UDC: 615.357.651:616.153.915]:618.173(497.7)"2024"
Professional paper

THE EFFECTS OF TRANSDERMAL ESTROGEN THERAPY ON LIPID PROFILE IN POSTMENOPAUSAL WOMEN

Sheval F. MEMISHI, Mergime ABDULI , Mije REÇI

Department of Biology, Faculty of Natural Sciences and Mathematics, University of Tetova, RNM
Corresponding author: sheval.memishi@unite.edu.mk

Abstract

Postmenopausal estrogen therapy exerts beneficial effects on plasma lipids by reducing plasma concentrations of LDL particles and increasing those of high-density lipoprotein (HDL) particles. Additionally, estrogen exhibits antioxidant effects by decreasing the susceptibility of LDL and HDL to oxidative modification. Low-density lipoprotein (LDL) is heterogeneous in size and density, and not all LDL subfractions are equally atherogenic. Smaller and denser LDL particles are associated with increased risk of coronary heart disease because they are more susceptible to oxidative modification, an initial step in the atherosclerotic process. The study subjects were 100 women aged 50-65 years, who had been amenorrhoeic for at least two years, which means they were in the menopausal period, divided into two groups of 50 individuals, to whom oral or transdermal estrogen therapy was applied, respectively. The material, specifically the statistical data for analyzing the levels of parameters, including total cholesterol, triglycerides, HDL, LDL, Apo L(a), and estradiol, was provided by the Biochemical Laboratory at the "Mother Teresa" Clinic in Skopje, during the period from June to December 2024.

Keywords: Estrogen, post menopause, LDL, women, transdermal therapy.

1. Introduction

Several studies have shown that the menopausal transition is associated with adverse effects on the lipid profile, characterized by increases in total cholesterol, low-density lipoprotein (LDL), triglycerides (TG), and lipoproteins, sometimes accompanied by a decrease in high-density lipoprotein (HDL) levels (Anagnostis et al., 2015). It is well known that an unfavorable lipid profile plays a crucial role in the development and progression of cardiovascular disease (McQueen et al., 2008), which is the leading cause of morbidity and mortality in postmenopausal women (Tandon et al., 2010). Menopause refers to the permanent cessation of menstruation because of the loss of ovarian follicular activity and estrogen deficiency. Since postmenopausal women have significantly higher LDL and cholesterol levels than premenopausal women (Ambikairajah et al., 2019), it has been found that estrogen plays a protective role in regulating lipid metabolism. In this case, estrogen-based menopausal hormone therapy (MHT) may affect the lipid profile in postmenopausal women. MHT has been reported to be the most effective treatment for menopausal symptoms caused by estrogen loss (Baber et al.,2016). In addition, MHT has been shown to have a favorable risk-benefit ratio for women without dyslipidemia who underwent treatment at the age of less than 60 years or within 10 years of menopause onset (2019 Surveillance of Menopause, 2019). A meta-analysis conducted in 2001 concluded that MHT can reduce total and LDL cholesterol levels and increase HDL levels (Godsland,2001). A review conducted in 2017 showed that MHT significantly reduced lipoprotein(a) concentration (Anagnostis et al.,2017). Some studies have shown that MHT negatively affects TG levels (Nii et al.,2016). However, a study conducted in 2016 showed that TG levels were lower in the MHT group than in the non-MHT group (Ki et al.,2016). Pu et al., noted that hormone therapy with 17β-estradiol offered more potential for reducing TG levels, while conjugated equine estrogen (CEE) showed a better effect in reducing HDL and LDL

https://doi.org/10.62792/ut.jnsm.v10.i19-20.p3080

levels (Pu et al.,2017). Oral and transdermal estrogen therapies have been found to increase HDL and decrease LDL and total cholesterol (Sacks and Walsh, 1994). However, oral estrogen therapy increases triglyceride production, whereas transdermal estrogen therapy has a neutral effect on triglyceride levels. Thus, estrogen therapy should be considered in women with hyperlipidemia since elevated triglycerides are known to be an independent risk factor for coronary heart disease and increased mortality (Fletcher et al., 2005). Furthermore, the American Association of Clinical Endocrinologists (AACE) recommends considering transdermal hormone therapy instead of oral therapy for women with elevated triglycerides or hypertension (American Association of Clinical Endocrinologists. AACE medical guidelines for clinical practice for management of menopause, 2006). C-reactive protein (CRP) is an acute-phase protein that has been recognized as a marker of vascular inflammation and atherosclerosis (Ridker et al., 2000). Elevated CRP levels are considered an important predictor of risk for first myocardial infarction and stroke in humans (Pradhan et al., 2002). Because of the usefulness of CRP in predicting future cardiovascular disease, the Centers for Disease Control (CDC) and the American Heart Association (AHA) recommend CRP testing and lipid screening in healthy individuals if they are at risk (Smith et al., 2004). Transdermal estrogen therapy does not affect CRP production and may even decrease levels to some extent (Sattar et al., 1999). Transdermal estrogen therapy affects the levels and activity of several blood-clotting factors. Antithrombin III (AT III) is a potent coagulation inhibitor that can increase the risk of thrombosis if not present at adequate levels (Bonduki et al., 1998). Oral estrogen therapy reduces AT III levels, while transdermal estrogen therapy appears to not affect antithrombin III levels. Numerous other studies have found that, compared with oral estrogen therapy, transdermal estrogen therapy has minimal negative effects on other coagulation factors, including fibrinogen, factor VII, von Willebrand factor, and prothrombin fragments 1 + 2 [(Oger et al., 2003) (Schmidt et al., 2006) (Menon and Vongpatanasin, 2006)]. In excess, SHBG reduces free testosterone levels and can thus decrease libido. Hepatic metabolism and continued hepatic exposure to estrogen and its metabolites after oral estrogen therapy increases SHBG production (Campagnoli et al., 1993). Conversely, transdermal estrogen therapy has little effect on SHBG production or circulating free testosterone. Therefore, women with low testosterone or those experiencing sexual dysfunction may benefit from transdermal estrogen therapy rather than oral estrogen therapy [(Campagnoli et al., 1993) (Vehkavaara et al., 2000)]. Human studies have shown that young adult women oxidize relatively greater amounts of fat and less carbohydrate than men when exercising at the same relative intensity (Horton et al., 1998). In addition, recent research has shown that postmenopausal women exhibit an increased incidence of type 2 diabetes, reduced insulin sensitivity, increased fat mass, and increased systemic inflammatory markers. The same features are seen in ovariectomized rodents, suggesting that estrogen may play a role in reducing the incidence of type 2 diabetes, insulin insensitivity, and weight gain in older women (Ribas et al., 2010).

The positive association of bone mass and density with estrogen in older women is well documented in the scientific literature (Brown, 2008). Bone mineral loss accelerates after menopause in women, and this accelerated bone loss is prevented by hormone replacement therapy (HRT) [(Brown, 2008) (Wu et al., 2002)].

Exercise and HRT may also independently help maintain bone mineral density in older women (Brown, 2008).

2. Materials and Methods

The material, including the statistical data for the analysis of the levels of parameters: total cholesterol, triglycerides, HDL, LDL, Apo L(a), and estradiol, was provided by the Biochemical Laboratory at the "Mother Teresa" Clinic in Skopje, during the period from June to December 2024.The study subjects were 100 women between the ages of 50 and 65 years who had a lack of menstruation for at least two years, indicating that they were in the menopause period. They were divided into two groups of 50 individuals, to whom oral and transdermal estrogen therapy was applied, respectively. Of the participants, menopausal women to whom oral therapy was applied in the form of pills (17 beta-estradiol), 2 mg/day, and equivalent transdermal estrogen therapy (17 beta-estradiol) 0.1 mg/day, in the form of (patches) for 30 consecutive days.
After this period, 5 ml of venous blood was collected from each individual and centrifuged to separate the serum. Serum samples were analyzed for total cholesterol, triglycerides, HDL, LDL, Apo L(a), and estradiol, by standard methods (immunoturbidimetry, immunometric immunoassay, competitive immunoassay, aminooxidase-oxidase-cholesterol-ODP4P).

3. Results and Discussion

The results of our analyses related to transdermal and oral administration routes of estrogen hormone replacement therapy in postmenopausal women, which include the parameters: total cholesterol, triglycerides, HDL, LDL, Apo L(a), BMI and estradiol, as well as their effect on the oxidative sensitivity of low-density lipoprotein (LDL) particles in postmenopausal women, are presented in tabular and graphical form as follows:

Table 1. Total cholesterol, triglycerides, HDL, LDL, Apo L(a), BMI, and Estradiol values obtained in postmenopausal women as a result of transdermal and oral administration of estrogen therapy

Parametrat	***Administrimi oral (n=50)***	***Administrimi transdermal (n=50)***	***p-vlera***
Kolesteroli total (mg/dL)	189.23±32	177.67±38.29	<0.01
Trigliceridet (mmol/L)	177.44±83.21	144.48±54.86	0.001
HDL (mg/dL)	35.86±7.86	40.63±8.62	0.05
LDL (mg/dL)	114.53±32.4	103.14±33.51	0.01
Apo L(a) (mg/dL)	126.16±29.03	100.79±24.70	0.05
BMI (kg/m^2)	24.77±2.19	24.77±1.76	NS
Estradioli (pg/ml)	32.48±13.02	17.62±7.36	<0.001

$p<0.05$ is considered significant, statistics expressed as arithmetic mean ($\bar{x}$) and standard deviation (SD). NS-not significant.

Table 2. Total cholesterol, triglycerides, HDL, LDL, Apo L(a), BMI and Estradiol values in normal weight and obese postmenopausal women with transdermal and oral administration of estrogen therapy.

Parameters	***Normal weight***	***Obese***	***p-value***
Kolesteroli total (mg/dL)	175.33±27.4	191.41±32.7	<0.001
Trigliceridet (mmol/L)	141.17±42.7	185.81±78.51	<0.001
HDL (mg/dL)	31.4±5.2	43.5±8.79	<0.01
LDL (mg/dL)	111.62±35.6	117.32±32.4	<0.05
Apo L(a) (mg/dL)	97.17±21.4	128.27±26.4	<0.01
BMI (kg/m^2)	22.61±1.72	28.73±3.13	<0.05
Estradiol (pg/ml)	15.6±3.37	30.4±12.3	<0.001

In postmenopausal women who received oral and transdermal estrogen replacement therapy, total cholesterol levels in individuals who received transdermal therapy were significantly lower ($p < 0.01$) than in those who received oral estrogen. The triglyceride level in individuals who received transdermal therapy was significantly ($p<0.001$) lower compared to individuals receiving oral estrogen.

The level of HDL in individuals who received transdermal therapy was significantly ($p<0.05$) higher compared to individuals who received oral estrogen.

The results show that in postmenopausal women who received oral and transdermal estrogen replacement therapy, the LDL level in individuals who received transdermal therapy was significantly ($p<0.01$) lower than in individuals who received oral estrogen.

Apo L(a), in individuals who have applied transdermal therapy is significantly ($p<0.05$), lower compared to individuals with oral estrogen application.

Regarding the analyzed parameter Body Mass Index (BMI), which accompanies other parameters in a positive correlation, the results show that in postmenopausal women, to whom oral and transdermal administration of estrogen hormone replacement therapy was applied, in both groups together, the total cholesterol level is significantly ($p<0.001$) higher in obese individuals, compared to those with normal weight.

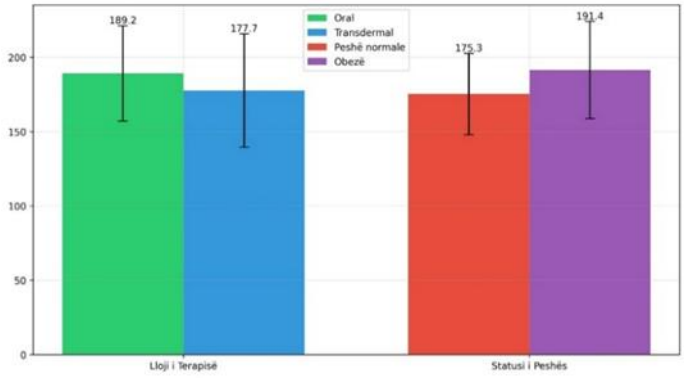

Figure 1. Cholesterol level depends on body weight

BMI results for triglycerides show that in postmenopausal women to whom oral and transdermal estrogen hormone replacement therapy was applied, the level is significantly ($p < 0.001$) higher in both groups together in obese individuals compared to those with normal weight. Regarding HDL and LDL levels, the results show that BMI in postmenopausal women to whom oral and transdermal administration of estrogen hormone replacement therapy was applied, in both groups together, the HDL level is significantly ($p<0.01$) higher in obese individuals, while the LDL level is significantly ($p<0.05$) lower, compared to normal weight individuals.

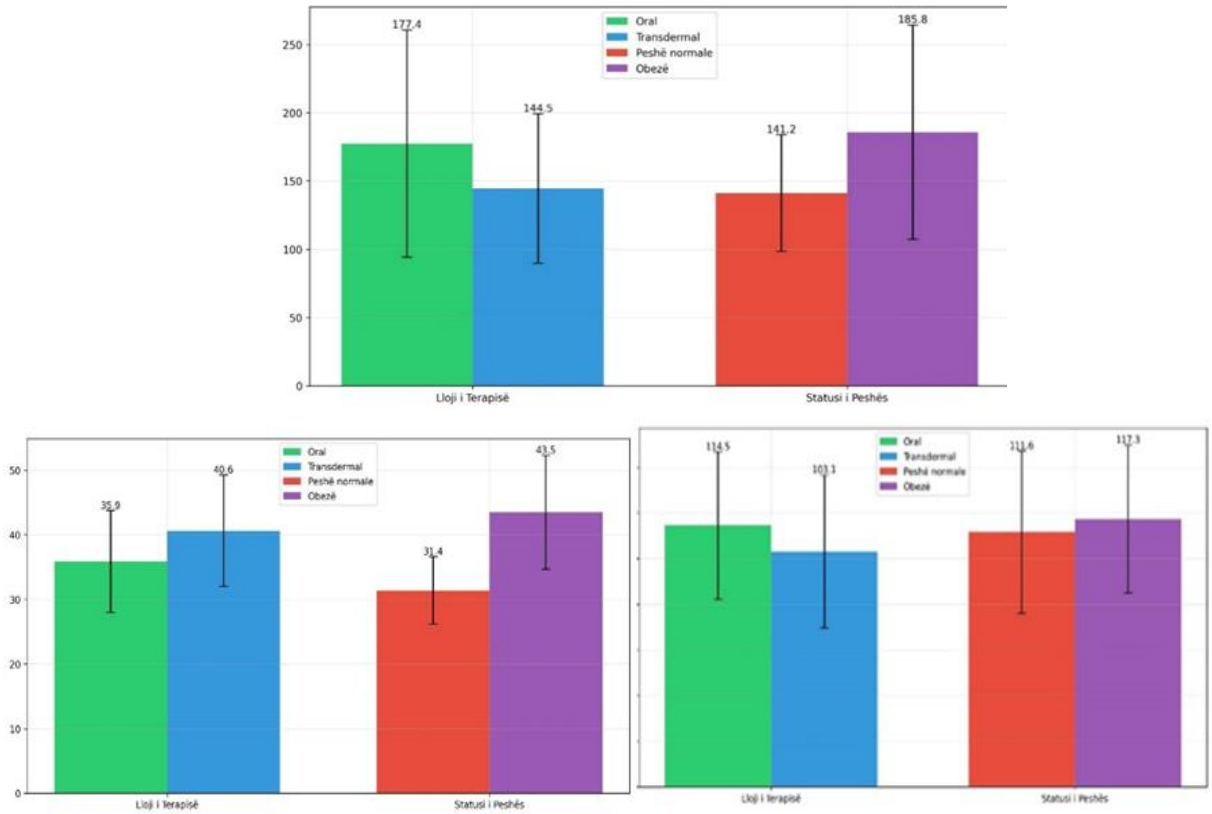

Figure 2.. Triglyceride, HDL, and LDL levels, in addition to body weight, in individuals on therapy.

Regarding triglycerides analyzed in postmenopausal women who have undergone estrogen hormone replacement therapy, with the transdermal application method, they correspond to the results of Wakatsuki (Wakatsuki A. et al., 2002), who found lower triglyceride values of (91.4±44.3 mg\dL), while the values of this parameter in women where estrogen was

administered orally, show that these values have increased from the level of (108.5±61.7 mg\dL, to 122.7±66.7 mg\dL), with a significance of $p<0.05$.
HDL analyzed in postmenopausal women who have undergone estrogen hormone replacement therapy, with the oral and transdermal application method, according to the results of Wakatsuki (Wakatsuki A. Et al., 2002), corresponds to our results because they find higher HDL values (63.1±12.5 mg\dL) in individuals with transdermal estrogen administration, compared to lower HDL values of (62.7±13.5 mg\dL) in women with oral estrogen administration.
Our results regarding the reduction of LDL levels, respectively the increase of HDL levels, correspond to the data of (Victor Guetta, Richard O. Cannon, III,), who in their study conclude that the effects of transdermal estrogen therapy and lipid lowering in postmenopausal women are evident.
Wakatsuki (Wakatsuki A. et al., 2002) also found higher LDL values (158.4 mg/dL vs 144.7 mg\dL) in postmenopausal women who had undergone hormone replacement therapy, with oral or transdermal estrogen.
The estradiol level analyzed in postmenopausal women who have undergone estrogen hormone replacement therapy, with oral and transdermal application, also corresponds to the results of Wakatsuki (Wakatsuki A. et al., 2002), who found lower estradiol values (8.8±8.8 pg\mL) in individuals with transdermal estrogen administration, compared to higher total cholesterol values (14.1±5.3 pg\mL) in women with oral estrogen administration.

4. Conclusions

From our results that include lipid profile analysis, after the application of transdermal therapy in women in the menopausal and postmenopausal period, the obtained values of these parameters are presented as follows:

- Total cholesterol levels were significantly ($p<0.001$) lower in women receiving transdermal therapy compared to those receiving oral estrogen.
- Triglycerides were also significantly ($p<0.001$) lower in women receiving transdermal therapy compared to those receiving oral estrogen.
- HDL or high-density lipoprotein levels, commonly known as good cholesterol, were significantly ($p<0.01$) higher in women receiving transdermal estrogen compared to those receiving oral estrogen.
- Regarding "bad cholesterol", namely LDL particles (low-density lipoproteins), their values are significantly ($p<0.05$) lower, after transdermal estrogen administration, in postmenopausal women, compared to oral administration in the same category of women.
- Even in the case of Apolipoprotein (a) particles, our results show significantly lower values ($p<0.05$), in women where the transdermal form of estrogen was applied compared to those with oral application.
- Looking at the values of estradiol analyzed after 30 days of transdermal and oral estrogen administration in postmenopausal women, a significant decrease in its level is also observed ($p<0.001$), in women with transdermal estrogen application, compared to those with oral application.
- In terms of comparing the method of estrogen administration in women during menopause and postmenopause, in relation to body mass, respectively BMI, there are no significant differences in the two analyzed groups.

References

[1] Anagnostis P., Stevenson J. C., Crook D., Johnston D. G., Godsland I. F. (2015). Effects of Menopause, Gender and Age on Lipids and High-Density Lipoprotein Cholesterol Subfractions. Maturitas 81 (1), 62–68. 10.1016/j.maturitas.2015.02.262

[2] McQueen M. J., Hawken S., Wang X., Ounpuu S., Sniderman A., Probstfield J., et al. (2008). Lipids, Lipoproteins, and Apolipoproteins as Risk Markers of Myocardial Infarction in 52 Countries (The INTERHEART Study): a Case-Control Study. Lancet 372 (9634), 224–233. 10.1016/S0140-6736(08)61076-4

[3] Tandon V. R., Mahajan A., Sharma S., Sharma A. (2010). Prevalence of Cardiovascular Risk Factors in Postmenopausal Women: A Rural Study. J. Midlife Health 1 (1), 26–29.10.4103/0976-7800.66993

[4] Ambikairajah A., Walsh E., Cherbuin N. (2019). Lipid Profile Differences during Menopause: a Review with Meta-Analysis. Menopause 26 (11), 1327–1333. 10.1097/GME.0000000000001403

[5] Baber R. J., Panay N., Fenton A. (2016). 2016 IMS Recommendations on Women's Midlife Health and Menopause Hormone Therapy. Climacteric 19 (2), 109–150 10.3109/13697137.2015.1129166

[6] 2019 Surveillance of Menopause (2019). Diagnosis and Management (NICE Guideline NG23) [Internet]. London: National Institute for Health and Care Excellence (UK).Copyright © NICE. Available at: https://www.ncbi.nlm.nih.gov/books/NBK563593/

[7] Godsland I. F. (2001). Effects of Postmenopausal Hormone Replacement Therapy on Lipid, Lipoprotein, and Apolipoprotein (A) Concentrations: Analysis of Studies Published from 1974-2000. Fertil. Steril 75 (5), 898–915. 10.1016/s0015-0282(01)01699-5

[8] Anagnostis P., Galanis P., Chatzistergiou V., Stevenson J. C., Godsland I. F., Lambrinoudaki I., et al. (2017). The Effect of Hormone Replacement Therapy and Tibolone on Lipoprotein (A) Concentrations in Postmenopausal Women: A Systematic Review and Meta-Analysis. Maturitas 99, 27–36. 10.1016/j.maturitas.2017.02.009

[9] Nii S., Shinohara K., Matsushita H., Noguchi Y., Watanabe K., Wakatsuki A.(2016). Hepatic Effects of Estrogen on Plasma Distribution of Small Dense Low-Density Lipoprotein and Free Radical Production in Postmenopausal Women. J. Atheroscler. Thromb. 23 (7), 810–818. 10.5551/jat.33175

[10] Ki E. Y., Hur S. Y., Park J. S., Do Han K., Park Y. G. (2016). Differences in the Lipid Profile and Hormone Replacement Therapy Use in Korean Postmenopausal Women: the Korea National Health and Nutrition Examination Survey (KNHANES) 2010-2012. Arch. Gynecol. Obstet. 294 (1), 165–173. 10.1007/s00404-015-3982-9

[11] Pu D., Tan R., Yu Q., Wu J. (2017). Metabolic Syndrome in Menopause and Associated Factors: a Meta-Analysis. Climacteric 20 (6),583591.10.1080/13697137.2017.1386649

[12] Sacks F, Walsh B. Sex hormones and lipoprotein metabolism. Curr Opin Lipidol. 1994;5:236–40. doi: 10.1097/00041433-199405030-00012.

[13] Fletcher B, Berra K, Ades P, et al. AHA Scientific Statement: Managing Abnormal Blood Lipids. A collaborative approach. Circulation. 2005;112:3184–209. doi: 10.1161/CIRCULATIONAHA.105.169180.

[14] Ridker PM, Cushman M, Stampfer MJ, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000;342:836–43. doi: 10.1056/NEJM200003233421202.

[15] Pradhan AD, Manson JE, Rossouw JE, et al. Inflammatory biomarkers, hormone replacement therapy, and incident of coronary heart disease: prospective analysis from the Women's Health Initiative observational study. JAMA. 2002;288:980–7. doi: 10.1001/jama.288.8.980.

[16] Smith SC, Jr, Anderson JL, Cannon RO, 3rd, et al. CDC/AHA Workshop on markers of inflammation and cardiovascular disease: Application to clinical and public health practice: report from the clinical practice discussion group. Circulation. 2004;110:e550–3. doi: 10.1161/01.CIR.0000148981.71644.C7.

[17] Sattar N, Perera M, Small M, et al. Hormone replacement therapy and sensitive C-reactive protein concentrations in women with type-2 diabetes. Lancet. 1999;354:487–8. doi: 10.1016/S0140-6736(99)02079-6.

[18] Bonduki CE, Lourenco DM, Baracat E, et al. Effect of estrogen-progestin hormone replacement therapy on plasma antithrombin III of post-menopausal women. Acta Obstet Gynecol Scand. 1998;77:330–33.

[19] Oger E, Alhenc-Gelas M, Lacut K, et al. Differential effects of oral and transdermal estrogen/progesterone regimens on sensitivity to activated protein C among post-menopausal women. A randomized trial. Arterioscler Thromb Vasc Biol. 2003;23:1671–76. doi: 10.1161/01.ATV.0000087141.05044.1F.

[20] Schmidt JW, Wollner D, Curcio J, et al. Hormone replacement therapy in menopausal women: Past problems and future possibilities. Gynecological Endocrinology. 2006;22:564–77. doi: 10.1080/09513590600927017.
[21] Menon DV, Vongpatanasin W. Effects of transdermal estrogen replacement therapy on cardiovascular risk factors. Treat Endocrinol. 2006;5:37–51. doi: 10.2165/00024677-200605010-00005.
[22] Campagnoli C, Biglia N, Altare F, et al. Differential effects of oral conjugated estrogens and transdermal estradiol on insulin-like growth factor 1, growth hormone and sex hormone binding globulin serum levels. Gynecol Endocrinol. 1993;7:251–58. doi: 10.3109/09513599309152509.
[23] Vehkavaara S, Hakala-Ala-Pietilä T, Virkamäki A, et al. Differential effects of oral and transdermal estrogen replacement therapy on endothelial function in post-menopausal women. Circulation. 2000;102:2687–93. doi: 10.1161/01.cir.102.22.2687.
[24] Horton TJ, Pagliasotti MJ, Hobbs K, et al. Fuel metabolism in men and women during and after long-duration exercise. J Appl Physiol. 1998;85:1823–32. doi: 10.1152/jappl.1998.85.5.1823
[25] Ribas V, Nguyen MTA, Henstridge DC, et al. Impaired oxidative metabolism and inflammation are associated with insulin resistance in ERα-deficient mice. Am J Physiol Endocrinol Metabol. 2010;298:304–19. doi: 10.1152/ajpendo.00504.2009.
[26] Brown M. Skeletal muscle and bone: effect of sex steroids and aging. Adv Physiol Ed. 2008;32:120–6. doi: 10.1152/advan.90111.2008.
[27] Wu F, Ames R, Clearwater J, et al. Prospective 10-year study of the determinants of bone density and bone loss in normal postmenopausal women including the effect of hormone replacement therapy. Clin Endocrinol. 2002;56:703–11. doi: 10.1046/j.1365-2265.2002.01534.x.
[28] Wakatsuki A, Okatani Y, Ikenoue N, Fukaya T. Different effects of oral conjugated equine estrogen and transdermal estrogen replacement therapy on size and oxidative susceptibility of low-density lipoprotein particles in postmenopausal women. *Circulation*. 2002 Oct 1;106(14):1771-6. doi: 10.1161/01.cir.0000032261.12632.d7.
[29] Guetta V, Lush RM, Figg WD, Waclawiw MA, Cannon RO. Effects of the antiestrogen tamoxifen on low-density lipoprotein concentrations and oxidation in postmenopausal women: Potential mechanisms for cardiovascular benefit. *American Journal of Cardiology*. 1995;76(14):1072-1073.