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# **Metabolic Impact of Estrogen Replacement Therapy**

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Menopause is associated with unfavourable changes in the blood lipid profile as well as with a deterioration of glucose tolerance, which may help in increasing the incidence of cardiovascular diseases. In the same way Hormone Replacement Therapy (HRT) has different metabolic impact in relationship to the dose of estrogen component, the type of progestin and the route of administration. Most of the studies analyzed the effect of the combined estroprogestin therapy, therefore, the impact of the estrogen component alone isn't always differentiable but principal results are generally consistent. This review aimes to expound the metabolic impact of the estrogen replacement administration in postmenopausal women. A literature review was conducted to identify all the prospective, the randomized trials and to compare the effects of both low and high-dose therapy and route of administration (oral and transdermal). The results of estrogen replacement therapy on glucose metabolism showed minimal changes and differences among treatments. Some studies showed that neither peroral nor transdermal estradiol replacement therapy induced any negative effects on glucose metabolism. The estrogen substitution increases the rate of apolipoprotein metabolism in various degrees, depending on the type of lipoprotein. At present a considerable data document an increase in HDL and a reduction of LDL cholesterol, following estrogen therapy. Studies have clearly established that the estrogen treatment decreases total plasma cholesterol and increases or maintains plasma triglyceride levels. In conclusion the studies of ERT's effects on glucose and lipid metabolism are heterogeneous but all together the ERT impact may be considered neutral. However the low doses of estrogen therapy may give some beneficial effects. Above all the treatment may prevent the physiological worsening of the glucose and lipid metabolism in menopause. **J Reproduktionsmed Endokrinol 2010; 7 (Special Issue 1): 119–24**.

Key words: menopause, ERT, lipid metabolism, glucose metabolism

#### Introduction

Menopause is associated with unfavourable changes in the blood lipid profile as well as with a deterioration of glucose tolerance, factors that are likely to increase the incidence of cardiovascular diseases [1].

These changes are in part due to the agerelated metabolic impairment, but may also be associated with postmenopausal hypoestrogenism [2].

The sharp decrease in circulating steroid hormones seems to reduce both insulin secretion and elimination, as well as to increase insulin resistance, thereafter bringing about an increase in the circulating insulin concentration and a higher incidence of both type II diabetes and metabolic syndrome [1].

Therefore the estrogen deficiency leads to increased levels of Low-Density Lipoprotein (LDL), total cholesterol, triglycerides, and lipoprotein(a) (Lp[a])and lowers the levels of High Density Lipoprotein (HDL) [3]. Postmenopausal women generally gain weight and show an android fat distribution [4]. There is a persistent perception that estrogen administration may have deleterious effects on lipid and glucose metabolism; this belief dates back to observation of metabolic effects of high- estrogen oral contraceptive use and depending on steroid composition and dosage [5]. In the same way, Hormone Replacement Therapy (HRT) has a different metabolic impact depending on the dose of the estrogen component, the type of progestin and the route of administration. When evaluating metabolic effects of HRT, it must be remembered that most of the studies analyzed the effect of the combined estro-progestin therapy; therefore, whereas the impact of the estrogen component alone is not always measurable, results are nonetheless consistent.

In particular this review aims at summarising the metabolic impact of the estrogen replacement administration in postmenopausal women.

#### Estrogens and Carbohydrate Metabolism

Estrogens play a role in glucose homeostasis, possibly through an effect on insulin secretion and clearance. Postmenopausal women have similar glucose and insulin levels to premenopausal ones, but produce 50 % less insulin and eliminate it slowly, thus compensating for the reduced secretion [1].

Measurement of plasma insulin concentration alone is insufficient for the assessment of pancreatic insulin secretion, because of the substantial and variable uptake of newly secreted insulin by the liver and its short half life. C-peptide is secreted simultaneously with insulin and in equimolar quantities but does not undergo liver uptake, therefore providing a good index of insulin secretion. Moreover many models arising from Intravenous Glucose Tolerance Test (IVGTT) or Oral Glucose Tolerance Test (OGTT) have been developed to measure the fraction of new secreted insulin passing through the liver and the rate of elimination of insulin from the general circulation.

At the same time different indexes of insulin sensitivity have been assessed from measurements in the fasting state and during oral glucose tolerance test. The most intensively validated among them are HOMA-IR (HOmeostasis Model As-

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Reference	No. of subjects	Duration of estrogen	Fasting glucose	Fasting insulin	AUC for glucose	AUC for insulin	Insulin sensitivity
Oral							
CEE 0.625 mg							
Cagnacci et al., 1992 [15]	15	3 months	$\checkmark$	Ν	Ν	Ν	
Godsland et al., 1993 [1]*	30	3 months			$\uparrow$	1. phase ↓ 2. phase N	Ν
Lobo et al., 1994 [14]	29	12 months	$\checkmark$	$\checkmark$	Ν	$\checkmark$	
Espeland et al., 1998 [11]	97	36 months	$\checkmark$	$\checkmark$			
CEE 0.45–0.30 mg							
Lobo et al., 1994 [14]	95/89	12 months	N	N	NN	N	N
Estradiol							
Karjalainen et al., 2001 [19] (2 mg)	35	6 months	Ν	Ν	Ν	Ν	Ν
Soranna et al., 2002 [20] (2 mg)	43	3 months	Ν	Ν	Ν	Ν	$\checkmark$
Li et al., 2003 [22] (1 mg/NETA 0.5)	40	12 months	$\checkmark$	$\checkmark$	Ν	N/ <b>↓</b>	$\uparrow$
Villa et al., 2008 [21] (1 mg)	48	3 months	Ν	$\checkmark$	Ν	Ν	$\uparrow$
Transdermal							
Cagnacci et al., 1992 [15]	15	3 months	Ν	$\checkmark$	Ν	$\downarrow$	
Godsland et al., 1993 [1]*	30	3 months			Ν	Ν	Ν
O'Sullivan & Ho, 1995	9	3 months	Ν	Ν	Ν	Ν	Ν
Cagnacci et al., 1997 [17]	9	2 months	Ν	N/ <b>\</b> **	Ν	N/ <b>↓</b> **	Ν
Cucinelli et al., 1999 [16]	21	12 weeks	Ν	Ν	Ν	N/V	N/ <b>↑</b>
Duncan et al., 1999 [18]	22	6 weeks	Ν	Ν			Ν
Karjalainen et al., 2001 [19] (1 mg)	38	6 months	Ν	Ν	Ν	Ν	Ν

AUC: area under the curve; CEE: conjugated equine estrogen; N: no statistically significant change;  $\Lambda$ : increase;  $\psi$ : decrease.

The women received combination therapy; these are the results of glucose metabolism studies at the end of the estrogen-alone phase; \*\* Decrease of insulin in oral glucose tolerance test, no change in intravenous glucose tolerance test.

sessment) and QUIKI (QUantitative Insulin sensitivity checK Index).

On the other hand the only direct measure of insulin sensitivity and the gold standard for this measurement remains the glucose clamp technique which determines the metabolic index (M) of insulin sensitivity.

#### Direct Effects on the Pancreas

Estrogens may have direct effects on the pancreas as well as an influence on other hormones which themselves affect insulin secretion or action. Receptor binding for estrogen is present in the pancreatic islets and at this level estrogens can increase the presence of progesterone receptors; for this reason, progesterone exposure of isolated islets augments insulin release [6, 7].

Estrogens administration increases glucocorticoid activity, especially in high doses and determines an increase in growth hormone secretion, thereby influencing insulin secretion [8, 9].

In humans estrogens may determine glucagone antagonism, a fact that may explain the reduction in fasting plasma glucose observed.

Estrogen deficiency is associated with deterioration in glucose tolerance and increased insulin resistance while estrogen replacement tends to annul these effects. Also an excess of estrogens is associated with deterioration in glucose tolerance and insulin resistance. This gradation in response to estrogens could be also present for the insulin receptor gene expression [10].

#### Estrogen Replacement Therapy

The "Postmenopausal Estrogen/Progestin Interventions (PEPI) study" was the first placebo-controlled trial evaluating

the effect of postmenopausal therapy on glucose metabolism. Researchers found a statistically significant decrease in fasting glucose levels over the 3 year duration of the study in patients who adhered to their hormone therapy assignment [11].

Two additional randomized clinical trials, carried out with the primary purpose of evaluating cardiovascular outcomes, found unexpectedly a significantly lower incidence of diabetes in patients receiving HRT [12, 13].

The "Heart and Estro-progestin Replacement Study" (HERS) published data on incidence of diabetes in 2029 postmenopausal women who had coronary heart diseases and had been assigned daily to 0.625 mg of conjugated equine estrogens (CEE) plus 2.5 mg of medroxyprogesterone acetate (MPA) or to placebo [12]. The incidence of diabetes in this 4-year study was 6.2 % in the treated group compared to 9.5 % in the placebo group (HR 0.65; 95 %-CI: 0.43-0.89).

Also the Women's Health Initiative study including 8014 healthy women having HRT showed a reduction in the incidence of diabetes possibly related to a decrease in insulin resistance. Data of this trial indicate a small but significant decrease in fasting glucose and fasting insulin levels [13]. Margolis et al by using the HOMA-IR calculation to estimate insulin resistance showed a significant decrease in insulin resistance unrelated to body size [13].

Table 1 shows that studies analysing the effects of estrogen administration on the specific parameters for the evaluation of the glucose metabolism have high-lighted differences in relationship to the dose or the route of administration.

Lobo et al. evaluated the effects of low oral doses of Combined Equine Estrogens (CEE) 0.45 mg and 0.3 mg as compared to 0.625 mg and showed minimal changes and differences among the 3 regimens [14]. The transdermal administration of estradiol (50 µg/day) to healthy women reduced insulin levels and increased pancreatic C-peptide response to glucose in one study, while another one showed significant changes only in hyperinsulinemic patients [15, 16]. The trans dermal administration of estrogens at high-doses seems to reduce post-hepatic insulin levels and to enhance the insulin clearance by the liver, while the effect of oral CEE on glucose metabolism is less evident [15, 17]. Some studies have shown only minimal positive changes in the carbohydrate metabolism [18, 19]. According to Karjalainen et al. neither oral nor transdermal estradiol replacement therapy induces negative effects on glucose metabolism; both treatments induce only a small, but significant reduction in Glycated Hemoglobin [HbA1c] levels and no change in postchallenge glucose and insulin levels.

Therefore treatment with high-doses oral 17 beta-estradiol ( $E_2$ ) may determine a slight decrease of insulin sensitivity tested by hyperinsulinemic euglycemic clamp, while the transdermal estrogen replacement alone in normo-insulinemic patients does not affect insulin sensibility [20].

These results were confirmed by our recent work showing that high doses oral estrogen therapy (oral micronized estradiol 2 mg) caused a slight deterioration in insulin sensitivity. On the contrary low-doses unopposed estradiol treatment determine an improvement in the peripheral insulin sensitivity made evident by an increase in the metabolic index (M) and a decrease of the insulin resistance index (HOMA-IR) [21].

Even in the case of low doses  $E_2$  oral therapy associated with progestin, researchers did not show any impairment of carbohydrate metabolism. Two recent studies evaluating the effects of the 1 mg  $E_2/0.5$  mg norethisterone acetate (NETA) administration showed a decline in fasting glucose and insulin levels (above all in women with higher basal fasting levels) and an amelioration in HbA1c and in the OGTT responses in treated groups respectively [22, 23].

In addition, studies exploring the effects of estrogen administration in patients with diabetes or metabolic syndrome showed neither impact on glucose metabolism nor any improvement in insulin resistance [24, 25]. Chu et al. in particular pointed out that transdermal  $E_2$  administration had more beneficial effects.

Recently a role has been suggested of the timing of estrogen administration in relationship to the time of menopause. In fact a longer interval between starting treatment and the occurrence of menopause seems associated with a reduced effect of  $E_2$  in increasing the whole body glucose disposal and in improving insulin metabolism [26].

#### Estrogen and Lipid Metabolism

During their reproductive years, women generally have levels of lipids (including triglycerides) and LDL lower than men; however, there is an increase after the menopause [27]. By contrast, the difference in high HDL levels between men and postmenopausal women remains the same. These changes are in part due to the age-related impairment of lipid metabolism, but may also be associated with postmenopausal hyp estrogenism. Estrogen effects on lipid metabolism are mediated by estrogen receptor  $\alpha$ (ER $\alpha$ ). It has been shown that polymorphisms of the ER $\alpha$  gene may influence the lipid response after HRT [28, 29]. Estrogens are involved in both lipogenesis and lipolysis. At the transcriptional level they increase the hepatic expression of apoprotein genes and the LDL receptors and decrease the transcription of the lipoprotein lipase (LPL) gene through ER $\alpha$ . Thus, when estrogen levels decrease after the menopause, an increase of the LPL activity is observed and this probably contributes to the increase of free fatty acids (FFA), as well as to the accumulation of abdominal fat. By inhibiting lipogenesis, estrogens alter the expression of hormone-sensitive lipase [30]. On the other hand, through ER $\alpha$  and estrogen receptor  $\beta$  (ER $\beta$ ), estrogens are involved in the proliferation of adipocytes, whereas their deprivation increases central obesity which is associated with a more atherogenic profile [31].

In general, menopause induces variations in lipoprotein plasma concentrations which are related to an increase in cardiovascular risk. Epidemiological data suggest a therapeutic role for estrogen replacement in the reduction of coronary heart disease (CHD) after menopause, with an improvement in lipid status supposedly accounting for 25-50 % of this protective effect. However, estrogen substitution has both positive and negative effects [32]. Negative effects are: increased occurrence of postprandial hyperlipidemia with increased triglycerides, generation of atherogenic of small LDL particles, increased risk of inflammatory changes in vascular wall and procoagulation effects. But estrogen therapy increases the synthesis of all lipoproteins including apolipoprotein (Apo) B and increases the rate of their metabolism in various degrees depending on the type of lipoprotein [33].

At present, considerable data have documented an increase in HDL and a reduction of LDL cholesterol following estrogen therapy [34]. Studies have clearly established that estrogens decrease total plasma cholesterol and increases or maintains plasma triglyceride levels [35–37].

#### Estrogen Replacement Therapy

Several reports have evaluated the effect of postmenopausal hormone therapy on lipid metabolism, but differences remain in results and conclusions [38–40].

Table 2: Lipid metabolism and estrogen or hormone replacement therapy										
Reference/Study	No. of patients	Duration	LDL	HDL	Trygl	Apo-A				
Oral										
CEE 0.625 mg or CEE 0.625 mg + MPA										
HERS study	2763	12 months	$\checkmark$	$\checkmark$	$\uparrow$	$\uparrow$				
ERA study	256	38 months	$\checkmark$	$\uparrow$	N(CEE); ↑(CEE+MPA	<b>↑</b>				
Davidson et al., 2000 [58]	270	months	$\checkmark$	$\uparrow$	$\uparrow$	$\uparrow$				
 CEE 0.30 mg or CEE 0.30 mg + MPA										
Sanada et al., 2003 [49]	51	3 months	$\checkmark$	$\uparrow$	$\checkmark$	$\checkmark$				
Mercuro et al., 2003 [50]	25	3 months	$\checkmark$	$\uparrow$	$\uparrow$	$\uparrow$				
Lobo et al., 2001 [51]	749	3 months	$\checkmark$	$\uparrow$	$\uparrow$	$\uparrow$				
Wakatsuki et al., 2003 [52]	51	3 months	$\checkmark$	$\uparrow$	Ν	$\checkmark$				
Schlegel et al., 1999 [53]	39	6 months	$\checkmark$	$\uparrow$	$\checkmark$	$\checkmark$				
Estradiol										
Loh et al., 2002 [57] (1 mg E <sub>2</sub> /0.5 NETA)	96	6 months	$\checkmark$	$\uparrow$	Ν					
Hodis et al., 2003 [55] (1 mg)	226		$\checkmark$	$\uparrow$	Ν					
Angerer et al., 2002 [60] (1 mg)	321	48 weeks	$\checkmark$	$\uparrow$	Ν					
Alexandersen et al., 2001 [61]	301	12 months	$\checkmark$	$\uparrow$	Ν					
Bruhat et al., 2001 [54] (1 mg)	440	6 months	$\checkmark$	$\uparrow$	$\uparrow$					
Hodis et al., 2001 [56] (1 mg)	222		$\checkmark$	$\uparrow$	$\uparrow$	$\checkmark$				
Davidson et al., 2000 [58]	270	months	$\checkmark$	$\uparrow$	$\uparrow$	$\uparrow$				
Peeyananjarassri et al., 2005 [48	]	months								
Villa et al., 2008 [21] (1 mg)	48	3 months	Ν	Ν	Ν	Ν				
Villa et al., 2008 21] (2 mg)	48	3 months	$\checkmark$	$\uparrow$	Ν					
Chu et al., 2006 [25] (1 mg)	50	3 months	$\checkmark$	$\uparrow$	Ν					
Transdermal										
Balci et al., 2004 (100 μg 17-β-Ε <sub>2</sub> /week)	43	3 months	$\checkmark$	$\uparrow$	$\checkmark$					
Chu et al., 2006 [25] (0.05 mg/die)	50	3 months	$\checkmark$	Ν						
Salpeter et al., 2006 [68]	311	18 months	$\checkmark$	$\uparrow$	Ν					

ERT: estrogen replacement therapy; HRT: estrogen plus progesterone replacement therapy; CEE: conjugated equine estrogen; MPA: medroxyprogesterone Acetate;  $17\beta$ -E<sub>2</sub>: 17-beta-estradiol; N: no statistically significant change;  $\uparrow$ : increase;  $\downarrow$ : decrease.

Table 2 summarizes the principal studies on the effect of estrogen replacement on lipid parameters.

Two major placebo-controlled trials have provided data on the effects of estrogen replacement therapy (ERT) on the lipid metabolism: The Heart and Estrogen/Progestin Replacement Study (HERS) showed that LDL levels decrease from baseline while triglycerides increase in the hormone treated group. At the same time HDL levels increase in the hormone group and decrease in the placebo group [12]. The Estrogen and Atherosclerosis (ERA) study, a placebocontrolled, randomized trial examined the effects of CEE (0.625 mg/day) or CEE (0.625 mg/day) plus MPA (2.5 mg/ day) on 256 post-menopausal women with established coronary atherosclerosis; it showed a reduction in plasma remnant lipoprotein concentrations in the context of no change or elevation in plasma triglycerides levels in the active treatment group with estrogen alone. A significant increases in HDL-C and Apo A-I levels has been observed [41, 42]. Authors of the study hypnotized that the mechanism by which estrogens lower LDL-C and increase HDL-C concentrations is different from that of other lipidlowering medications and it may be the key to the documented lack of protection observed with estrogen replacement in postmenopausal women with CHD.

Variations in treatment effects may be attributable to the differences in baseline characteristics among individuals and/or also to differences in preparations, doses and routes of hormone administration [14, 43, 44].

Davidson et al. divided 270 women in 4 treatment groups (placebo,  $E_2$ ,  $E_2/0.25$ NETA,  $E_2/0.5$  NETA) and showed an increase in triglycerides, HDL cholesterol and Apo A-I levels induced by unopposed 17 $\beta$ - $E_2$  compared to placebo and combined therapy. Moreover, in the  $E_2$ group, estrogen therapy which prevents the increase in Lp(a) observed among subjects taking placebo is consistent with results from previous studies in which reductions in Lp(a) have been observed with ERT [45].

Unopposed  $17\beta$ -E<sub>2</sub>, despite lowering LDL level, has little effect on Apo B level and thus does not appear to reduce the number of circulating atherogenic lipoprotein particles. Estrogens increase expression of hepatic LDL receptors, resulting in enhanced removal of LDL particles from the circulation and increase the rate of very-low-density lipoprotein (VLDL) secretion [46, 47].

Most differences observed may be due to different doses of hormone administration.

A recent review analysed the effects of low-dose hormone therapy on lipid metabolism. Studies comparing low-dose (estrogens plus progestin) and standarddose hormonal therapy (HT) (estrogen plus progestin) showed that CEE 0.3 mg significantly increased levels of HDL cholesterol and reduced levels of LDL cholesterol and total cholesterol by the same order of magnitude as standarddose HT [48–53].

Therefore widely different effects on triglyceride levels have been observed.

In some studies triglyceride levels significantly increased with the higher doses of CEE 0.625 mg and CEE 1.25 mg, but decreased with low-dose (CEE 0.3 mg) [49, 53]; 1 study showed no difference between CEE 0.3 mg and CEE 0.625 mg doses while others showed that CEE 0.3 mg increased triglyceride levels as much as standard-dose [50–52].

There was no dose-related effect on LDL cholesterol or total cholesterol [50]. Significantly increased levels of HDL cholesterol and reduced LDL cholesterol and total cholesterol were seen with administration of 1 mg of oral estradiol and 0.025 mg of transdermal estradiol [54–59].

The effects of estradiol 1 mg on triglycerides were variable, with some studies showing no change while others reporting a significant increase [54–61].

There were varying effects of HT on Apo A-1. One study showed increased Apo A-1 by both CEE 0.3 and 0.625 mg, but another showed a decrease by CEE 0.3 mg [51, 53]. This study showed that Apo B was decreased in both standarddose and low-dose HT while others showed no change with low-dose HT but a significant decrease with high-dose HT [53, 58]. Finally Lp (a) was significantly decreased by both the standard-dose and the low-dose HT [50, 51, 53, 60]. The reason for varying effects observed remains unclear.

Few studies have examined the effect of estrogen therapy at different dosages on lipid metabolism.

In a previous study [21], we evaluated the different influences of 2 dosages of oral formulations of unopposed  $E_2$  (1 mg vs 2 mg) compared with a placebo treatment, both on glucose tolerance and lipid metabolism in 48 healthy nonobese normoinsulinemic postmenopausal women.

The study showed that total cholesterol level did not change, after treatment, in all groups. Patients treated with 1 mg  $E_2$  showed no increase in triglycerides, HDL-C and VLDL-C concentrations after treatment, while a slight, but not significant, decrease in LDL-C subfractions was noticed. This study showed that the low-dose therapy did not adversely affect triglycerides plasma concentration. On the other hand, other beneficial effects on the lipoprotein profile

(increase in HDL cholesterol and decrease in LDL cholesterol levels, with a significant reduction of the LDL/HDL ratio) were observed in the  $E_2$ -2 mg treatment only. In contrast with previous studies on unopposed low-dose oral estrogen treatment, our data showed only a trend towards a decrease in LDL cholesterol levels, a neutral effect on the triglyceride levels and no change in the production of VLDL particles, which are clearly involved in the atherogenesis [63–66].

With regards to the route of estrogen therapy administration, few studies analyzed the effect of transdermal therapy on lipid metabolism. Balci et al. conducted a randomized, double blind trial on hysterectomized women by administering transdermal  $E_2$  100 µg. Mean serum HDL levels in the ERT group were significantly higher than in control group. Total cholesterol and LDL cholesterol showed an increase, while triglycerides levels were significantly decreased [67].

One of the few studies comparing the effects of oral  $E_2$  (1 mg) or transdermal  $E_2$  (0.05 mg) therapy on lipids was conducted in obese postmenopausal women [25]. This study showed an increase in HDL and a decrease in LDL with no significant change in triglycerides after oral therapy. After transdermal therapy a non significant increase in HDL and a decrease in LDL were observed. In summary, there were no changes in lipid parameters between oral and transdermal therapy in women with metabolic syndrome.

A recent meta-analysis showed that oral therapy produced greater reduction of LDL/HDL ratio than transdermal therapy but increased triglycerides levels. On the contrary the transdermal therapy had an overall neutral effect [68].

#### Conclusion

Overall the studies of ERT effects on glucose and lipid metabolism are heterogeneous but all together the ERT impact may be considered neutral. However, low dose estrogen therapy may give some beneficial effects. Above all the treatment may prevent the physiological worsening of the glucose and lipid metabolism.

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