followed by a 7-day pause, after 6 months of the therapy, have resulted in decrease of TC, LDL-C and Apo-B levels, followed by a slight increase in the levels of TG, producing cardioprotective effects.

The effect of transdermal estrogen therapy (50 μg of estradiol), in combination with progestogen (sequential administration of 5 mg medroxyprogesterone acetate – MPA). on the lipid status was examined. There was a decrease in the serum levels of TC, and LDL-C. A higher dose of estradiol (100 μg) led to an increase in HDL-C level, especially HDL2 fraction, while HDL3 one decreased [20].

An analysis of 248 studies published in the period from 1974 to 2000 gave data for 42 different MHT regimens. Regimens including only estrogens increased only HDL-C, and lowered LDL-C and TC. Oral estrogens increased the serum levels of TC. Transdermal estradiol-17-beta lowered TC levels. Progestagens had a small effect on the estrogen-induced reduction of LDL-C and TC. The estrogen-induced increase in HDL-C and TG levels was followed by different effects of progestagens depending on their type [21]. Metabolic effects of progestin added were correlated with a dose, a relative androgenic potential of hormone preparation, and a dose of estrogen. C-21 derivatives of hydroxyprogesterone (e.g., medroxyprogesterone and medrogestone) are less metabolically active than 19-nortestoterone derivatives (e.g., norethindrone and levonorgestrel) [22].

In our study, MHT (estrogen/progestagen combination), regardless of the route of administration, led to the continuous decrease of TC, LDL-C and Apo-B levels in the serum. Statistically significant reduction of TC levels were recorded only after 2–5 years from the MHT beginning, while statistically significant reduction of LDL-C and Apo-B levels was evident already after 6 months of MHT administration and it was maintained in the following 2–5 years of the therapy. The serum levels of TG had a nonsignificant tendency to decline during the period of observation, which was in accordance with results of other studies.

An increase of only 0.26 mmol/L of HDL-C leads to 42–50% of reduction in the risk for coronary disease [23]. In our study, a significant increase in HDL was observed only after 2–5 years of MHT administration. A statistically significant increase in Apo-A level was observed after 6 months of MHT administration and it was maintained during 2–5 years of the therapy. The results of our study also showed that oral administration of estroprogestagen therapy over 2–5 years led to a significant increase in HDL-C level (from 1.26 ± 0.40 mmol/L to 1.57 ± 0.31 mmol/L) while transdermal and intramuscular MHT had nonsignificant influence on the serum level of HDL-C.

Several studies showed a significant increase in Lp(a) level in menopause as well as an increased risk for CVD, which did not depend on LDL-C level [7]. Soma et al. [24] found a significant reduction in Lp(a) level in women in menopause who used 1.25 mg of conjugated equine estrogen (CEE) per day, in combination with 10 mg MPA for 10 days in a month. This result becomes more important when we highlight the fact that in some women, reduction of Lp(a) levels by the use of pharmacological agents or diet has not occurred. Bukowska et al. [25] found that after 3 months of MHT, Lp (a) level in the serum did not significantly deviate from baseline, regardless of the route of administration. MHT generally has lowered Lp(a) levels as presented in 41 studies including 20 different drug formulations [21].

In this study, a nonsignificant decrease of Lp(a) serum level was found. During MHT, independently of the route of administration, serum levels of estradiol were significantly increased whereas FSH and LH levels were significantly reduced. A significant reduction in testosterone levels was observed after 6 months and progesterone levels after 2–5 years of the MHT administration.

After oral administration, concentrations of estradiol in portal circulation have been 4–5 times higher than concentrations in systemic circulation [26]. This finding explains why estrogens are more presented in hepatocytes than in cells of other organs. Because of that, orally administered estrogens have more effects on the liver when compared to their effects after parenteral administration. Treatment with estrogens may increase the hepatic production of triglycerides, very low density lipoproteins (VLDL) and Apo-B100 secretion. Walsh et al. [26] found that 2 mg per day of micronized estradiol administrated orally increases the production of Apo-B in large VLDL particles to a much greater extent than in smaller VLDL particles.

Faith et al. [27] compared the effect of oral (2 mg/day) and transdermal (50 mcg/day, 7-day patch) estrogen substitution therapy (EST) on the lipid profile within 12 weeks in women at 49 ± 6 years of age. While TC level did not change, TG level was increased from 1.39 to 1.61 mmol/L after oral EST. An increase in HDL-C level after oral administration of EST was more significant than after transdermally administered EST. Changes in LDL levels were also significant: LDL levels were decreased after oral administration of EST, compared to a nonsignificant decrease after transdermal administration. Taking into consideration these changes in LDL levels depending on the route of EST administration as well as the fact that a physician is familiar with patient's lipid profile, a physician can initiate personalized EST.

Some studies suggest that transdermal estrogen substitution compared to the oral one has a significant influence on the rise in HDL serum level. Thus, Camilli et al. [28] have found statistically significantly higher HDL levels during transdermal therapy. Nanda et al. [29] found lower serum levels of HDL in hysterectomized women (less than 40 mg/dL in 87% women). A significant decrease in TC and LDL-C, as well as a significant increase in HDL-C levels were observed after EST (both oral and transdermal); the response to oral therapy was relatively faster. After 3 and 6 months, the number of cases with HDL-C level above 40 mg/dL, from initial 13% increased to 63% during MHT administered orally, while during transdermal MHT that increase was from 30% to 60%. Serum levels of TG decreased significantly when transdermal EST was administrated whereas their elevation was noticed when EST was given by oral route. EST, either oral or transdermal, has a beneficial effect on the serum lipid profile of women in the menopause. The oral route had higher impact on an increase in serum levels of HDL-C, while the transdermal route was better for decrease of the serum TG levels. Therefore, the transdermal route should be a therapeutic choice for women with elevated serum TG levels. Such findings, referring to TG, are in accordance with our results, which showed that longer transdermal MHT administration (over 2–5 years) helped to achieve statistically significantly lower TG levels when compared to the oral route of MHT administration. It should be noted that such results we obtained by estroprogestagen MHT while in the above mentioned study EST was administrated.

Natural progesterone does not significantly affect plasma lipoprotein levels. Synthetic progestins, especially those with evident androgenic activity (e.g., norethindrone, levonorgestrel), may have significant metabolic effects, especially when TG level reduction is concerned, although the mechanism of this effect is not quite clear [22].

Oral progestogene leads to concentrations of the hormone 10–15 times higher than those obtained after its intramuscular administration [30]. A study by Hirvonen et al. [31] found a 20% reduction in HDL-C in women who were on norethindrone and norgestrel therapy but did not find changes in women treated by MPA and natural progesterone,

which confirms the hypothesis that progestagens do not erase the effects of estrogen on lipid metabolism.

A meta-analysis of 24 selected studies showed that MHT significantly reduced Lp(a) concentrations compared to placebo. Oral administration of estrogen led to a greater reduction of Lp(a) compared to the transdermal one. There was no difference between continuous and cyclic MHT treatment, conventional therapy and low dose estrogen therapy, mono estrogen therapy and combined estrogen/progestagen therapy [32].

Meschia et al. [33] compared the effects of oral and transdermal administration of EST on the lipid status. Lp(a) level decreased after 3 months of EST administered either transdermally or orally (12% and 22%, respectively). There was no further decline after 3 months. Total cholesterol and LDL-C levels decreased significantly after 3 months of the therapy administered by both routes. There was no difference in these effects on Lp(a), LDL and TC levels depending on the route of administration. The concentrations of HDL-C and TG were increased only in the group on therapy with oral estrogens. The lowering effect was quickly achieved because the maximal effect was observed after 3 months of the therapy.

There are data indicating that transdermal patches with estrogen are safer and potentially more effective than oral estrogen therapy [34].

Our study showed that oral, transdermal and intra-muscular route of estroprogestagen MHT did not differ significantly in the effects on TC, LDL-C, HDL-c, Lp(a), Apo-A and Apo-B levels in the serum after 6 months and 2–5 years from the MHT beginning. A significant increase in Apo-A and a significant decrease in Apo-B levels were observed after more than 6 months of the MHT beginning regardless of the route of administration.

Estradiol level in the serum was continuously increasing by all MHT regimens used, and no statistically significant difference was found in parameters of the lipid status among different routes of the MHT administration in the observation period. It was also confirmed that an increase of estradiol levels in the serum statistically significantly correlated with an increase of Apo-A levels and decrease of LDL-C and Apo-B levels, regardless of the MHT route of administration.

Conclusion

Estroprogestagen therapy in menopause, introduced on time, regardless of the route of administration, has beneficial effects on the lipid status of menopausal women and consequently might prevent numerous cardiovascular diseases that are the leading cause of mortality.

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