3

Changes in lipid metabolism in postmenopausal women

Because the effect on CVR is only observed ten to fifteen years following menopause, the mechanisms whereby CVR increases with menopause have not been explained satisfactorily. The most likely explanation is the loss of female hormonal function and its impact on major CVD risk factors such as lipid and lipoprotein blood levels and other factors involved in atherosclerosis.

Impact of menopause on lipid metabolism

Approximately thirty different epidemiological studies have been analysed to assess the impact of menopause on lipid metabolism and related blood parameters. These studies, devoted to an evaluation of these variables in post-menopausal women, were performed between 1948 and 1993. Within these 45 years, the concept of lipids and lipoproteins as risk factors has evolved tremendously and many variables related to the risk of CVD have been characterised. At the moment, almost thirty different blood parameters are available, most of them described less than a decade ago. Thus, this analysis has been focused on the ten most explored variables : total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL) and its subfractions HDL2 and HDL3, the very low density lipoproteins (VLDL), triglycerides (TG), apolipoproteins A1 (apoA1) and B (apoB) and lipoprotein a (Lp(a). For chronological reasons, all these variables could not be explored in all the studies retained. They may represent either risk factors (TC, LDL, apoB) or protective factors (HDL, apoA1), and others are still under discussion (HDL2, HDL3, VLDL, Lp(a), TG). Some studies report more recent lipid and lipoprotein variables and confirm the trends obtained with conventional variables.

Two major types of studies were analysed : longitudinal studies consisting in a follow-up from the occurrence of menopause of womens cohorts ; and transversal studies, cross sectional population-based or case-control studies, comparing menopausal women with controls. Studies involving large numbers of subjects have been favoured to ensure maximal statistical significance.

The objective of this analysis was to select lipid and/or lipoprotein variables consistently related both to the loss of female hormonal function at menopause and to CVD occurrence in various countries.

Given the difficulty in defining an unbiased control group, case-control designs are rare. In fact, there is a systematic difference in age between cases (postmenopausal women) and controls (non postmenopausal women, i.e. premenopausal or reproductively active women) ; this difference affects lipid and lipoprotein blood levels (Sacks and Walsh, 1990) and impairs the quality of age-adjustments. Consequently, longitudinal studies following variations of lipid and lipoprotein variables in the same women before and after menopause were retained in this analysis. However, the very long follow-up period (up to ten years) needed in these expensive studies limits the number of lipid and lipoprotein parameters available at their beginning. Thus, observational transversal studies conducted as part of longitudinal and population-based epidemiological studies were also analysed. In these last reports, numerous lipid and lipoprotein parameters were available.

The different studies (tables 3.I and 3.II) were selected because the quantitative values they provide are shown to be statistically significant or can be considered as such : in longitudinal studies changes were estimated from baseline values ; in transversal studies, they were estimated from the values obtained in menopausal versus non menopausal women. In fact, the absence of international standardization in the measurement techniques precludes any conclusions from absolute values. The above approach allows to compare different studies. Some trends, reported in other selected studies, are unquantifiable (mainly because the information is not presented in a way suitable to appreciate modifications) but they are described below because they may improve the consistency of the overall data.

Changes in postmenopausal lipid profiles in longitudinal studies

Five longitudinal population-based studies (table 3.I) report quantitative changes in lipid and lipoprotein variables. In American, European and Asian populations an increase in TC was always observed (range 5 to 19 %), and an increase in LDL (range 6 to 10 %) was seen in an American and a European study. Such a tendency was also reported for TC and LDL in two other American studies, the Framingham Offspring Study (Anderson et al., 1987) and the Lipid Research Clinic Study (Bush et al., 1983), as well as in the Swedish Göteborg study (Lindquist et al., 1982).

In the Healthy Women Study (Matthews et al., 1989), the Danish study (Jensen et al., 1990) and the Framingham Offspring Study (Anderson et al., 1987) a significant decrease in HDL (range –6 % to –8 %) was reported, but not in the Framingham study (Kannel et al., 1976).

Table 3.I : Lipid and lipoprotein changes in postmenopausal women: results of longitudinal studies.

Authors	Population	N	Age range	Study period	Percentage change from baseline									
					TC	LDL	HDL	HDL2	HDL3	VLDL	TG	ApoA1	ApoB	Lp(a)
Hjortland et al., 1976	USA, Framingham study NatMp and SurMp	1 686	40-51	1948-1966	+7									
Matthews et al., 1989	USA, Healthy Women Study, Pittsburgh - NatMp	541	42-50	1983-1989	+5	+6	–6	ns	ns		+3	+3	+3	+6
Jensen et al., 1990	Denmark, type Mp: not reported, follow-up: 2 to 3 years	170	30-75	nr	+6	+10	–8				+11			
Van Beresteijndal et al., 1993	The Netherlands, type Mp: not reported	167	49-56	1979-1989	+19									
Akahoshi et al., 1996	Japan, Radiation Effect Research Foundation, Nagasaki NatMp and SurMp	713	35-58	1958-1989	+17									

In the Framingham Offspring Study (Anderson et al., 1987), the Healthy Women Study (Matthews et al., 1989), the Danish study (Jensen et al., 1990) and in the Swedish Göteborg study (Lindquist et al., 1982) an increase in TG was consistently reported.

The most recent study, the Healthy Women Study (Matthews et al., 1989), also reported an increase in apolipoproteins A1, B and Lp(a).

Changes in postmenopausal lipid profiles in transversal studies

Out of the fourteen studies dealing with TC (table 3.II), this variable was shown to be significantly increased in thirteen (range 9 to 25 %) and non significantly increased in one. A marked but unquantifiable increase in TC was also reported in a transversal analysis of the Healthy Women Study (Eichner et al., 1990).

This increase in TC can be partly explained by the increase in the LDL fraction observed in all the studies (range 15 to 58 %). Concerning HDL, the other main fraction of TC, it was found increased in three studies (range 8 to 15%), decreased markedly in three (range –7 to –23 %), apparently lowered in two others (Eichner et al., 1990 ; Meilhan et al., 1991) and not significantly modified in eight. One of the two major fractions of HDL, HDL2, was decreased in one study (Stevenson et al., 1993) and non significantly modified in three others. Conversely, the second major fraction of HDL, HDL3, was found increased in three studies (range 5 to 9 %) and non significantly modified in one.

Triglycerides were consistently increased in all the studies (range 6 to 70 %). Only one study did not find a significant modification (Campos et al., 1998). Similarly, VLDL was increased in all studies (range 11 to 64 %) but one, in which the variation was not significant (Campos et al., 1998).

ApoA1 was increased in two studies (range 4 to 6 %) and in a transversal analysis of the Healthy Women Study (Eichner et al., 1990). In all other studies apoA1 did not vary significantly in postmenopausal women.

Conversely, apoB was significantly increased in five studies (range 12 to 25 %) and in the transversal analysis of the Healthy Women Study (Eichner et al., 1990). Only one study did not show a significant variation (Campos et al., 1998).

Lp(a) was significantly increased in all but one study (range 19 to 143 %).

Another recent lipoprotein parameter, the size of LDL, was explored in transversal analyses of the Framingham Offspring study (Schaefer et al., 1994 ; Li et al., 1996). Two major groups of LDL have been described : a large and buoyant fraction associated with a lower cardiovascular disease risk, and a small and dense fraction associated with a higher risk. Postmenopausal

Table 3.II : Lipid and lipoprotein changes in postmenopausal women: results of transversal studies

Authors	Population	N	Age	Study period	Percentage change from the baseline									
					TC	LDL	HDL	HDL2	HDL3	VLDL	TG	ApoA1	ApoB	Lp(a)
Lindquist et al., 1980	Göteborg, Sweden, NatMp	596	≥50	1968-1975	+10						+70			
Shibata et al., 1987	Japan, NatMp	787	45-54	1980-1983	+10		ns							
Campos et al., 1988	USA, Framingham Offspring study, NatMp	163	49±10	nr	ns	+16	ns			ns	ns	ns	ns	
Bonithon-Kopp et al., 1990	France, Paris health care centre, HRT excluded, NatMp and SurMp	435	45-54	1986-1988	+13	+16	ns				+21	+4	+15	
Wu et al., 1990	China, NatMp	598	40-54	1987	+12		+15				+23			
Heinrich et al., 1991	Germany, type Mp not reported	373	16-65	1989										+143
Razay et al., 1992	UK, menopause defined as age≥50, HRT excluded, type Mp not reported	394	40-69	1987-1989	+19		+8	ns	+9		+31			
Jenner et al., 1993	USA, Framingham Offspring study, type Mp not reported	1 394	≥20	nr										+19
Slunga et al., 1993	Sweden, type Mp not reported	782	25-64	1990										+34
Brown et al., 1993	USA, Atherosclerosis Risk In Communities (ARIC), type Mp not reported	8 005	45-64	1986-1989		+17	ns	ns	ns			ns	+12	

Table 3.II : Lipid and lipoprotein changes in postmenopausal women: results of transversal studies *(continued)*

Authors	Population	N	Age	Study period	Percentage change from the baseline									
					TC	LDL	HDL	HDL2	HDL3	VLDL	TG	ApoA1	ApoB	Lp(a)
Stevenson et al., 1993	UK, NatMp	542	18-45	nr	+14	+27	–7	-25	+7		+12			
Schaeffer et al., 1994a, 1994b	USA, Framingham Offspring study, type Mp not reported	1 597	49±10	nr	+19	+24	ns			+50	+49	ns	+24	
Salomaa et al., 1995	Finland, type Mp not reported	1 202	45-64	1992	+9	+11	ns				ns			ns
Dallongeville et al., 1995	France, Lille health care centre, HRT excluded, NatMp	2 167	45-65	1991-93	+9						+20	+6	+18	
Williams et al., 1996	USA, type Mp not reported	220	44±10	nr	+17		ns				+65			
Hunter et al., 1996	USA, type Mp not reported	220	17-77	nr	+18	+15	ns	ns	+5	+64	+70			
Li et al., 1996	USA, Framingham Offspring study, type Mp not reported	146	49±7	nr	+16	+23	–8			+65	+62	ns	+25	
Senöz et al., 1996	Turkey, NatMp and SurMp	86	19-67	1992-94	+25	+58	–23			+11	+14			
Sunayama et al., 1996	Japan, angiography series, menopause defined as age≥55, HRT excluded, type Mp not reported	354	60±10	1987-93		+21	+11				+6			+27

women have a decrease in the percentage of the large and buoyant LDL fraction (Austin et al., 1988).

Other sophisticated variables explored in the Framingham Offspring study (Li et al., 1996) were modified, with an increase in the B-containing lipoproteins (LpB, LpB:CIII, LpB:E) which have all been associated with an increased risk of CVD, and a non significant variation in A1-containing-lipoproteins (LpA1, LpA1:A2) highly correlated with HDL fractions.

Critical analysis

Longitudinal studies clearly demonstrate that menopause precedes a consistent rise in TC. As explored in the Framingham study (Hjortland et al., 1976), this rise is due to a general displacement toward higher values in all postmenopausal women and not to a sharp rise in TC levels in only a restricted number of women. A sharper rise was observed within the three years preceding menopause and the following year (Van Beresteijn et al., 1993 ; Akahoshi et al., 1996). Thus, the menopause-associated rise in TC is not explained by a tendency of TC to increase with age (Sacks and Walsh, 1990). Another point confirming the consistency of the association between TC increase and menopause is the information brought by the type of menopause. Indeed, natural menopause and surgical bilateral oophorectomy-induced menopause showed the same trend, in contrast with unilateral oophorectomy. However, because in longitudinal studies data are collected during a long period (at least 10 years), two biases may arise : firstly, the methods used for TC measurement have evolved with time, but the results are often adjusted for this bias ; secondly, a cohort effect has been observed in Japanese subjects who were born recently, i.e. TC levels are higher although they have been measured in age-matched subjects (Akahoshi et al., 1996). Except in the most recent report (Matthews et al., 1989), longitudinal studies did not take into account the use of hormone replacement therapy (HRT). However, in these populations recruited 15 to 40 years ago, such therapy was rarely prescribed and only for short periods. Finally, lipid and lipoprotein variables other than TC were mostly not available at the time of recruitment. Although less accurate, all the transversal studies also reported a significant increase in TC, except the Campos' report (1988) in which the statistical power was too low to detect any difference.

Conversely, HDL changes are inconsistent. Three longitudinal studies out of four and three transversal studies out of fourteen reported a decrease in HDL levels. Three transversal studies reported an increase, and most of the others did not show any significant changes. However, if the HDL subfractions are considered, HDL3 tends to increase while HDL2 tends to decrease. Conversely, if apoA1, one of the major protein components of HDL, is taken into account, an increase in this protein is mostly found, and no variation in the

related lipoparticles enriched in this apolipoprotein (i.e. LpA1 and LpA1:A2, Li et al., 1996). In postmenopausal women, HDL levels seem to be more strongly influenced by environmental determinants (sedentarity, alcohol consumption, body mass index) as shown by Cauley et al. (1982) and Williams et al. (1996), than by genetic determinants (Harris et al., 1993).

LDL cholesterol levels were also consistently increased in all the studies (longitudinal or transversal) in which it was measured. The same observation was reported for TG, that was consistently increased in all studies but one, for the same reasons as above (Campos et al., 1988). Similarly, apoB levels, correlated with LDL levels, are consistently increased. The increased percentage of small dense LDL particles adds to the overall risk increase

TG are consistently increased in postmenopausal women. This observation is reported in almost all the relevant longitudinal and transversal studies. Moreover, the VLDL fraction, which correlates with TG levels, is also increased.

Finally, Lp(a) is consistently increased in postmenopausal women. It represents a controversial risk factor since it can induce a cardiovascular event linked either to the lipid metabolism or to a thrombotic event.

Although all these longitudinal and transversal studies differ in terms of population sampling, assay methods, adjustments for other risk factors and HRT, and statistical power, consistent results are obtained.

To conclude, lipid and lipoprotein profiles worsen in postmenopausal women. This appears within three years before menopause and persists thereafter, supporting the hypothesis that the cardiovascular disease risk increases gradually, given the time needed for atherosclerotic lesions to build up.

This worsening consists of an increase in total cholesterol, LDL, apoB and apoB containing lipoproteins (for the established risk factors of CVD) and an increase in TG, VLDL fraction, and Lp(a) for the more controversial risk factors of CVD.

As regards the HDL fraction, a decrease in which is considered as a risk factor, things are less clear. However, a modification in the distribution of HDL subfractions, with an increase in HDL3 and a decrease in HDL2, may suggest a worsening of the risk. Moreover, the relatively higher increase in LDL fraction and in TG may also enhance the total cholesterol versus HDL ratio, which is considered as a major risk marker in some studies.

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