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Blood pressure, diabetes and BMI in postmenopausal women on HRT

As the age-related incidence of cardiovascular disease (CVD) in women accelerates after 50 years, it was suggested that menopause, with the accompanying estrogen decline, was responsible for the suppression of the protection seen usually in women. Consequently, several epidemiological studies have been conducted to assess the beneficial impact of estrogen supplements on cardiovascular disease in postmenopausal women. A meta-analysis has demonstrated that postmenopausal estrogen therapy may result in a 50 % reduction in coronary heart disease (Stampfer and Colditz, 1991).

Hormone replacement therapy (HRT) seems to favorably influence the lipid and lipoprotein profile. However, the cardioprotective effects of HRT appear to be multifactorial, as the effects on lipid metabolism may account for only 25 to 30 % of the benefit. Menopause could have detrimental effects on interrelated cardiovascular risk factors (body-fat distribution, blood pressure, glucose and insulin metabolism) and HRT may affect many of these factors. Thus, later studies examined these potential mechanisms.

In order to reduce the risk of endometrial cancer potentially induced by estrogens alone, combined progestogens have been prescribed for several years. But both these steroid hormones have metabolic effects. Their influence on the cardiovascular system is not well known. In addition, their effects may depend on the type of steroid, the dose and route of administration.

The purpose of this chapter was to assess the effect of HRT on glucose and insulin metabolism, as well as on blood pressure, weight and body-fat distribution. Another focus was the influence of HRT in women with disturbances in these risk factors, such as diabetic or hypertensive women.

Observational studies have the limitation of a treatment selection bias. Women who are taking postmenopausal HRT tend to be healthier, better educated and more compliant with lifestyle modifications reducing the cardiovascular risk (Derby et al., 1995 ; Matthews et al., 1996). Moreover, the decision to treat may well depend on a woman's cardiovascular risk profile. Finally, these studies often classified women as estrogen users or nonusers, and sometimes a past-user group was added. But most did not provide a

description of the hormones used. As a consequence, these studies can only be used to reinforce the consistency of available results.

Undoubtedly, the best way to assess the effect of HRT on cardiovascular risk factors is in prospective randomized placebo-controlled trials. At present, this kind of study is rare. Despite their disavantage because of the absence of placebo group, cross-over studies, comparing active treatments given in a random sequence to the same women, may partly compensate for this lack. However, the number of clinical trials as well as the number of women included are insufficient given the variety of available treatments.

The most recent reports on glucose and insulin metabolism, blood pressure, weight and body-fat distribution were specially selected. Special attention was given to clinical trials but epidemiological studies are also reported in the tables.

Diabetes, glucose and insulin metabolism

The results of clinical trials are reported on table 13.I. Although subcutaneous implants of 25 or 50 mg 17-β estradiol failed to improve glucose metabolism in surgically postmenopausal women (Notelovitz et al., 1987), oral oestrogen replacement therapy may improve glucose levels in postmenopausal women (Cagnacci et al., 1992). These results are consistent with those of the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, which remains the best study because of the number of subjects and methodology (3-year follow-up, randomized, double-blind, placebo-controlled). As compared with placebo, all actively treated groups had an increase in post-challenge glucose levels and a decrease in fasting glucose (PEPI, 1995).

Oral conjugated equine estrogen (CE) seem to have a dose-dependent effect on insulin sensitivity with an amelioration of 25 % at the lowest dose (0.625 mg) but a deterioration of 25 % at the 1.25 mg dose (Lindheim et al., 1993).

In addition, when comparing the effects of oral conjugated equine estrogens and transdermal estradiol after 3-month continuous administration, it seemed that transdermal treatment had a more beneficial effect on glucose metabolism. It reduced fasting insulin levels and improved the glucose-stimulated insulin response, as well as hepatic insulin clearance, whereas CE only decreased fasting glucose levels (Cagnacci et al., 1992). Two other investigators studied the effect of estrogen substitution on insulin sensitivity in relation to the administration route. They included respectively 22 and 9 postmenopausal women in clinical studies. In an insulin tolerance test, the first found that transdermal estradiol improved insulin sensitivity as compared to oral equine estrogens, despite the comparable estrogenicity of the respective doses (Lindheim, 1994). This beneficial effect of transdermal treatment was

Table 13.I : Glucose, insulin metabolism and HRT in clinical trials

Authors	Study Design	Study Population	HRT	Results
Notelovitz et al. (1987)	6-month randomized study USA	12 SurMp (hysterectomy + bilat. oophorectomy)	Random HRT group : 25 or 50 mg E2 subcutaneous implants	no differences in carbohydrate and insulin metabolism
Cagnacci et al. (1992)	3-month cross-over study USA	30 NatMp for ≥ 2 y mean age 53 free of medications for at least 1 year	In random sequence continuous transderm. E_2T or oral CE 0.625 mg	E2T: ↘ in mean fasting insulin levels + ↗ pancreatic islet response to glucose challenge oral CE : ↘ in mean fasting glucose levels
Godsland et al. (1993)	18-month randomized study UK	61 healthy Caucasian Nat postMp with HRT 29 Mp without HRT range of age? no medications	Random HRT group : 1- cont. oral CE 0.625 mg + seq. oral *dl*-NG 2- E_2T + transdermal norethindrone acetate 3-Without HRT	Oral HRT group : deterioration in glucose tolerance and overall ↗ in insulin secretion Transd. HRT group : no significant changes in glucose or insulin metabolism
Lindheim et al. (1993)	2-month randomized study USA	15 healthy postMp 47 to 62 years - 9 preMp 22 to 41 years - no HRT or medication > 4 weeks	Random HRT group : 1-CE 0.625 mg 2-CE 0.625 mg + progestin 3-CE 1.25 mg	Improved insulin sensitivity with CE 0.625 mg (+25 %) Altered insulin sensitivity (–25 %) with CE 1.25mg and progestin (–17 %)
Lindheim et al. (1994)	2-month study USA	22 healthy Hispanic postMp 43-62 years free of medications for at least 4 weeks	Random HRT group : 1- E_2T (n=7) 2- E_2T + MPA (n=7) Other group : 3-CE 1.25 mg (n=8)	Improved insulin sensitivity with transdermal E_2 alone Delayed insulin clearance with E_2 + MPA or with CE
PEPI (1995)	3-year (since 1989-91), multicenter, randomized, double blind, placebo-controlled trial USA	Community-based sample of 875 healthy postMp 45-64 years	Random HRT group 1-Placebo 2-CE 3-CE+cyclic MPA 4-CE+cont. MPA 5-CE+cyclic MP	↗ in 2h-glucose levels (++ for CE and MPA groups) and ↘ in fasting glucose (++ CE alone) in all active treatment groups vs placebo
O'Sullivan and HO (1995)	6-month randomized, cross-over study Australia	9 healthy postMp mean age 61 free of medications for at least 2 months	Random HRT group : 1- E_2T 2-CE 1.25 mg	Lower ↘ in nonesterified free fatty acid levels for CE

confirmed in terms of improved insulin action on lipid metabolism (O'Sullivan and Ho, 1995).

In a randomized study including 61 healthy postmenopausal women in the United Kingdom, no changes in glucose or insulin levels were observed with transdermal therapy. As for oral therapy, it caused a deterioration in glucose tolerance and an overall increase in insulin levels because of a reduction in insulin response to glucose, as estimated by an intravenous glucose tolerance test. None of the estrogen treatments caused insulin resistance but during the combined treatment (CE + the androgenic progestogen levonorgestrel), a deterioration of glucose tolerance was observed with alterations of insulin secretion and development of insulin resistance (Godsland et al., 1993).

Similarly, the addition of medroxyprogesterone acetate (MPA) to the estradiol treatment reversed the beneficial effects of percutaneous treatment and altered the clearance of insulin (Lindheim et al., 1994).

In observational studies (table 13.II), cross-sectional comparisons generally showed lower mean fasting insulin and/or glucose levels in postmenopausal women taking estrogens at the time of the study, with or without progestins, than in non treated postmenopausal women (Barrett-Connor and Laasko, 1990 ; Manolio et al., 1993 ; Nabulsi et al., 1993 ; Ferrara et al., 1995 ; Dallongeville et al., 1995). Only MPA was shown to reverse the protective effect of conjugated estrogens (Barrett-Connor and Laasko, 1990).

Estrogen therapy succeeded in counteracting the detrimental effects on glucose and insulin metabolism which occurred with thiazide diuretics in hypertensive postmenopausal women (Saxman et al., 1994).

Table 13.III summarizes studies on diabetes and HRT. A report of the Nurse's Health Study, involving more than 21 000 women free of disease at entry, showed that the 12-year incidence of diabetes was significantly reduced (RR=0.8) in current users of estrogens as compared with never users (Manson et al., 1992).

As for HRT use in diabetic women, the data of a large cross-sectional American study showed that current use of estrogens resulted in a higher increase in triglycerides and HDL-cholesterol levels in diabetic than in non diabetic postmenopausal women. Moreover, this negative effect was more pronounced in users of estrogen alone than of combined HRT (Robinson et al., 1996). According to a randomized controlled study, the combination of percutaneous 17-β estradiol and natural progesterone did not alter systolic and diastolic blood pressure in non insulin-dependent diabetics after 6 months of treatment (Mosnier-Pudar et al., 1991). Using an euglycemic hyperinsulinemic glucose clamp method in a randomized, double blind, cross-over study, the administration of 17-β estradiol to 25 postmenopausal women with NIDDM improved their glucose homeostasis (decrease fasting glucose, increase glucose disappearance, p=0.10) after estrogen substitution but there was a slight increase in body fat and body weight (Anderson et al., 1997).

Table 13.II : Glucose, insulin metabolism and HRT in observational studies

Authors	Study Design	Study Population	HRT	Results
Barrett-Connor and Laakso (1990)	Cross-sectional (1984-1987) The Rancho Bernardo Study USA	469 nondiabetic postMp women 55-92 years	Current use - Estrogen nonusers - Premarin (CE) - Premarin (CE) + Provera (MPA)	Lower mean fasting insulin level in estrogens users vs nonusers (+ fasting glucose in CE group) But no differences in HRT group
Manolio et al. (1993)	Cross-sectional The Cardiovascular Health Study USA	Random sample of Health Care lists 2 955 ≥ 65 years	- Current use of estrogens (alone or combined) - Past use/- Never used	Lower mean levels of fasting insulin and glucose for current users vs non users
Nabulsi et al. (1993)	Cross-sectional (1986-1989) The Atherosclerosis Risk in Communities Study USA	4 958 postMp from 4 multiracial populations 45-64 years	Current, former or past users of HRT For current use, estrogens or estrogens plus progestins	Lower mean fasting insulin and glucose levels in estrogen current users vs non users But no differences between alone estrogens and combined HRT
Saxman et al. (1994)	Cross-sectional The Rancho Bernardo Study USA	Population-based sample 1 047 white postMp 50-89 years - free of diabetes users and nonusers of thiazide diuretics	Current use of estrogen (yes/no) with or without progestins	Estrogen users vs no medications lower fasting glucose estrogen use reversed deleterious effect of thiazide on fasting glucose and insulin but no improved means for 2h-glucose and insulin
Ferrara et al. (1995)	Cross-sectional (1984-1987) The Rancho Bernardo Study USA	Population-based sample 849 W (35 postMp) - mean age 68 free of known diabetes	Current use of estrogens	Lower mean fasting insulin levels in estrogens users than non users Also lower fasting glucose
Dallongeville et al. (1995)	Cross-sectional (1991-1993) France	Volunteers for a standard check-up 1 746 postMp 45-65 years No gynecological surgery	Current use Combined estrogen and progestin only	Lower mean fasting glucose levels in HRT users

Table 13.III : Diabetes and HRT

Authors	Study Design	Study Population	HRT	Results
Mosnier-Pudar et al. (1991)	6-month randomized, controlled study France	32 postMp with NIDDM 46-64 years no HRT for at least 1 month	Random HRT group : 1-E_2T + natural progesterone 2-no treatment	No variations in bodyweight, SBP and DBP in either group
Manson et al. (1992)	Prospective (12-year follow-up) The Nurses Health Study USA	21 028 postMp 30-55 years free of diabetes, CVD and cancer at entry	- Current use of estrogens (alone or combined) - Past use - Never used	Incidence of diabetes RR=0,80 for current vs never users
Robinson et al. (1996)	Cross-sectional (1987-1989) The Atherosclerosis Risk in Communities Study USA	694 diabetic; 5 321 nondiabetic postMp women from 4 multiracial populations 45-64 years	Current, former or past users of HRT For current use, estrogens or estrogens plus progestins	higher triglycerides and lower HDL increase for estrogen users in diabetics than in nondiabetics higher triglycerides levels in alone estrogen users than combined HRT users diabetics
Andersson et al. (1997)	3-month randomized, double-blind, placebo-controlled cross-over study Sweden	21 NatMp and 4 SurMp postMp with NIDDM	Active treatment : E2 + norethisterone acetate	Decrease in mean fasting glucose (–2.6 mmol/l) Slight increase in mean bodyweight (+1.3 kg) and bodyfat (+0.4 kg)

Blood pressure and hypertension

In clinical trials (table 13.IV), all the randomized studies showed no significant changes in mean SBP or DBP after estrogen treatment. The type of estrogen, the route of administration and combination with a progestin did not alter these results.

The three observational studies reported are cross-sectional (table 13.V). They gave controversial results. In a community-based sample from the Rancho Bernardo cohort, the mean SBP was lower in women treated by both conjugated estrogens and MPA as compared with estrogen nonusers. The statistically non significant difference observed for estrogen alone was attributed to a lack of power (Barrett-Connor et al., 1989). For the volunteers in France, women who took combined estrogens and progestins had lower mean SBP and DBP, even after adjustment for confounders such as age, body-mass index, smoking, alcohol intake, exercise status, parity (Dallongeville et al., 1995). In contrast, no differences in SBP or DBP were observed in a large sample of middle-aged women from four multiracial American populations (Nabulsi et al., 1993).

Obesity and body-fat distribution

Among the clinical studies (table 13.VI), a 3-month cross-over study with transdermal estradiol or conjugated equine estrogens showed that neither treatment had an effect on BMI in a sample of 30 women in natural menopause for more than 2 years (Cagnacci et al., 1992). No changes were observed with estradiol valerate in a 15-month study (Utian, 1978) or with estradiol plus nomogestrol acetate in a French randomized placebo-controlled trial (Conard et al., 1995).

A 2-year, randomized, blinded, placebo-controlled study assessed the relationships of HRT with body-fat distribution (Dual-Energy X-ray Absorptiometry) rather than overall obesity. Estradiol valerate, combined with CPA or LNG, prevented the increase in abdominal fat observed in the non treated group (Haarbo et al., 1991).

Finally, in the PEPI trial there was an increase in both weight and WHR in all groups, which was significantly higher on the placebo than on estrogen alone (PEPI, 1995).

Among the four epidemiological studies reported (table 13.VII), three focused on postmenopausal women and the most recent was prospective. Their results were consistent : women who were current estrogen users at the time of the studies had a lower mean BMI as compared with nonusers, after adjustment for age. This association was not affected by additional progestin

Table 13.IV : Blood pressure and HRT in clinical trials

Authors	Study Design	Study Population	HRT	Results
Utian, 1978	Prospective (15-month follow-up) USA	50 healthy white SurMp (hysterectomy + bilat. oophorectomy) 45-55 years	Sequence : 6 month E2V (2×3month) 3 months placebo 3 months CE	No significant changes in DBP on any form of treatment
Notelovitz et al. (1987)	Prospective (6 months) randomized study USA	12 SurMp (hysterectomy + bilat. oophorectomy)	Random HRT group : 25 or 50 mg E2 subcutaneous implants	No differences in SBP and DBP
PEPI (1995)	3-year (since 1989-1991), multicenter, randomized, double blind, placebo-controlled trial USA	Community-based sample of 875 healthy postMp 45-64 years	Random HRT group G1-Placebo G2-CE G3-CE+cyclic MPA G4-CE+cont. MPA G5-CE+cyclic MP	No differences in change between groups for the mean SBP and DBP

Table 13.V : Blood pressure and HRT in observational studies

Authors	Study Design	Study Population	HRT	Results
Barrett-Connor et al. (1989)	Cross-sectional (1984-87) The Rancho Bernardo Study USA	Upper middle-class community 1 057 postMp 50-79 years	Current use - Estrogen nonusers - Premarin (CE) - Premarin (CE) + Provera (MPA)	Lower mean SBP and DBP for CE+MPA group vs nonusers No differences between CE and CE+MPA groups
Nabulsi et al. (1993)	Cross-sectional (1986-89) The Atherosclerosis Risk in Communities Study USA	4 958 postMp from 4 multiracial populations 45-64 years	Current, former or past users of HRT For current use, estrogens or estrogens plus progestins	No differences in mean SBP and DBP between estrogen current users vs nonusers No differences CE vs non users Neither between estrogens alone and combined HRT
Dallongeville et al. (1995)	Cross-sectional (1991-1993) France	Volunteers for a standard check-up 1 746 postMp 45-65 years No gynecological surgery	Current use Combined estrogen and progestin only	Lower mean SBP and DBP in HRT users

Table 13.VI : Body weight, body-fat distribution and HRT in clinical trials

Authors	Study Design	Study Population	HRT	Results
Utian, 1978	15-month study USA	50 healthy White surgically Mp (hysterectomy + bilat. oophorectomy) 45-55 years	Sequence : 6 months E2V (2×3months) 3 months placebo 3 months CE	No significant changes in bodyweight on any form of treatment
Harrbo et al. (1991)	2-year, randomized, blind, placebo-controlled study USA	62 healthy Danish postMp women for at least 6 months 45-55 years no diseases and no medications	Random HRT group G1-Placebo G2-E_2V+ CPA G2-E_2V+ LNG	DEXA measurements Combined estrogen-progestin therapy prevented the increase in abdominal fat
Cagnacci et al. (1992)	3-month cross-over study USA	30 women in natural menopause for ≥ 2 y mean age 53 free of medications for at least 1 year	In random sequence continuous transderm. transdermal E_2 or oral CE	No changes in BMI after estrogen administration (both groups)
Conard et al. (1995)	Randomized, double-blind, placebo-controlled prospective trial France	57 healthy naturally menopausal women mean age 52 free of medications for at least 2 months	Random group G1 - Placebo G2 - nomogestrol acetate 2.5 + E_2 G2 - nomogestrol acetate 3.75 + E_2	No significant changes in weight
PEPI (1995)	3-year (since 1989-1991), multicenter, randomized, double blind, placebo-controlled trial USA	Community-based sample of 875 healthy postMp 45-64 years	Random HRT group G1-Placebo G2-CE G3-CE+cyclic MPA G4-CE+cont. MPA G5-CE+cyclic MP	Increase in weight and WHR for all groups (weight ++ Placebo vs CE alone)

Table 13.VII : Body weight, body-fat distribution and HRT in observational trials

Authors	Study Design	Study Population	HRT	Results
Wallace et al. (1987)	Cross-sectional The Lipid Research Clinics Program Prevalence Study USA	Random samples of 10 North American White populations 13 852 20-69 years	Reported current estrogen use (yes/no)	for women 45-69 years lower mean BMI in estrogens users
Barrett-Connor et al. (1989)	Cross-sectional (1984-1987) The Rancho Bernardo Study USA	Upper middle-class community 1 057 postMp 50-79 years	Current use - Estrogen non users (past+never) - Premarin (CE) - Premarin (CE) + Provera (MPA)	Lower mean BMI in both CE, CE+MPA and past-users group vs non users
Manolio et al. (1993)	Cross-sectional The Cardiovascular Health Study USA	Random sample of Health Care lists 2 955 ≥ 65 years	- Never used - Past use - current use of estrogens (alone or combined)	Lower mean BMI and WHR for current users vs non users
Kritz-Silversteinand Barrett-Connor (1996)	Prospective (15-year follow-up) The Rancho-Bernardo Study USA	Upper middle-class community 671 postMp W 65-94 years at entry	use for the 15 years - estrogen never used - intermittent use - continuous use	Lower mean BMI at baseline for continuous users vs never users But no differences in change of BMI during the follow-up

use (Barrett-Connor et al., 1989). In the Cardiovascular Health Study, current users also had lower central adiposity, as measured by the Waist-to-Hip Ratio (Manolio et al., 1993).

As concerns longitudinal data, after a 15-year follow-up of 671 postmenopausal women over 65 years at entry, there were no differences in BMI changes between women who were continuous estrogen users, intermittent users or never users (Kritz-Silverstein et Barrett-Connor, 1996).

Critical analysis

Clinical studies suggest that transdermal 17 β-estradiol has a beneficial effect on glucose metabolism decreasing fasting insulin levels and increasing hepatic insulin clearance (Cagnacci et al., 1992). In contrast, the effect of oral CE could be dose-dependent : high doses may have detrimental effects on carbohydrate metabolism (Lindheim et al., 1993). Oral preparations result in high steroid concentrations in the liver, the major site of insulin processing and action. Thus, it is possible that the transdermal route could be more favourable than the oral route as regards insulin and glucose metabolism, because of a lesser impact on the liver.

In addition, progestogens may produce adverse effects on glucose and insulin metabolism. In a randomized placebo-controlled trial, the combination of transdermal 17β-estradiol with norethisterone acetate had no effects on carbohydrate metabolism (Godsland et al., 1993). Moreover, the combined oral CE/norgestrel phase of treatment, compared with estrogen alone, was associated with a deterioration of glucose tolerance, an increase in insulin resistance and alterations of insulin secretion (Godsland et al., 1993). Further studies are needed to assess whether the use of less androgenic progestogens could avoid these negative changes.

There is no evidence of an increased incidence of diabetes in women on HRT (Manson et al., 1992). However, some lipid and lipoprotein disturbances have been observed in diabetic users of oestrogen replacement therapy (Robinson et al., 1996). The changes in terms of weight (Anderson et al., 1997) and blood pressure (Mosnier-Pudar et al., 1991) were small or absent, and their importance is unknown.

A decade ago, Maschkak et Lobo (1985) reviewed epidemiological and clinical studies assessing postmenopausal estrogens, with or without added progestogens, in relation to SBP and DBP. Few studies have since been conducted.

According to the most carefully designed studies, blood pressure does not change with estrogen therapy in normotensive subjects (Utian, 1978 ; Notelovitz et al., 1987 ; PEPI, 1995). Consequently, the positive relationships observed in some cross-sectional studies may be due to the pretreatment

characteristics of postmenopausal women. In addition, the potential reduction in blood pressure is perhaps not sufficient to have a marked clinical effect on the development of atherosclerosis.

As for hypertensive postmenopausal women, Bealeet Collins (1996) noted that one study found no effect of HRT on blood pressure in patients with hypertension. However, because of the lack of randomized placebo controlled studies, no conclusions can be drawn concerning an association between HRT and hypertension.

The results concerning the impact of HRT on weight differ according to the type of studies. The lower mean BMI observed in current estrogen users in observational studies may be attributed to their better cardiovascular profile at baseline. As regards clinical trials, HRT does not normally cause a significant increase in weight or in BMI (Utian, 1978 ; Cagnacci et al., 1992 ; Conard et al., 1995 ; PEPI, 1995). Weight increases with age. In contrast, replacement hormones after menopause may improve the redistribution of fat by limiting the android pattern (Haarbo et al., 1991). This observation may be of importance since central fat is associated with other adverse metabolic changes, such as increased triglyceridemia, blood pressure and insulin resistance, as well as decreased HDL-cholesterolemia.

To conclude, the favourable impact of HRT on carbohydrate metabolism may depend on the estrogen products, the dose, the route of administration and on the androgenicity of the added progestogen. The studies involving estrogen and blood pressure showed slight decreases or no changes in blood pressure. HRT may prevent the atherogenic body-fat distribution (android) which occurs after menopause. However, for diabetic women, the use of HRT needs to be fully weighed up.

Finally, it is important to remember that most studies have been conducted in the United States where the cardiovascular risk and the estrogen/progestogen products are different from in France. Thus, the benefit of HRT needs to be clearly established in the French context in a large randomized placebo-controlled study.

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