4

Influence of HRT on lipid metabolism

The loss of female hormones (mainly estrogens) after menopause is associated with a worsening of certain cardiovascular disease (CVD) risk factors such as lipid and lipoprotein metabolism. The effects of estrogens on the metabolic pathways of lipoprotein subfractions have been studied (Fahraeus, 1988; Samaan et al., 1995)

To assess the impact of HRT on lipid metabolism and related blood parameters, more than 50 different studies dealing with HRT effects in postmenopausal women have been analysed here.

Preliminaries

The first issue is to choose the appropriate lipid and lipoprotein variables to assess this impact, as discussed in chapter 3.

The second major issue is that treatments differ in administration route, dose and type of estrogen. Estrogens may be natural or synthetic and dosages depend upon their potency. The administration of estrogens alone to postmenopausal women has been shown to increase the risk of endometrial carcinoma. Thus, a progestogen is frequently administered either cyclically (to induce a monthly withdrawal bleed) or continuously (to induce amenorrhoea). Progestogens may have various androgenic properties which could abolish estrogen benefits.

The third major issue is the design of studies to assess the effect of HRT. The most desirable design would be a randomised, placebo-controlled, double-blind trial including enough subjects to test the different combinations of estrogens and progestins.

The objective of this analysis was to select lipid and/or lipoprotein variables consistently related to the postmenopausal loss of female hormonal function and to analyse their modifications according to the HRT prescribed.

Major biases are associated with such trials, related to the indication, treatment duration, age of patients and type of menopause (natural or surgical) and also to the impossibility of comparing metabolic modifications according to the administration route. The studies analyzed have been classified in five

different groups in descending order of evidence, from randomized placebo-controlled studies to uncontrolled studies. Blinding is often precluded by the occurrence of cyclic bleeding on HRT.

Twenty studies published since 1990 have been retained because they provided full protocol descriptions and quantitative relative values of lipid and lipoprotein variables which were either statistically significant or considered significant. Modifications were expressed as the percentage change from the values obtained either in the placebo group in placebo-controlled studies or during the appropriate period in cross-over studies. In active treatment studies, controlled but without a placebo group, modifications were expressed as a percentage of change from baseline. In cross-sectional uncontrolled studies, modifications were expressed as a percentage of change from the non HRT group.

A detailed review of the studies published between 1984 and 1990 is provided by Rijpkema et al. (1990). The present analysis focused on the most recent ones.

Randomised placebo controlled studies

These studies, offering the highest quality, are described in table 4.I. Their duration ranges from three weeks to three years. Three out of seven are cross-over. Two included surgical menopause and estrogens alone ; two included natural menopause and estroprogestogen treatment or estrogen alone in one of these two ; two included both surgical and natural menopause and both estrogen alone and combined HRT. Overall, 1 262 women were included, most of them over 43 years old, except in one small study involving surgical menopause (Griffin et al., 1993). In all these studies, HRT consistently decreased TC (range –4 to –9 %), LDL (range –6 to –24 %), apoB (range –5 to –21 %) and Lp(a) (range –10 to -19 %), and increased HDL (range 7 to 21 %), HDL2 (range 23 to 59 %), HDL3 (6 %), TG (range 7 to 38 %), VLDL (range 16 to 30 %) and apoA1 (range 14 to 15 %). One small study (Griffin et al., 1993) reported an increase in small dense LDL particles.

However, all these changes occurred differently according to the type of HRT : estrogen alone had all the above effects, while combination HRT reduced or abolished the HDL increase and reduced the TG increase.

All estrogen-alone treatments seem to give similar effects, except transdermal estradiol, but the duration of this study was short (six weeks) and the number of subjects treated (nine) was small (Walsh et al., 1991). Equivalent active doses of conjugated or natural estrogens seem to have similar effects.

C21 and C19 progestogens but not natural progesterone abolished the effect of estrogens on HDL. The effect on LDL remained mostly unchanged. Cyclic

Table 4.I : Effects of postmenopausal HRT on lipids and lipoproteins : results of randomised placebo controlled studies

Authors	Group definition	N	Age	Study period	Percentage change from the baseline									
					TC	LDL	HDL	HDL2	HDL3	VLDL	TG	ApoA1	ApoB	Lp(a)
Walsh et al., 1991	USA, cross-over, NatMp		43-69	nr										
	• CE 0.625 (mg/day), 3 months	31			–4	–15	+16	+50	+6	+16	+24			
	• CE 1.250 (mg/day), 3 months	31			–6	–19	+18	+59	+6	+30	+38			
	• E2M, 6 weeks	9			ns	–14	+15	+39	ns	ns	+24			
	• E2T, 6 weeks	9			ns	ns	ns	+23	ns	ns	ns			
Haarbo et al., 1991	Denmark, 12 weeks, NatMp		45-55	nr										
	• E2V+CPA continuous	24			–5	–6	ns					ns	ns	
	• E2V+MPA cyclic	23			–9	–14	ns					ns	–9	
	• Placebo	25												
	• E2+DG cyclic	24			–6	–11	ns					ns	–8	
	• E2V+LNG cyclic	23			–7	–11	ns					ns	ns	
	• Placebo	20												
Griffin et al., 1993	UK, 16 weeks, SurMp		28-51	nr										
	• E2V	12			ns	ns	+12	+24	ns	ns	ns	+14	ns	
	• Placebo	5												
PEPI trial, 1995	USA, 3 years, NatMp and SurMp		45-64	89-94										
	• CE 0.625	175			ns	–10	+9				+14			
	• CE 0.625+MPA cyclic	174			–6	–13	ns				+14			
	• CE 0.625+MPA continuous	174			–6	–12	ns				+11			
	• CE 0.625+MP cyclic	178			ns	–11	+7				+14			
	• Placebo	174												
Haines et al., 1996a	Hong-Kong, 12 months, cross-over, SurMp	91	44±5	nr										
	• E2	91			–4	–15	+13	+41	ns		+7	+15	–5	–10
	• Placebo													
Tonstad et al., 1996	Norway, 48 weeks, NatMp		nr	nr										
	• E2+NETA continuous/cyclic	46				–23	ns						–21	–19
	• Placebo	29												
Anderson et al., 1997	Sweden, 68 days, cross-over, NatMp		45-65	nr										
	and SurMp	25			–9	–24	+21				ns			
	• E2	25												
	• Placebo													

and continuous administration of progestogen had a similar impact on the lipid profile.

Other studies

Table 4.II presents two placebo-controlled studies. The study reported by Kim et al. (1996) was not randomised because surgically menopaused women were all assigned to estrogen alone. However, its results are consistent with the studies reported above and of mostly equivalent value. Moreover, Lp(a) seemed to decrease whatever the HRT used. The second study (MRC GP Research Framework, 1996) tested the effect of norgestrel following surgical menopause. In women treated with conjugated estrogen norgestrel did not modify the decrease in TC and LDL but decreased HDL and TG.

Studies presented in table 4.III did not included placebo or reference groups but they are mostly consistent with the previous ones (although most dealt with small samples).

Table 4.IV presents cross-sectional observation studies. The type of treatment is frequently omitted. Most of them describe a decrease in TC and LDL, an increase in HDL (mainly in the HDL2 subfraction) and in TG. Only one study was discordant concerning TG (Dallongeville et al., 1995). ApoA1 levels were increased, while apoB and Lp(a) were decreased.

Two small uncontrolled studies with consistent results are shown in table 4.V. Rajman et al. (1996) and Griffin et al. (1993) reported an increase in small dense LDL particles.

Critical analysis

The best way to assess the effect of HRT on the lipid and lipoprotein profile consists of estimating changes in randomized placebo-controlled studies. Unfortunately such studies are rare given the multiple combination of products, doses, administration routes and cyclic or continuous combinations of hormones. Given the various effects of such combinations, it is very difficult in 1 262 subjects to draw any firm conclusions on the best way to improve the lipid profile.

The non placebo controlled groups are subject to regression to the mean bias. However, despite this bias, consistent results were obtained. But these studies dealt with too few women. All but one included surgically menopaused women and thus estrogens alone were prescribed.

Some clues can be obtained from observational studies. But the cross sectional design has several severe limitations. To begin with, the comparison of postmenopausal with premenopausal women is confounded by age.

Table 4.II : Effects of postmenopausal HRT on lipids and lipoproteins : results of other controlled studies

Authors	Group definition	N	Age	Study period	Percentage change from the baseline									
					TC	LDL	HDL	HDL2	HDL3	VLDL	TG	ApoA1	ApoB	Lp(a)
Kim et al., 1996	Korea, 1 year, NatMp and SurMp		29-71	1991-1993										
	• CE 0.625 (mg/day) (S only)	140			ns	−11	+16			ns	+9			−37
	• CE 0.625+MPA cyclic (5mg/d)	97			−4	−14	+11			ns	ns			−27
	• CE 0.625+MPAcyclic (10mg/d)	109			−4	−11	+14			−23	−10			−30
	• E2V+NG cyclic	134			−13	−18	ns			−31	−33			−30
	• Placebo	71												
MRC GP Research Framework (1996)	UK, 1 year, SurMp		51±6	1991-1994										
	• CE 0.625	86			−5	−14	+8				+24			
	• CE 0.625 + NG cyclic	99			−9	−13	ns				ns			

Table 4.V : Effects of postmenopausal HRT on lipids and lipoproteins : results of uncontrolled studies

Authors	Group definition	N	Age	Study period	Percentage change from the baseline									
					TC	LDL	HDL	HDL2	HDL3	VLDL	TG	ApoA1	ApoB	Lp(a)
Van der Mooren et al., 1993	The Netherlands, 2years,NatMp E2+DD	23	49-59	1990	−9	−18	+13			ns	ns	+16	ns	−16
Rajman et al., 1996	UK, 6 weeks, SurMp, CE 0.625 (mg/day)	17	30-52	nr	−9	−22	+21				ns			

Table 4.III : Effects of postmenopausal HRT on lipid and lipoprotein : results of controlled studies with active treatment, without placebo group.

Authors	Group definition	N	Age	Study period	Percentage change from the baseline									
					TC	LDL	HDL	HDL2	HDL3	VLDL	TG	ApoA1	ApoB	Lp(a)
Muesing et al., 1992	USA, 3 months, SurMp		40-60	nr										
	• CE 0.625 (mg/day)	31			–5	–15	+12	ns	ns	ns	+19	+13	–9	
Van der Mooren et al., 1994	The Netherlands, randomized, 1 year, SurMp		50-59	nr										
	• CE 0.625	18			–2	–11	+25	+47	+18	ns	+23	+23	ns	
	• CE 0.625+MED cyclic	15			–7	–14	+12	+24	+11	ns	ns	+15	ns	
Watts et al., 1995	USA,randomized, 2years, SurMp		21-60	nr										
	• CE 1.250	31			–5	–11	+7				+20	+8	ns	
	• CE 1.250+MT	29			–9	ns	-16				-30	-21	ns	
Bruschi et al., 1996	Italy, 1 year, SurMp		46-53	1993-1994										
	• CE 0.625	19			–15	–42	+26				+37			–38
Haines et al., 1996b	Hong-Kong, 12 months, NatMp		42±9	nr										
	• E2+MPA cyclic	39			–5	–9	ns	ns	ns		ns	+6	–4	–19
Haines et al., 1996c	Hong-Kong, 12 months, SurMp		43±4	nr										
	• E2G	26			ns	ns	ns	ns	ns		ns	ns	ns	ns

Table 4.IV : Effects of postmenopausal HRT on lipids and lipoproteins : results of cross sectional uncontrolled studies

Authors	Group definition	N	Age	Study period	Percentage change from the baseline									
					TC	LDL	HDL	HDL2	HDL3	VLDL	TG	ApoA1	ApoB	Lp(a)
Egeland et al., 1990	USA, Healthy Women Study, Pittsburgh, NatMp	211	42-50	1983-1985										
	• CE	15			ns	–5	+7				+49	+14	ns	
	• CE+MPA	39			ns	ns	ns				+37	+13	ns	
Hong et al., 1991	USA, coronarography series, NatMp and Sur Mp	90	≥55	nr										
	• E	18			ns	ns	+31				ns			
Nabulsi et al., 1993	USA, Atherosclerosis Risk In Communities (ARIC), NatMp and Sur Mp	4 958	45-64	1986-1989										
	• E	855				–13	+19	+38	+12		+11	+16	–6	–16
	• E+P	173				–13	+21	+38	+12		ns	+14	–6	–33
Vaziri et al., 1993	USA, Framingham Offspring Study, type Mp: not reported	938	56±7	1983-1987										
	• CE 0.625 (mg/day)	52			ns	ns	+10				ns	+13	ns	
	• CE 0.625+MPA cyclic	28			ns	–11	+10				ns	+14	ns	
Dallongeville et al., 1995	France, Lille health care centre, HRT excluded, NatMp	1 746	45-65	1991-1993										
	• E+P	369			–5						–16	ns	–8	
Salomaa et al., 1995	Finland, type Mp: not reported	1 202	45-64	1992										
	• HRT	351			–5	–7	+3				ns			ns
Robinson et al., 1996	USA, Atherosclerosis Risk In Communities (ARIC), type Mp: not reported	4 569	45-64	1987-1989										
	• HRT	1 217			–3	–13	+20	+37	+13		+13	+14	–5	

Secondly, the type of drug, the time of ingestion, compliance and the duration of the treatment are mostly unknown. Thirdly, following the decision to treat, a population at lower risk of CVD can be selected on the basis of contra-indications such as dyslipidemia or pre-existing CVD. Moreover, wealthier and better educated women would be more inclined to adhere to such treatments. Finally, more frequent medical controls may be suspected as a direct consequence of the ongoing treatment, thus favouring a better cardiovascular prevention.

An in-depth analysis of potential biases can be found in several reviews (Seed, 1994 ; Stevenson, 1995 ; Sullivan, 1994 ; Tikkanen, 1996 ; Rijpkema et al., 1990 ; Stampfer and Colditz, 1991).

To conclude, as expected from numerous studies, HRT can significantly improve the lipid and lipoprotein profile in postmenopausal women. To date, this conclusion is supported (quantitatively or not) by a large number of epidemiological studies. The main effects comprise a decrease in TC and LDL obtained with estrogens both alone and combined. A major increase in HDL, attributed massively to the HDL2 protective subfraction, is observed with estrogens alone, but not with their combination with progestogen. According to some authors (Bush, 1996) who consider that, in women, HDL seems to be a more potent predictor of major cardiovascular events than LDL or TC, it can be concluded that the increase in HDL should be preserved. The use of natural progesterone may be a solution, since it reduces but does not abolish the HDL increase. On the other hand, estrogens tremendously increase TG and VLDL, meaning that an increase in the risk of pancreatitis and consequently in CVD may be feared. The use of parenteral routes may be tested to avoid the hepatic first pass effect. However, the benefit in terms of HDL increased may be severely reduced. Finally, a marked decrease in Lp(a) is obtained, but its role as a risk factor is still controversial.

Until now, the only study that affords some help to prefer one or other type of HRT is the PEPI trial (1995) that suggested a favourable effect of conjugated estrogen combined with natural progesterone in a randomized double-blind placebo-controlled study including 875 postmenopausal women. Thus larger trials including oral or parenteral estrogens combined with either medroxyprogesterone acetate or natural progesterone are urgently needed.

A secondary prevention trial, the HERS study, is currently in the pipeline (Schrott et al., 1997). This trial dealing with postmenopausal women with heart disease may answer the question of whether HRT protects against CVD. After such a trial, it may be unethical to continue placebo-controlled trials. Moreover, because of its favourable impact on other outcomes such as osteoporosis and cognitive functions (Wickelgren, 1997), HRT is spreading in the industrialised countries and it will soon be too late and very difficult to randomize a placebo-controlled study.

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