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ORIGINAL STUDY

Lipid profile changes during the menopausal transition

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Abstract

Objectives: There is evidence that the menopausal transition in women is accompanied by changes in the metabolic profile. We evaluated the lipid profile during the perimenopause to postmenopause transition and its association with menopausal status.

Methods: This is a retrospective observational study of laboratory studies from women presenting to the gynecology unit of Hospital Quirón Salud, Madrid (2007-2018) with irregular menstruation, amenorrhea or menopausal symptoms. Inclusion criteria were one or more blood samples with determinations of fasting glucose and lipids (total cholesterol, low-density lipoprotein cholesterol [LDL-c], high-density lipoprotein cholesterol [HDL-c] and triglycerides [TGs]) from women with a menopause diagnosis recorded in the hospital database. The determinations were classified as perimenopausal or postmenopausal based on the date of last menstruation.

Results: In total, 13,517 laboratory studies (3,073 perimenopausal and 10,444 postmenopausal) from 275 women were analyzed. Total cholesterol, LDL-c, and TG levels were significantly higher in postmenopausal women than in perimenopausal women, whereas HDL-c levels were significantly lower ($P < 0.05$ in all cases). Further adjustment by age showed differences only in LDL-c levels. Menopausal status, TG levels, and the number of pregnancies were independently related with total cholesterol and LDL-c levels. HDL-c levels were independently affected by menopausal age, TG levels, and number of pregnancies. Finally, TG concentration was independently affected by total cholesterol, LDL-c, and HDL-c levels.

Conclusion: Our study suggests that significant changes in LDL-c levels occur during the menopausal transition. Total cholesterol and LDL-c changes are independently affected by menopausal status and HDL-c is influenced by menopausal age.

Key Words: Lipid – Menopausal transition – Menopause – Perimenopause.

According to the World Health Organization, cardiovascular disease is the main cause of mortality in women older than 60 years.[1] In Europe in 2016, the most common cause of death in women was ischemic heart disease, with 3,220,000 deaths in the age group 50 to 59 years, and 9,560,000 deaths in the age group 60 to 69 years.[2] Factors associated with cardiovascular risk include metabolic changes such as dyslipidemia (high levels of total cholesterol and low-density lipoprotein cholesterol [LDL-c] and low levels of high-density lipoprotein cholesterol [HDL-c]) and obesity.[3]

The loss of ovarian function produces a number of physiological changes that may impact health.[4] Although several studies have suggested that the menopausal transition is accompanied by unique changes in the metabolic profile, but these changes may not clearly be related to menopause.[5] The Study of Women's Health across the Nation (SWAN) evaluated data from 3,302 minority and white women during the menopausal transition and found that 1,054 achieved postmenopausal stage within 10 years of follow-up.[6] The study found a significant increase in total and LDL-c independently of aging, but an aging-related decrease in HDL-c levels.[6] Similarly, other studies have described variations in the lipid profile during menopause in Asian[7-10] and European populations,[11,12] but there is a paucity of studies testing these associations in the Spanish population.[13,14]

Our hypothesis was that changes in the lipid profile are associated with the menopausal transition. Accordingly, the main objective of the present study was to evaluate the changes in the lipid profile during the transition from perimenopause to postmenopause, and its association with menopausal status.

METHODS

This is a retrospective observational study of laboratory studies from women who came to the gynecology unit at Hospital

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Quirón Salud, Madrid, from 2007 to 2018 because of irregular menstruation, amenorrhea, or menopausal symptoms. The inclusion criteria were women with physician-diagnosed menopause recorded in the hospital database (menopause, perimenopause, climacteric symptoms) and, at least, having one blood sample with one or more of the following laboratory studies per patient: fasting glucose and lipid profile (total cholesterol, LDL-c, HDL-c, and triglycerides [TGs]). Data collected from blood samples were lipid profile, fasting glucose, glycated hemoglobin, uric acid, calcium, creatinine, free T4, thyroid-stimulating hormone, 25-hydroxi-vitamin D, albumin, and phosphorus. Unavailable or invalid data in the laboratory studies were excluded. Based on the 2011 Stages of Reproductive Aging Workshop criteria,[4] the determinations were classified as perimenopausal if the blood sample was taken up to 11 months after the date of last menstruation (DLM) or postmenopausal if it was taken 1 year after DLM (Fig. 1). Based on this classification two groups were created: perimenopausal determinations and postmenopausal determinations. Blood samples were taken after a 10-hour overnight fast. Plasma glucose, total cholesterol, HDL-c, and TG levels were measured by standard enzymatic methods. LDL-c concentration was calculated using the Friedewald formula.

The study was approved by the Investigation Ethical Committees of Hospital Quirón Salud Madrid and Fundación Jiménez Díaz (Madrid). Patient information was collected anonymously from the hospital database.

Qualitative variables were expressed as absolute (n) and relative (%) frequencies. The Kolmogorov-Smirnov test was used to evaluate the parametric behavior of the quantitative variables. Mean values ± standard deviation are given for normal distributions; for non-normal distributions, the data are reported as medians with interquartile range.

For quantitative variables, Student *t*, or Mann-Whitney *U* tests (depending on the normality distribution) were applied to analyze differences between perimenopausal and postmenopausal values. Chi-square or Fisher exact test were used for qualitative variables. For perimenopausal and postmenopausal comparisons, determinations were adjusted by age at the moment of the blood sample but not adjusted for lipid medications and hormone therapy as rises in lipids around the DLM would lead to treatment. To evaluate changes during the menopausal transition from the same woman, we have analyzed the determinations from a subgroup of women who had both perimenopausal and postmenopausal determinations with a pair-matched analysis (paired samples Student *t* or Wilcoxon test according to normality distribution). For these analyses, the mean value of the laboratory studies carried out during the perimenopause and the mean value of the laboratory studies carried out during the postmenopause for every woman were used. The regression analysis was made to assess the associations between the change in total cholesterol, LDL-c, HDL-c, and TGs and the variables included: menopausal status, laboratory study age, menopausal age, alcohol intake, familial history of cardiovascular disease, fasting plasma glucose

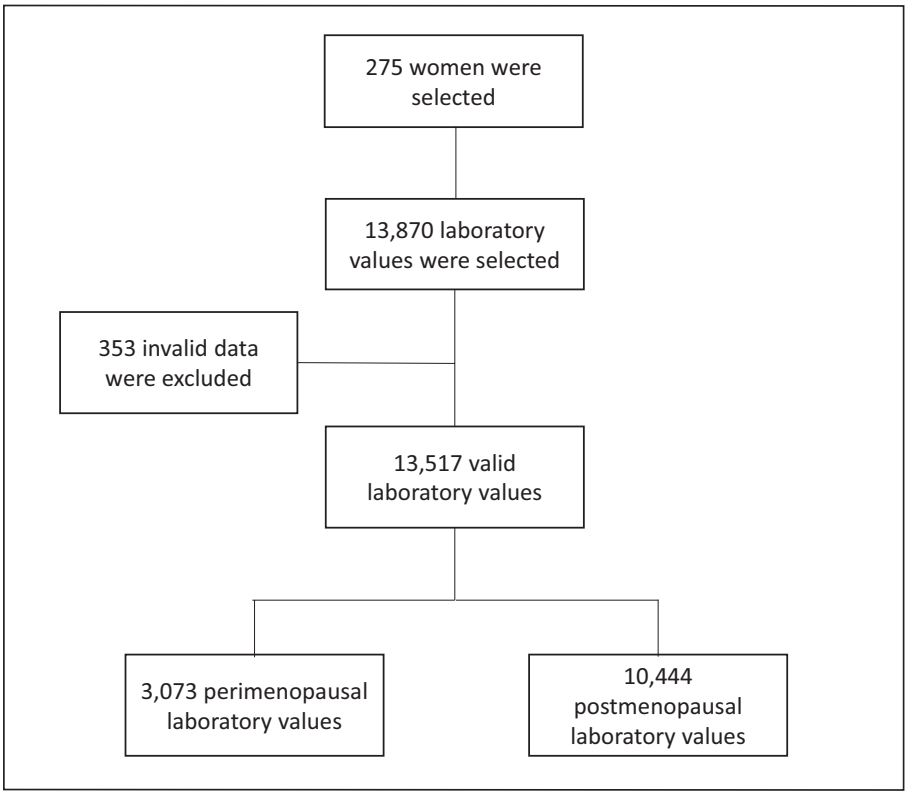

FIG. 1. Selection of laboratory studies. Laboratory values included lipid profile, fasting glucose, glycated hemoglobin, uric acid, calcium, creatinine, free T4, thyroid-stimulating hormone (TSH), 25 hydroxi-vitamin D, albumin, and phosphorus.

TABLE 1. *Characteristics of the women by menopausal status at the first blood sample*

Characteristics	Total (N women = 275)	Perimenopausal[a] (N women = 120)	Postmenopausal[a] (N women = 155)	*P*
Smokers, n (%)	49[b] (24.3)	18 (36.7)	31 (63.3)	0.382
Alcohol consumers, n (%)	13[b] (18.1)	8 (61.5)	5 (38.5)	0.064
Gestational diabetes, n (%)	6 (2.2)	4 (66.7)	2 (33.3)	0.088
Hypertension, n (%)	40 (14.55)	7 (17.5)	33 (82.5)	**0.030**
Cardiovascular disease, n (%)	70 (25.45)	21 (30.0)	49 (70.0)	0.624
Osteoporosis, n (%)	46 (16.7)	5 (10.9)	41 (89.1)	**0.001**
Osteoporotic fractures, n (%)	10 (3.6)	2 (20.0)	8 (80.0)	0.508
Family history				
Cardiovascular disease, n (%)	50 (18.2)	19 (38.0)	31 (62.0)	0.346
Diabetes, n (%)	47 (17.1)	23 (48.9)	24 (51.1)	**0.008**
Hypertension, n (%)	9 (3.3)	3 (33.3)	6 (66.7)	1.000
Osteoporosis, n (%)	14 (5.1)	3 (21.4)	11 (78.6)	0.559
Treatments				
Antidiabetics, n (%)	13 (4.73)	4 (30.8)	9 (69.2)	1.000
Lipid-lowering agents, n (%)	57 (20.7)	16 (28.1)	41 (71.9)	0.436
Anticoagulants, n (%)	13 (4.7)	3 (23.1)	10 (76.9)	0.558
Antihypertensives, n (%)	38 (13.8)	6 (15.8)	32 (84.2)	**0.019**
Antiosteoporotics, n (%)	43 (15.6)	4 (9.3)	39 (90.7)	**0.000**
Hormone therapy, n (%)	102 (53.1)	31 (30.4)	71 (69.6)	0.066
Hormonal contraception, n (%)	121 (75.2)	41 (33.9)	80 (66.1)	0.872
Antidepressants, n (%)	24 (92.3)	6 (25.0)	18 (75.0)	0.474

Boldface represents significant *P*-values.
Women characteristics were classified by menopausal status in the moment of the first analytic sample.
[a]Menopausal status in the moment of the first analytic.
[b]Available data from 202 women.

(FPG), total cholesterol, LDL-c, HDL-c, TGs, and number of pregnancies.

The values of each lipid profile component were represented by year before and after the DLM. A longitudinal model was performed to evaluate the change of each lipid profile factor by dividing the menopausal transition into two segments relative to the DLM: (1) before the DLM and up to 11 months after the DLM (perimenopause) and (2) more than 12 months after the DLM (postmenopause). To assess the potential changes of each lipid profile factor, we calculated the perimenopausal and postmenopausal slopes with crude values by month in the period from year −6 to year +6 (year + or − 6 also included those determinations with >6 years) regarding the DLM and comparisons between perimenopausal and postmenopausal slopes (unadjusted and adjusted by age at the moment of the blood sample) were assessed with *t* Student test. The results were adjusted by age at the moment of the blood sample.

A *P* value less than 0.05 was considered statistically significant. Data analysis was performed with the IBM-SPSS statistical software program, version 21.0 (IBM Inc., Chicago, IL).

RESULTS

From the 275 women that met the inclusion criteria, 49 had only perimenopausal blood samples, 70 had perimenopausal and postmenopausal blood samples and 156 had only postmenopausal blood samples, with a mean of 7.68 ± 10.48 blood samples/woman (see Supplement 1, http://links.lww.com/MENO/A565). The 2,112 blood samples collected included 13,517 laboratory values: 3,073 (22.7%) during perimenopause and 10,444 (77.3%) during postmenopause. There were 4,767 determinations from the lipid profile (1,049

TABLE 2. *Comparison of determinations according to menopausal status*

	Perimenopause (N = 2,685; n = 120)		Postmenopause (N = 9,272; n = 225)		*P*	
Determinations	N (n)	Mean ± SD/Median [IQR]	N (n)	Mean ± SD/Median [IQR]	Unadjusted	Adjusted by age
Total cholesterol, mg/dL	287 (107)	205.0 [49.0]	996 (140)	214.0 [54.5]	**<0.001**	0.124
LDL-c, mg/dL	245 (103)	122.7 ± 34.8	874 (135)	134.0 ± 35.7	**<0.001**	**0.035**
HDL-c, mg/dL	242 (101)	66.0 [17.3]	882 (136)	62.0 [20.0]	**<0.001**	0.584
Triglycerides, mg/dL	275 (107)	76.0 [41.0]	966 (137)	87.5 [45.0]	**<0.001**	0.072
Fasting glucose, mg/dL	445 (116)	92.0 [14.0]	1,459 (150)	96.0 [16.0]	**<0.001**	**0.002**
Creatinine, mg/dL	440 (117)	0.8 [0.2]	1,439 (150)	0.8 [0.2]	**0.002**	**0.005**
Uric acid, mg/dL	193 (90)	4.3 [1.8]	657 (113)	4.6 [1.5]	**<0.001**	0.706
Calcium, mg/L	161 (77)	94.0 [5.0]	633 (110)	95.0 [6.0]	**0.032**	**<0.001**
25 (OH) vitamin D, ng/mL	45 (47)	25.8 ± 10.6	283 (71)	28.6 ± 11.0	0.104	**0.017**
Free T4, ng/dL	147 (70)	1.1 [0.3]	441 (98)	1.1 [0.2]	0.650	0.367
TSH, mUI/L	205 (91)	1.3 [1.1]	642 (114)	1.7 [1.6]	**<0.001**	**0.024**

Boldface represents significant *P*-values.
Data from glycated hemoglobin, albumin, and phosphorus not shown.
HDL-c, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-c, low-density lipoprotein cholesterol; N, number of determinations; n, number of women; SD, standard deviation; TSH, thyroid-stimulating hormone.

TABLE 3. *Comparison of lipid profile factors according to menopausal status from subgroup of women with perimenopausal and postmenopausal blood samples*

	Perimenopause (N = 692; n = 70)		Postmenopause (N = 1,046; n = 70)		*P*	
Analytic value	N (n)	Mean ± SD/median [IQR]	N (n)	Mean ± SD/median [IQR]	Unadjusted	Adjusted by age
Total cholesterol, mg/dL	188 (58)	207.3 ± 38.1	280 (58)	220.5 ± 29.5	**0.010**	0.131
LDL-c, mg/dL	163 (55)	125.0 ± 35.9	241 (55)	136.5 ± 29.8	**0.011**	0.281
HDL-c, mg/dL	161 (53)	65.1 ± 15.4	247 (53)	67.8 ± 14.3	**0.037**	0.574
Triglycerides, mg/dL	180 (56)	83.4 [48.0]	278 (56)	77.9 [35.8]	0.218	0.269

Boldface represents significant *P*-values.
Not all the women had valid determination values for every lipid profile factor.
HDL-c, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-c, low-density lipoprotein cholesterol; N, number of determinations; n, number of women; SD, standard deviation.

[22.0%] perimenopausal and 3,718 [78.0%] postmenopausal). From those, we analyzed a subgroup of 1.738 lipid profile's laboratory values from women with perimenopausal and postmenopausal blood samples during the study period.

Characteristics of the women by menopausal status at the first blood sample are presented in Table 1. The mean age at the first blood sample was 46.7 ± 5.43 years (perimenopausal) and 58.2 ± 8.82 years (postmenopausal). A total of 93.4% of women (n = 254) have been pregnant, 25.1% (n = 68) have had a miscarriage and 20.5% (n = 55) a cesarean. Menopause was natural in 85.95% (n = 208) of the women, and the median age of menopause was 50 [5] years. Regarding cardiovascular risk factors, there were more postmenopausal women with hypertension, osteoporosis, or with familiar history of diabetes than among perimenopausal women at the moment of the first blood sample. Concerning treatments, 4.7% were receiving an antidiabetic, 20.7% a lipid-lowering agent, 13.8% an antihypertensive, 4.7% an anticoagulant, and 15.6% were taking an antiosteoporotic drug. There were more postmenopausal women taking an antihypertensive or antiosteoporotic treatment compared with perimenopausal women at the moment of the first blood sample. Almost 75% of women had used hormonal contraception and more than a half had received hormone therapy for a median of 4 (5) years. The median age of first menstruation was 13 (2) and the frequency of pregnancy was 2 (1) pregnancies per women.

Table 2 shows the differences between perimenopausal and postmenopausal laboratory values. When comparing the lipid profile, the postmenopausal samples showed a significantly higher level of total cholesterol (*P* value <0.001) and LDL-c (*P* value <0.001) than the perimenopausal samples. By contrast, HDL-c levels were significantly lower in the postmenopausal period (*P* value <0.001), whereas the TG concentration was significantly increased in postmenopause (*P* < 0.001). The *P* value adjusted by age at the moment of the blood sample showed significant differences in LDL-c (*P* value = 0.035) but not in total cholesterol, HDL-c, and TGs. When only considering for the analysis those women who did not receive any lipid-lowering agent and/or hormone therapy (n = 65), significant differences in total cholesterol and LDL-c between perimenopause and postmenopause were detected, even when adjusted by age (*P*-value = 0.045 and 0.034 respectively, Supplement 2, http://links.lww.com/MENO/A566).

The pair-matched analysis of the laboratory values from the subgroup of women who provided both the perimenopausal and postmenopausal blood samples revealed differences in the lipid profile (Table 3). Total cholesterol (n = 468 determinations), LDL-c (n = 404 determinations), and HDL-c (n = 408 determinations) levels significantly increased from perimenopause to postmenopause (*P* value = 0.010, *P* = 0.011 and *P* = 0.037, respectively). The increase in TG (n = 458 determinations) levels was not significant from perimenopause to postmenopause (*P* value = 0.218). Total cholesterol, LDL-c, HDL-c, and TG concentration differences were not significant when adjusted by age at the moment of the blood sample.

For the global sample of determinations, Figures 2-5 represent the levels of the different lipid profile components by years

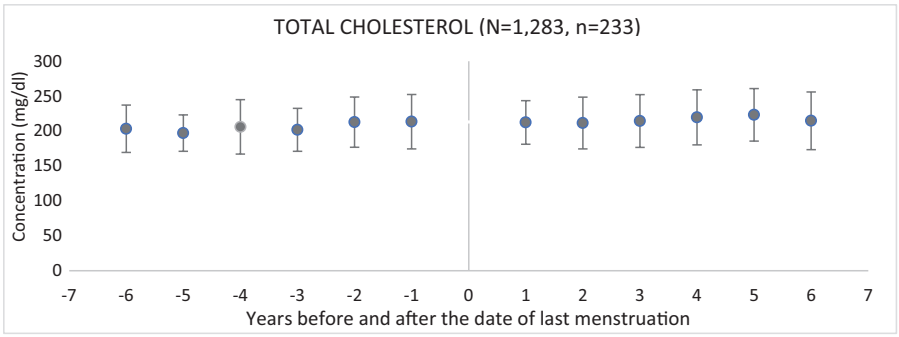

FIG. 2. Total cholesterol change by years before and after the date of last menstruation. Number determinations TC by year (year – 6: 50; year – 5: 13; year – 4: 21; year – 3: 38; year – 2: 44; year – 1: 72; year 1: 68; year 2: 77; year 3: 70; year 4: 60; year 5: 54; year 6: 716). N, number of determinations; n, number of women; TC, total cholesterol.

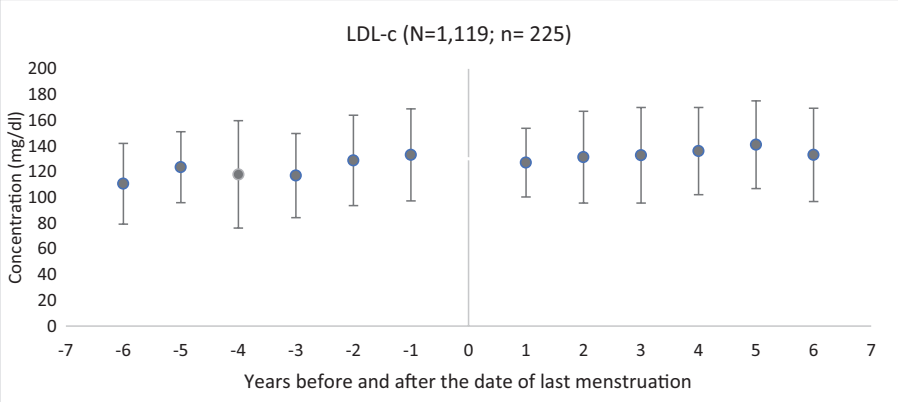

FIG. 3. LDL-c change by years before and after the date of last menstruation. Number determinations LDL-c by year (year – 6: 35; year – 5: 9; year – 4: 17; year – 3: 35; year – 2: 38; year – 1: 69; year 1: 59; year 2: 63; year 3: 58; year 4: 50; year 5: 50; year 6: 636). LDL-c, low-density lipoprotein cholesterol. N, number of determinations; n, number of women.

before and after the DLM. Table 4 shows the slopes for every lipid profile factor regarding the DLM unadjusted and adjusted by age at the moment of the blood sample. When comparing the perimenopausal and postmenopausal periods, total cholesterol and LDL-c slopes before and after the DLM were significantly different (P value = 0.024 and <0.001 respectively), even when adjusted by age (P value = 0.013 and 0.001, respectively). HDL-c slopes in perimenopause and postmenopause showed no significant difference when adjusted by age and TGs did not show any difference in the slope between the perimenopausal and postmenopausal periods.

Univariate regression analysis of factors potentially affecting the concentration of the lipid profile showed that total cholesterol and LDL-c levels were significantly increased in the postmenopausal period and by increased menopausal age and related with alcohol consumption, family history of cardiovascular disease, and TG levels (Table 5). The number of pregnancies was negatively associated with total cholesterol and LDL-c. FPG also affected LDL-c levels. In contrast, HDL-c levels showed a positive relationship to menopausal age and an inverse relationship to menopausal status, age, alcohol intake, familial history of CVD, fasting glucose, TG levels and number of pregnancies. Stepwise multivariate regression analysis showed that menopausal status, TG levels, and number of pregnancies independently affect total cholesterol and LDL-c levels. HDL-c levels were independently related with menopausal age, TG levels and number of pregnancies. The TG concentration was independently affected by total cholesterol, LDL-c, and HDL-c levels.

DISCUSSION

Our results reveal changes in the lipids (total cholesterol, LDL-c, HDL-c, and TG) during the menopausal transition when comparing perimenopausal and postmenopausal laboratory values, whereas the differences were significant only in LDL-c levels when adjusted by age indicating that increasing age is related to the changes in blood lipids. Our results are in line with other studies showing higher total cholesterol, TG, and LDL-c levels in postmenopause compared with perimenopause.[6-10] For instance, results from a retrospective study in 1,015 Chinese women showed that postmenopausal women had higher total cholesterol, LDL-c, and TG levels and lower HDL-c concentration than perimenopausal peers.[7] Another cross-sectional study with 1,553 Korean women showed an

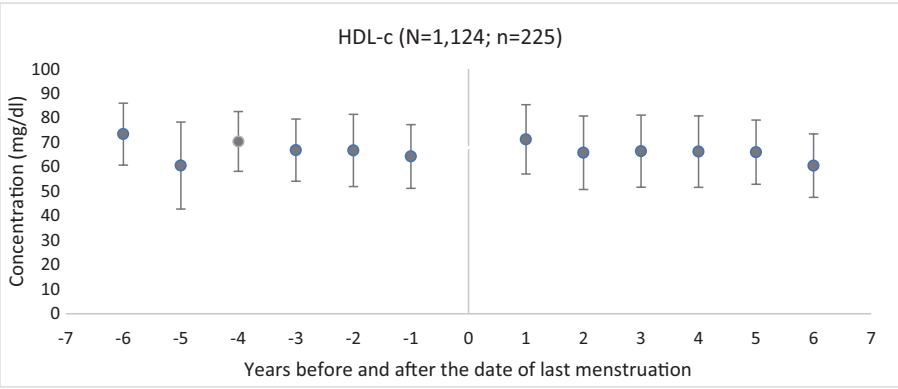

FIG. 4. HDL-c change by years before and after the date of last menstruation. Number determinations HDL-c by year (year – 6: 35; year – 5: 9; year – 4: 17; year – 3: 34; year – 2: 39; year -1: 67; year 1: 59; year 2: 64; year 3: 59; year 4: 51; year 5: 50; year 6: 640). HDL-c, high-density lipoprotein cholesterol; N, number of determinations; n, number of women.

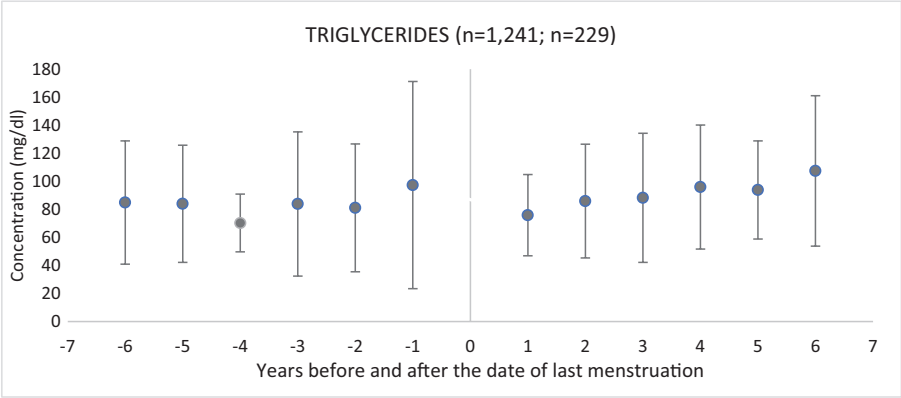

FIG. 5. Triglycerides change by years before and after the date of last menstruation. Number determinations triglycerides by year (year – 6: 46; year – 5: 13; year – 4: 20; year – 3: 35; year – 2: 42; year – 1: 71; year 1: 66; year 2: 74; year 3: 69; year 4: 60; year 5: 54; year 6: 691). N, number of determinations; n, number of women.

increase in total cholesterol and LDL-c levels in early postmenopause.[8] The Third French MONICA cross-sectional survey found that total cholesterol and LDL-c were significantly different between perimenopausal and postmenopausal women, but TG and HDL-c levels did not differ between menopausal status after adjustment for age as occurred in our study.[11] Only two studies, to our knowledge, found significant increases in HDL-c during the menopausal transition,[15,16] with an increase of HDL-c levels 2[15] or 3 years[16] after menopause. Our study covers a longer period than the latter studies and a greater number of blood samples, and this could explain the observed decrease of HDL-c levels with menopause, in addition to differences in the characteristics of the populations. Our results differ from a previous Spanish study[13]; the Pizarra Study (Málaga, Spain) evaluated a group of 475 women aged 18 to 65 years during 6 years divided into three groups: nonmenopausal women (n = 322), women reaching menopause at the end of the study (n = 66), and women menopausal during the whole study (n = 87).[13] No significant changes were found in LDL-c, HDL-c, and TG levels between the three groups after adjusting for age. The variables were compared between the three groups but not perimenopausal and postmenopausal data, as we did here.

In the subgroup of laboratory studies from women with perimenopausal and postmenopausal blood samples during the study period, the changes in total cholesterol and LDL-c confirmed the results shown in the global comparison between perimenopausal and postmenopausal laboratory values. On the contrary, HDL-c levels were significantly higher and TG levels were lower in the postmenopausal laboratory studies. These results are probably different from the global comparison because we compared the mean value during the different periods for each woman, not the crude values and the determinations sample is smaller. Moreover, an initial increase in HDL-c levels followed by a later decrease cannot be ruled out. Similar results were obtained in another study in Badajoz (Spain) where the authors found higher total cholesterol ($P < 0.005$), LDL-c, and HDL-c levels and lower TG concentrations in a study with 19 premenopausal and 33 postmenopausal women.[14] In the Pizarra study mentioned previously, the group of women that reached menopause during the study showed no significant changes in LDL-c, HDL-c, and TG after adjusting for age as in our study. In the Pizarra study there was no pair-matched comparison of the beginning and the end of the study of this group transitioning to postmenopause as we did.[13]

When analyzing the change of the lipid profile regarding the DLM, we observed that total cholesterol and LDL-c levels increased during perimenopause and decreased in postmenopause. Both, total cholesterol and LDL-c showed a significant change of behavior before and after the DLM, indicating that menopause could influence them (*P* value adjusted by age = 0.013 and 0.001, respectively). HDL-c levels decreased

TABLE 4. *Lipid profile change expressed as slope before and after the date of last menstruation*

Determination, mg/dL (N/n)	Specific unadjusted slope before DLM (SE)	Specific unadjusted slope after DLM (SE)	*P* value unadjusted	*P* value adjusted by age
TC (1,283/233)	0.138 (0.079)	−0.062 (0.012)	**0.024**	**0.013**
LDL-c (1,077/225)	0.202 (0.091)	−0.057 (0.012)	**<0.001**	**0.001**
HDL-c (1,083/225)	−0.098 (0.036)	−0.022 (0.004)	**0.037**	0.063
TG (1,193/229)	−0.117 (0.126)	0.079 (0.015)	0.762	0.346

Boldface represents significant *P*-values.
The slope was calculated by months before and after the DLM.
DLM, date of last menstruation; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; N, number of determinations; n, number of women; SE, standard error; TC, total cholesterol; TG, triglycerides.

TABLE 5. *Linear regression analysis of lipid profile*

	Total cholesterol (N = 1,283; n = 233)				LDL-c (N = 1,119; n = 225)				HDL-c (N = 1,124; n = 225)				Triglycerides (N = 1,241; n = 229)			
	Univariate regression		Multivariate regression		Univariate regression analysis		Multivariate regression analysis		Univariate regression		Multivariate regression		Univariate regression		Multivariate regression	
	β	*P*	Partial	*P*	β	*P*	Partial	*P*	β	*P*	Partial	*P*	β	*P*	Partial	*P*
Menopausal status	0.098	**<0.001**	0.122	**<0.001**	0.131	**<0.001**	0.162	**<0.001**	−0.105	**<0.001**		NS	0.08	**0.005**		NS
Lab study age	0.015	0.580	–	–	0.001	0.969	–	–	−0.151	**<0.001**		NS	0.194	**<0.001**		NS
Menopausal age	0.126	**<0.001**		NS	0.068	**0.025**		NS	0.089	**0.003**	0.097	**0.002**	0.059	**0.041**		NS
Alcohol	0.106	**0.020**		NS	0.132	**0.006**		NS	−0.056	0.241	–	–	0.057	0.215	–	–
Fam history CVD	0.081	**0.004**		NS	0.102	**0.001**		NS	−0.056	0.061	–	–	0.047	0.101	–	–
FPG	0.016	0.568	–	–	−0.078	**0.011**		NS	−0.066	**0.030**		NS	0.294	**<0.001**		NS
TC	–	–	–	–	–	–	–	–	–	–	–	–	0.227	**<0.001**	0.979	**<0.001**
LDL-c	–	–	–	–	–	–	–	–	–	–	–	–	0.121	**<0.001**	0.107	**<0.001**
HDL-c	–	–	–	–	–	–	–	–	–	–	–	–	−0.346	**<0.001**	−0.346	**<0.001**
TG	0.227	**<0.001**	0.247	**<0.001**	0.121	**<0.001**	0.164	**<0.001**	−0.346	**<0.001**	−0.326	**<0.001**	–	–	–	–
N pregnancies	−0.155	**<0.001**	−0.212	**<0.001**	−0.174	**<0.001**	−0.224	**<0.001**	−0.165	**<0.001**	−0.129	**<0.001**	0.123	**<0.001**		NS

Boldface represents significant *P*-values.
The (−) represents data not included in the regression analysis.
CVD, cardiovascular disease; Fam, familiar; FPG, fasting plasmatic glucose; HDL-c, high-density lipoprotein cholesterol; Lab, laboratory; LDL-c, low-density lipoprotein cholesterol; N, number of determinations; n, number of women; NS, nonsignificant; TC, total cholesterol; TG, triglycerides.

during the perimenopausal and postmenopausal time periods with a lower decrease seen after the DLM. The HDL-c slopes were not significantly different when adjusted by age (*P* value adjusted by age = 0.063). TG concentration showed a decrease during perimenopause, due to a decrease in year 4. During the postmenopausal period, the slope changed to an increase in TG levels. The tendency changed during postmenopause with an increase in concentration. There was no significant difference between perimenopause and postmenopause behavior of TG concentration (*P* value adjusted by age = 0.346). Therefore, HDL-c and TG levels seem to be more related to the aging process. Our results are similar to those of the SWAN study, where changes in the slope of total cholesterol and LDL-c before and after the DLM were significantly different and the increase in total cholesterol and LDL-c was substantial around the DLM.[6] Our study shows a great decrease of HDL-c in year 5, followed by an increase in year 4; however, the slope in both perimenopausal and postmenopausal periods is descendant with no statistical difference when adjusted by age. The SWAN study reported an increase of HDL-c levels that occurred during the perimenopausal period and decreased at postmenopause, resulting in little net change during the menopausal transition.[6] This could be one of the reasons for the difference in HDL-c result between the two studies.

Multivariate regression analysis showed that menopause status is an independent risk factor for total cholesterol and LDL-c, but not for HDL-c and TG levels. HDL-c was the only lipid profile component independently affected by menopausal age; this could explain the loss of significant difference when the comparison of perimenopause and postmenopause was adjusted by age. TG levels were not independently related to menopause or age. Overall, our results confirm the effect of the menopausal status on the lipid profile shown in previous studies.[10,12] The Virgilio Menopause Health Project and the 2005 Korea National Health and Nutrition Examination Survey found that total cholesterol and LDL-c were independently associated with menopausal status.[10,12] The number of pregnancies was also independently associated with total cholesterol, LDL-c, and HDL-c levels. Similar results were obtained in the Rancho Bernardo study, where low levels of HDL-c were associated with multiparity (5 or more pregnancies) in a population of older women.[17]

The present study has several limitations that warrant consideration. As this is a retrospective study, the selection of the laboratory studies was limited to the diagnostic criteria applied by the gynecologist and the recorded DLM. We analyzed two different pools of data with two different designs: a transversal methodology to collect information about patients' characteristics and a retrospective review of laboratory study data. The strengths of the study include the long period analyzed and the number of laboratory studies collected, which allowed us to evaluate a significant information sample before and after the DLM. As there was no diagnostic date for cardiovascular disease, hypertension, osteoporosis, or diabetes, we do not know whether the diagnosis was made during perimenopause or at postmenopause. This could be an interesting aspect to evaluate in future investigations, to confirm whether menopausal transition is a risk factor for cardiovascular disease, hypertension, osteoporosis, or diabetes. Large longitudinal studies with limited confounding variables are necessary to investigate the real influence of menopausal transition in women.

CONCLUSIONS

In conclusion, our study suggests that there are significant changes in LDL-c levels during the menopausal transition that could increase cardiovascular risk in postmenopausal women. The change in total cholesterol and LDL-c levels was significantly different during perimenopause and postmenopause. Total cholesterol and LDL-c changes were independently affected by menopausal status; additionally, HDL-c change was related to menopausal age.

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