Cardiovascular risk factors in postmenopausal women: effects of estrogen therapy on glucose and lipid profiles

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Summary
The menopause is associated with unfavorable changes in the lipid profile as well as in glucose metabolism, which may help to increase the incidence of cardiovascular diseases. The metabolic impact of hormone replacement therapy differs in relation to the dose of the estrogen component, the type of progestin, and the route of administration used. Since most studies analyze the effect of combined estro-progestin therapy, the impact of the estrogen component alone is not always differentiable, however the main results are generally consistent. A review of the recent literature was conducted to analyze the impact of estrogen replacement therapy (ERT) on glucose and lipid metabolism and the differences linked to different doses, associations and routes of administration. Studies were selected on the basis of quality of data and relevance to the present topic. Many studies showed that both oral and transdermal estrogen therapy induced positive effects on glucose metabolism, with minimal changes and differences between treatments. A considerable amount of data documented increases in HDL and decreases in LDL cholesterol. Low-dose estrogen therapy showed no negative effect on triglycerides and a neutral effect on the whole lipid panel.
In conclusion, low-dose ERT may prevent the physiological worsening of glucose and lipid metabolism in menopausal women without showing any significant negative effects.

KEY WORDS: estrogen replacement therapy, glucose, hormone replacement therapy, insulin, lipid metabolism.

Introduction

The incidence of cardiovascular diseases increases substantially after the menopause, and the menopause may play a causative role in this increase, even independently of chronological aging. The falling estrogen levels observed in the peri- and postmenopause may be involved in this process, as may the subsequent androgen-dominated metabolic environment (1). The menopausal transition and the menopause itself are associated not only with unfavorable changes in the blood lipid profile (2) and with a deterioration of glucose tolerance and insulin sensitivity, but also with increases in blood pressure, body weight and anthropometric measurements (3). The loss of hormones with the menopause seems to reduce insulin secretion and elimination and increase insulin resistance, thereafter bringing about an increase in the circulating insulin concentration and a higher incidence of both diabetes and metabolic syndrome (4). The increased cardiovascular risk in diabetes is, in part, mediated by the associated dyslipidemia, which is mainly due to the insulin-resistance state. Therefore, hyperinsulinemia and dyslipidemia are classical components of the metabolic syndrome and this syndrome increases with the menopause independently of age, exacerbating the cardiovascular risk in older women. It was long believed that estrogen administration might have deleterious effects on lipid and glucose metabolism, a perception dating back to the steroid composition- and dose-dependent metabolic effects observed in high-estrogen oral contraceptive use (5). In the same way, the metabolic impact of hormone replacement therapy (HRT) differs in relation to the dose of the estrogen component, the type of progestin, and the route of administration used. Current hormone therapy seems to be associated with a decreased prevalence of abdominal obesity and better glucose metabolism, and prior use of hormone therapy has been associated with a lower risk of abdominal obesity and high blood pressure.
Because the majority of studies analyze the effect of the combined estro-progestin therapy, the impact of the estrogen component alone is not always differentiable. Since, according to the latest clinical recommendations, it is opportune to treat postmenopausal symptoms with the lowest effective dose, we reviewed recent literature data on low-dose treatments or on low- versus high-dose replacement therapies. Significant differences seem to exist between oral and transdermal estrogens in terms of

hormonal bioavailability and metabolism, with implications for the clinical efficacy, potential side effects, and risk profile of the different hormone therapy options. However, the results of the studies are not uniform. The present literature review, focusing on estrogen-only replacement therapy, aims to highlight the metabolic impact of estrogen administration on different cardiovascular risk parameters in the menopausal period.

Estrogens and carbohydrate metabolism

Estrogens play a role in glucose homeostasis, possibly through effects on insulin secretion and clearance. Postmenopausal women had similar glucose and insulin levels to premenopausal women but produced 50% less insulin and eliminated it slowly, thus compensating for the reduced secretion (4).

Estrogens may have direct effects on the pancreas and may also influence other hormones which themselves affect insulin secretion or action. Receptor binding for estrogen occurs in the pancreatic islets and at this level estrogen can increase the presence of progesterone receptors, whose activation after progesterone exposure in isolated pancreatic islets increases insulin release (6,7).

The administration of estrogens, especially at high doses, increases glucocorticoid activity and brings about an increase in growth hormone secretion, influencing insulin secretion (8,9).

The possibility that, in humans, estrogens cause glucagon antagonism could provide an explanation for the reduction in fasting plasma glucose often observed in subjects administered estrogens.

Estrogen deficiency is associated with reduced glucose tolerance and increased insulin resistance, while estrogen replacement leads to reversal of these effects. Estrogens in excess (high-dose HRT) may also be associated with glucose tolerance deterioration and insulin resistance. These different responses to various levels of estrogens could be linked to insulin receptor gene expression (10).

Clinical evaluation

Because of the substantial and variable uptake of newly secreted insulin by the liver and the short half-life of insulin, pancreatic insulin secretion cannot be assessed through measurement of plasma insulin concentration alone. C-peptide is secreted simultaneously with insulin and in equimolar quantities but does not undergo uptake by the liver. Many models using intravenous or oral glucose tolerance tests have been developed to derive the fraction of newly secreted insulin passing through the liver and the rate of insulin elimination from the general circulation.

Although the glucose clamp technique remains the only direct measure of insulin sensitivity and the gold standard for this measurement, many different indexes of insulin sensitivity have been assessed. The most validated are measurement of the fasting insulin/glucose ratio, evaluation of the glycemic and insulinemic area under the curve (AUC) during the oral glucose tolerance test (OGTT), and the HOMA-IR (homeostasis model assessment) and QUIKI (quantitative insulin sensitivity check index) assessments.

Estrogen replacement therapy and carbohydrate metabolism

The three-year Postmenopausal Estrogen/Progestin Interventions (PEPI) study was the first placebo-controlled trial to evaluate the effect of postmenopausal therapy on glucose metabolism. The researchers found a statistically significant decrease in fasting glucose levels in patients who adhered to their assigned hormone therapy (11). Two randomized clinical trials, carried out with the primary endpoint of evaluating cardiovascular outcomes, unexpectedly found a significantly lower incidence of diabetes in patients receiving HRT (12,13). The Heart and Estro/progestin Replacement Study (HERS) published data on the incidence of diabetes in 2029 postmenopausal women who had coronary heart disease (CHD) and had been assigned to daily estrogen (0.625 of conjugated equine estrogen, CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) therapy or to placebo (12). The incidence of diabetes in this four-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).

Along the same lines, the Women's Health Initiative, which included the study of 8014 healthy women receiving HRT, showed a reduction of the incidence of diabetes possibly related to a decrease in insulin resistance. Data from this trial indicated a small but significant decrease in fasting glucose and fasting insulin levels (13). Margolis et al., using the HOMA-IR calculation to estimate insulin resistance, showed a significant decrease in insulin resistance unrelated to body size (13).

Table 1 shows studies analyzing the effects of low-dose estrogen administration (including ones comparing low and high doses and ones evaluating only low-dose formulations, with or without progestin) on specific parameters for the evaluation of glucose metabolism. This table highlights differences related to the dose and route of administration used.

Lobo et al. evaluated the effects of low oral doses of CEE 0.45 and 0.3 as compared with 0.625 and found only minimal changes and differences between treatments (14). Further studies showed only minimal positive changes in carbohydrate metabolism (15,16). According to Karjalainen et al., neither oral estradiol (2 mg/day) nor transdermal estradiol (1 mg/day) replacement therapy had any negative effects on glucose metabolism, both treatments being found to induce only a small significant reduction in HbA1 levels and no change in post-challenge glucose and insulin levels (16).

A recent study by our group showed that high-dose oral estrogen therapy (2 mg) caused a slight deterioration in insulin sensitivity. On the contrary, low-dose estradiol unopposed treatment led to an improvement in peripheral in-

sulin sensitivity as shown by an increase in the metabolic index and a decrease in the insulin resistance index (HOMA-IR) (17).
Researchers have not found any impairment of carbohydrate metabolism even in the case of low-dose estradiol oral therapy associated with progestin. Some recent studies evaluating the effects of 1mg estradiol/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 improvement in HbA1c and OGTT challenge in the treated groups (18-21). Similarly, the low-dose estrogen/drospirenone combination therapy did not show any negative effect on carbohydrate metabolism but a slight positive effect on insulin secretion (21).
Transdermal administration (50μg/day) to healthy women seems to reduce insulin levels; in one study it seemed to increase pancreatic C-pep response to glucose, whereas in another significant changes were found only in hyperinsulinemic patients (22,23).

Some studies exploring the effects of estrogen administration in patients with diabetes or metabolic syndrome showed neither an impact on glucose metabolism nor any improvement of insulin resistance (24,25). The latter study in particular pointed out that transdermal estradiol administration had a more beneficial effect.

Estrogens and lipid metabolism

A large number of studies demonstrated that postmenopausal status is associated with increased levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and lipoprotein(a), and decreased levels of high-density lipoprotein cholesterol (HDL-C) (26).
The effects of estrogens on lipid metabolism are mediated by ER . It has been demonstrated that polymorphisms of the ER gene may influence the lipid response after HRT (27,28). Estrogens are involved in both lipogenesis and lipolysis. At transcriptional level

Table 1- Effects of estrogen replacement therapy on glucose metabolism

References	No. of subjects	Duration of therapy	Fasting glucose	Fasting insulin	AUC glucose	AUC insulin	HBA1c 1c	Insulin sensitivity
Oral low-dose CEE								
Lobo et al., 2001 CEE 0.3-0.45 mg	95/89	12 months	=	=	=	=	=	=
Oral estradiol								
Li et al., 2003 E2 1mg / NETA 0.5mg	40	12 months	↓	↓	=	=/↓		↑
Kernohan et al., 2007 E2 1mg / NETA 0.5mg	15	3 months	↓	=				
Villa et al., 2008 E2 1mg	48	3 months	=	↓	=	=		↑
Bingol et al., 2009 E2 1mg / NETA 0.5 mg	40	6 months	=	=	↓			
Villa et al., 2011 E2 1mg / DRSP 2mg	40	6 months	=	=	=	↓	=	
Transdermal estradiol								
Cagnacci et al., 1997 E2 50μg	9	2 months	=	=/↓*	=	=/↓*		=
Cucinelli et al., 1999 E2 50μg	21	12 weeks	=	=	=	=/↓		=/↑
Duncan et al., 1999 E2 50μg	22	6 weeks	=	=				=
Karjalainen et al., 2001 E2 1mg	38	6 months	=	=	=	=	↓	=

AUC: area under the curve; E2: estradiol; CEE: conjugated equine estrogen; NETA: norethisterone acetate; DRSP: drospirenone; = : no statistically significant change; ↓: increase; ↓: decrease; *Decrease of insulin in oral glucose tolerance test, no change in intravenous glucose tolerance test.

they increase the hepatic expression of apoprotein genes and LDL receptors and decrease transcription of the lipoprotein lipase (LPL) gene through ER . Thus, when estrogen levels decrease after the menopause, an increase in LPL activity is observed and this probably contributes to the increased levels of free fatty acids as well as to the accumulation of abdominal fat. By inhibiting lipogenesis, estrogens alter the expression of hormone-sensitive lipase (29). On the other hand, through ER and ER , estrogens are involved in the proliferation of adipocytes, whereas their reduction increases central obesity which is associated with a more atherogenic profile (30).

Epidemiological data suggest a role for estrogen replacement in reducing CHD after the menopause, with an improved lipid status supposedly accounting for 25-50% of this protective effect. However, estrogen substitution has both positive and negative effects (31). Negative effects might be: increased occurrence of postprandial hyperlipidemia with increased triglycerides, generation of atherogenous small dense LDL particles, increased risk of inflammatory changes in the vascular wall and procoagulation effects.

Estrogen replacement therapy and lipid metabolism

At present most available data document increased HDL and reduced LDL cholesterol as well as lower total plasma cholesterol and sometimes increased triglyceride levels (32-35) following estrogen replacement therapy. However, there remain many differences in the results and conclusions of the different studies (36-38).

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

Two major placebo-controlled trials document the effects of ERT on lipid metabolism. One study, the HERS, showed that LDL cholesterol levels decreased from baseline in the treated and in the placebo group, while HDL cholesterol levels increased in the treated group and decreased in the placebo group. Mean triglyceride levels increased in both groups (12).

The Estrogen and Atherosclerosis (ERA) trial was a placebo-controlled, randomized trial that examined the effects of conjugated equine estrogen (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 (39).

This study showed reduced plasma remnant lipoprotein concentrations in the context of unchanged or raised plasma triglyceride levels as well as significant increases in HDL-C and apo A-I levels.

Variations in treatment effects may be attributable to differences in baseline characteristics among individuals as well as also to differences in preparations, doses and routes of hormone administration.

Studies comparing oral low-dose estrogen or estrogen+progestin and standard/high dose hormone therapy showed that CEE often increased levels of HDL cholesterol and reduced levels of LDL and total cholesterol by the same order of magnitude as standard-dose hormone therapy (40-44).

Therefore, different effects on triglyceride levels have been reported.

In some studies triglyceride levels increased significantly with higher doses (0.625 and 1.25 mg), but not with low-dose treatment (CEE 0.3 mg) (40-44); one study showed no difference between CEE 0.3 mg and CEE 0.625 mg doses (43), while others showed that low-dose CEE (0.3 mg) increased triglyceride levels as much as the standard-dose (41,42).

There emerged no dose-related effect on LDL cholesterol or total cholesterol (41). Significantly increased levels of HDL cholesterol and reduced LDL cholesterol and total cholesterol were seen with administration of oral estradiol 1 mg, with or without progestin (45-49).

The effects of estradiol 1 mg on triglycerides were mainly neutral.

In a previous study, we evaluated the different influences of two dosages of oral formulations of unopposed estradiol (1 mg vs 2 mg) compared with a placebo treatment, both on glucose tolerance and lipid metabolism in 48 healthy non-obese normoinsulinemic postmenopausal women (17). We found that the total cholesterol level did not change, after treatment, in any group. Patients treated with 1 mg estradiol showed no increase in triglyceride, HDL cholesterol and VLDL cholesterol concentrations after treatment, while a slight but not significant decrease in LDL cholesterol sub-fractions was observed. This study showed that the low-dose therapy did not adversely affect plasma concentration of triglycerides. On the other hand, the beneficial effect on the lipoprotein profile (increase in HDL cholesterol and decrease in LDL cholesterol levels, with a significant reduction of the LDL/HDL ratio) was observed in the high-dose estradiol treatment only (17). A subsequent study showed that low-dose estrogen (1 mg) in combination with drospirenone (2 mg) can reduce total cholesterol levels as well as the LDL fraction (21).

As regards the route of administration few studies analyzed the effect of transdermal ERT on lipid metabolism in healthy menopausal subjects (50).

One of the few studies that did compare the effects of oral and transdermal (0.05 mg) estradiol on lipids was conducted in postmenopausal women with type 2 diabetes. A non-significant increase in HDL and a decrease in LDL cholesterol and no significant triglyceride changes were observed following transdermal therapy (24). Also in the study by Chu et al. (25), conducted in patients with metabolic syndrome, transdermal therapy showed an overall neutral effect. These results in pathological subjects have been also confirmed in a wide and accurate meta-analysis (51).

Concluding remarks

Significant differences appear to exist between oral and transdermal estrogens in terms of hormonal bioavailability and metabolism, with implications for the clinical efficacy, potential side effects, and risk profile of the different hormone therapy options, but neither the results nor the designs of the various studies are uniform.

Overall, HRT has been shown to improve insulin resistance in postmenopausal women. Randomized studies

Table 2 - Effects of estrogen replacement therapy on lipid metabolism

References	No. of subjects	Duration of therapy	LDL	HDL	Trigl.	Apo-A1	T-chol
Oral low-dose CEE or low-dose CEE+MPA							
Sanada et al., 2003	18	3 months	↓	↑		↓	
Mercuro et al., 2003	25	3 months	↓	↑	↑		↓
Lobo et al., 2001	124	3 months	=	↑	↑	↑	
Wakatsuki et al., 2003	25	3 months	=	↑	=		
Schlegel et al., 1999	13	6 months	↓	↑	=	↓	↓
Oral estradiol							
Loh et al., 2002 E2 1mg / NETA 0.5 mg	48	6 months	↓	=	=		↓
Hodis et al., 2003 E2 1mg or E2 1mg / MPA 5mg	150	12 months	↓	↑(E2group)	=		=
Alexandersen et al., 2001 E2 1mg / NETA 0.5 mg	50	12 months	↓	↑	=		↓
Bruhat et al., 2001 E2V 1mg / MPA 2.5 / 5 mg	137	6 months	↓	=	=		
Davidson et al., 2000 E2 1mg	67	6 Months	↓	↑	↑	↑	
Kernohan et al., 2007 E2 1mg / NETA 0.5mg	15	3 Months	=	=	=	=	↓
Villa et al., 2008 E2 1mg	48	3 months	=	=	=	=	=
Bingol et al., 2009 E2 1mg / NETA 0.5mg	40	6 months	↑	=	=	=	=
Chu et al., 2006 E2 1mg	25	3 months	↓	↑	=		=
Villa et al., 2011 E2 1mg / DRSP 2 mg	40	6 months	↓	=	=	=	↓
Transdermal estradiol							
Chu et al., 2006 E2 50 μg	25	3 months	↓	=	=	=	=
Araújo et al., 2002 E2 50 μg / Prog 300 mg	10	6 months	=	=	=		=
Callejon et al., 2010 E2 1 mg / MPA 5mg	30	12 months	=	=	=		=

CEE: conjugated equine estrogen; NETA: norethisterone acetate; DRSP: drospirenone; MPA: medroxyprogesterone acetate; Prog: progesterone E2: 17-beta-estradiol; E2V: valerate estradiol; T-chol= total cholesterol; Trigl: trigycerides; =: no statistically significant change; ↓: increase: ↓: decrease.

have already demonstrated a reduced incidence of diabetes in patients receiving standard-/high-dose HRT but these treatments may sometimes reduce insulin sensitivity. Conversely, low-dose estradiol replacement therapy showed neutral or positive effects on glucose metabolism often improving insulin sensitivity or reducing basal levels of glucose or insulin. From the perspective of lipid metabolism, both oral and transdermal delivery systems seem to have beneficial effects on the HDL/LDL ratio, while the transdermal system has more favorable effects on triglycerides. The incidence of metabolic syndrome and weight gain appears to be slightly lower with a transdermal delivery system. This review confirms that low-dose estrogen therapy not only has no direct negative effects on glucose and lipid metabolism but actually shows some positive effects, suggesting that its administration might be warranted in selected subjects with pre-existing metabolic risk factors.

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