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Comparison of serum lipid profile between pre and postmenopausal healthy women

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Abstract
Background: Different studies have presented conflicting results concerning the effect of menopause on lipid levels.
Aim: This research was conducted to find the difference in serum lipid profile between premenopausal and postmenopausal women**.**
Patients and Methods: A cross-sectional survey of serum lipid profile in apparently two groups of healthy women in Mosul city in northern Iraq. First group involved (79) women before menopause, while the second group involved (103) women after menopause. The study was conducted during a period of 6 months commencing from 1st October 2018 to 1st April 2019.
Serum lipid profile including TC, TG, and HDL-C were measured, while LDL-C and Atherogenic Index were calculated from above values.
Results: Compared to premenopausal women, postmenopausal women had significantly increased levels of total cholesterol (15.7%), low density lipoprotein (LDL) cholesterol (23.3%), and triglycerides (24%). The difference did not show a trend towards an increase with the number of postmenopausal years. The high density lipoprotein (HDL) cholesterol significantly higher in premenopausal women compared with postmenopausal women (5.78%). The difference in Atherogenic index is apparent which is higher in postmenopausal women (4.59 ± 2.02 kgm/ m^2) compared to premenopausal women (3.42 ± 0.66 kgm/ m^2. The mean for BMI was higher in the postmenopausal compared with premenopausal women and significant differences in body weight were observed between them. The mean of age at menopause was occurring is 49, 47 years. Regarding the dyslipidimia and according to NECP (ATP III), 5 subjects (6.3%) of premenopausal women were dyslipidimic comparing with 40 subjects (39.2%) of postmenopausal women, (significant difference P<0.001).
Conclusion: we conclude that the menopause is associated with potentially adverse changes in lipids and lipoproteins, independent of any effect of ageing.

Keywords: serum lipid profile, premenopausal women, postmenopausal women

Introduction

Menopause is a permanent ending of menstruation after which the ovarian activity is lost. It is derived from Greek words, “men” which means (month) and pauses. This is the transition from fertility to infertility and occupies that decade from 45-55 years when a woman passes from her reproductive into her post-reproductive years. It is attended by a wide scale of symptoms, signs, and metabolic adjustments, the ultimate cause of which is a major reduction in the level of circulating estrogen [1, 2]. The exact age of menopause varies [3]. Menopause occurs in women frequently, between 50 and 55 years, and the mean age was of 51 years, but some women reach menopause as early as the fourth decade, on the contrary, a few may continue to menstruate till the age of 60s [4]. Spontaneous cessation of the periods before reaching 45 years, with decreasing of estrogen and increasing of LH and FSH secretion defined as premature menopause. The ovary produces a sequence of hormones during a normal menstrual cycle, each sequence being induced by gonadotropic hormones from the pituitary. The cholesterol from the liver is converted by the control of LH, in theca cells to pregnenolone. The pregnenolone then becomes the substrate for all further ovarian sex steroid genesis, and under the influence of enzymes within the granulosa and luteal cells, progesterone, androgen, and estrogen are produced. The induction of these sex hormones depends on the presence of viable ova and normal ovarian stroma and the production of follicular-stimulating hormone and luteinizing hormone in adequate amounts [4, 5]. The effects of Gn-RH on the releasing of both LH and FSH are powerfully regulated by negative feedback control effects exerted by oestradiol and progesterone [6]. At the start of the cycle, ovarian follicles are undeveloped and plasma oestradiol concentrations are low [7]. Late in the menstrual cycle, the arcuate of the hypothalamus produces carefully timed pulsation of gonadotrophin- releasing hormone (GnRH) which stimulates cells of the anterior lobe of the pituitary gland, so follicle stimulating hormone (FSH) will be produced and, to a smaller extent, luteinizing hormone (LH). In the right proportion, FSH will recruit a cohort of ovarian follicles to develop. Meanwhile, FSH / LH circulate back to the hypothalamus exerting negative feedback control on GnRH pulses limiting recruitment to the initial cohort. From these recruited ovarian follicles, a dominant follicle is selected by cycle day 7. It is the destiny of this one follicle to mature and proceed to ovulation, usually on cycle day 14. While achieving maturity, the main follicle secretes rising levels of the estrogen, estradiol, which will eventually initiate an ovulation trigger (LH surge) by positive feedback influence by the hypothalamus /pituitary.

Increasing estradiol levels also serves to prevent other follicles from interfering with ovulation by inhibiting FSH release through negative feedback. The follicle estradiol stimulates the proliferative growth within the endometrial layer of the uterus so that embryo implantation can occur later in the cycle. Once the LH trigger has been sent by the pituitary, the ovum is released and the follicle collapses to become the corpus luteum [5]. The Progesterone transforms the already proliferative endometrium, increasing glandular production and preparing for embryo implantation. If implantation fails, then the corpus luteum will involute at 10 days and progesterone production is withdrawn. With progesterone withdrawal, endometrial lining collapses resulting in menses [8, 9]. Any heterogeneous groups of fats and fat-like substances are characterized by their insolubility in water and solubility in non-polar solvents, such as alcohol, ether, chloroform, benzene, etc [10]. The main plasma lipids are cholesterol, triglycerides, phospholipids, and fatty acids. Lipids are transported in plasma incorporated in lipoproteins [7]. The functions of lipids are diverse. Several types of lipids molecules (e.g. phospholipids) are important structural components in the cell membrane. Another type of fat and oil (both of which are triglycerides) is an efficient form of stored energy. Other types of lipid molecules serve as chemical signals, vitamins, or pigments. Finally, some lipid molecules which occur in the outer coating of various organisms, have protective or waterproofing function [11].

Patients and Methods

A study of cross-sectional design was chosen. Two groups of healthy women were allocated and enrolled from Mosul city, northern Iraq. The study was conducted for 5 months commencing from 1st November 2018 to 30th April 2019. A total of 182 healthy women who attend Mosul Teaching Hospital as accompaniers of the patients, the author's relatives, and friends were enrolled. They were allocated into two groups by menstrual status.The first group is premenopausal women (n = 79), all were healthy with regular menstruation, aged 25-50 with a mean ± SD of 40.77 ± 4.44. The second group is postmenopausal women (n = 103) all were healthy with amenorrhea over 1year without gynecological diseases, aged 47-64 with a mean ± SD of 54.28 ± 4.22.

The participants underwent a clinical evaluation, which included a questionnaire that inquired age, menopausal age, hypertension and diabetes history, smoking status, and any history of coronary heart disease (CHD). BMI was calculated from the measured weight and height.

Exclusion criteria:

1. Any woman with diseases that influence lipid levels, such as diabetes mellitus, chronic liver disease, infectious diseases, or other endocrine diseases, women using hormonal therapy as a contraceptive and other steroids or hypolipidemic drugs and smoker subjects.
2. Subjects who had undergone a hysterectomy or oophorectomy
3. Any woman with a history of hypertension or coronary heart disease.

The subjects classified according to ranges of the different components of lipid profile [10].

- Serum total cholesterol: desirable (< 5.17 mmol /L or < 200mg/dl), borderline (5.17-6.2mmol/L or 200-239mg/dl), high (>6.2mmol /L or > 240 mg/dl).
- Serum triglycerides: desirable (< 1.7 mmol/L or < 150 mg/dl), borderline (1.7–2.25 mmol/L or 150-199 mg/dl), high (2.26–5.64mmol/L or 200-499 mg/dl), very high (>5.65mmol/L or > 500mg/dl).
- Serum LDL-Cholesterol: optimal (<2.58 mmol/L or <100 mg/dl), near-optimal (2.58-3.33 mmol/L or 100–129 mg /dl), Borderline (3.36-4.11 mmol/L 130-159 mg/dl), high (4.13-4.88 mmol/L or 160-184 mg/dl), very high (>4.91mmol/L or > 190 mg/dl).
- Serum HDL-Cholesterol: average (0.46–.69 mmol/L or 18-27 mg/dl), below average (0.69–1.03 mmol/L or 27–40 mg/dl), protection probable (>1.03 mmol/L or >40 mg/dl).
- Atherogenic index (serum total cholesterol: HDL – C ratio): < 4, 4 – 4.9, 5 – 5.9, > 6
- Classification of dyslipidemia according to cut-off values of different components of lipid profile. This classification was made according to the recommendations by the NECP (ATP III), at the following cut-off levels [12].

1. Serum total cholesterol > 5.17 mmol/L (>200mg/dl).
2. Serum LDL-cholesterol > 2.60 mmol/L (>100mg/dl).
3. Serum HDL-cholesterol < 1.03 mmol/L (<40 mg/dl).
4. Serum triglycerides > 1.70 mmol/L (>150mg/dl).

Current guidelines for both men and women define overweight as BMI of 25.0 to 29.9 and obesity as BMI of 30.0 and greater. BMI equal to the weight measured by kilograms divided by the square of the height calculated using unit of meters [13]. Samples from venous blood were obtained from all subjects included in the study, by antecubital venepuncture between 8.00 a.m. and 10.00 a.m. All subjects were carefully informed to fast for the night for not less than 10-12 hours. About a 5 ml blood sample was taken from every subject and placed in a plain tube. The blood sample was left for 30 min in the water bath at 37 C. This allows blood to clot and the serum sample was then got by centrifugation with speed of 3000 rpm for 10 min. Serum samples were then stored frozen until analyses. Serum lipid profile including TC, TG, and HDL-C was measured, while LDL-C and Atherogenic Index were calculated from the above values. The reagents used throughout this study were obtained from the Clinical Chemistry Laboratory of the Department of Biochemistry, College of the Medicine/ University of Mosul, and from the Biochemical Laboratory belong to the Mosul Teaching Hospital. The instruments used were: Cecil, Ce 3031 Granting spectrophotometer (England), Centrifuge 2E-1 (Sigma, USA). Water bathes, Gallen Kamp (England). All data were recorded and organized by Excel. Minitab (version 18) was used to calculate percentages, Chi-square, t-test, one way ANOVA, and p-value.

Results

Table (1) demonstrates the Mean age, BMI, and other characteristics in 79 women before menopause and 103 women after menopause participating in this study. Postmenopausal women were significantly older (mean age ± SD; 54.28 ± 4.22) than premenopausal women (mean age ± SD; 40.77 ± 4.44).

Table 1: The Demographic and baseline Characteristics

Parameters	Pre-menopause		Post-menopause
Number	79		103
Age (year) Mean ± SD	40.77 ± 4.44		54.28 ± 4.22
BMI (kg/m^2) Mean ± SD	24.25 ± 2.13		26.27 ± 2.29
Period after menopause	year	No.	%
	<3	32	31.1
	3-6	44	42.7
	>6	27	26.2
Mean ± SD	-		4.82 ± 3.35
Age of menopause (year), Mean ± SD	-		49.47 ± 2.49

Table (2) demonstrates the distribution of study groups according to their BMI and shows that 74.7% of premenopausal and 27.2% postmenopausal women have BMI ranging 18.5-25. At BMI range, 25-29.9; premenopausal women and postmenopausal women represent 25.3% and 69.9% respectively. Regarding obese subjects (BMI ≥ 30); 1.6% of postmenopausal women against 0% of premenopausal women. The difference in BMI between pre and postmenopausal women significant (P-value <0.001).

Table 2: Difference in BMI between pre and postmenopausal women

BMI	Pre		Post		p-value*
	No.	%	No.	%	
18.5-25	59	74.7	28	27.2	<0.001
25-29.9	20	25.3	72	69.9	
30-34.9	0	0.0	3	1.6	
Total	79	100	103	100	

* Chi square test

Table (3) shows the distribution of the atherogenic index value in both pre and postmenopausal women and reveals a very highly significant differences (p <0.001), with frequencies distribute as: AI level <4; (79%) of premenopausal group and (33%) of postmenopausal group. AI level 4-4.9; (20.3%) of premenopausal and (35%) of postmenopausal group. The interval of 5-5.9 included only (12.6%) of subjects from postmenopausal group. While interval of > 6 includes only (9.7%) of subject from postmenopausal group.

Table 3: Atherogenic index results distribution.

Subject: AI	Pre (n=79)		Post (n= 103)		p-value*
	No.	%	No.	%	
<4	63	79.7	34	33.0	<0.001
4-4.9	16	20.3	36	35.0	
5-5.9	0	0.0	23	12.6	
>6	0	0.0	10	9.7	

***** Chi square test

Table (4) illustrates the differences in means of lipid parameters between pre and postmenopausal women and reveals that postmenopausal women has significantly increased level of total cholesterol (4.78 ±1.02 mmol/L) in comparison to premenopausal women (4.13 ± 0.73 mmol/L), LDL-C (2.80 ± 0.94 mmol/L), TGs (1.91 ± 0.68 mmol/L), Atherogenic index (4.59 ± 2.02 kgm/ m^2) with (P<0.001). While HDL-C were lower significantly in postmenopausal women (1.14 ± 0.36 mmol/L) compared to premenopausal women (1.21 ± 0.18mmol/L, P < 0.001).

Table 4: Differences in means of lipid parameters between the pre and post-menopausal women

Parameters	Mean ± SD		p-value*
	Pre-menopause n=79	Post-menopause (n=103)	
Total cholesterol (mmol/L)	4.13 ± 0.73	4.78 ± 1.02	<0.001
HDL-c (mmol/L)	1.21 ± 0.18	1.14 ± 0.36	<0.001
LDL-c (mmol/L)	2.27 ± 0.66	2.80 ± 0.94	<0.001
TG (mmol/L)	1.54 ± 0.44	1.91 ± 0.68	<0.001
Atherogenic Index	3.42 ± 0.66	4.59 ± 2.02	<0.001

* t-test independent 2 means

Table (5) demonstrates the distribution of means and standard deviations of TC, HDL-C, LDL-C, TG and AI according to age groups intervals for women before menopause and displays insignificant statistical differences. Total cholesterol concentration: shows no significant difference between age groups.

Table 5: Distribution of premenopausal women according to age groups

Parameters Mean ± SD	Age (year)				p-value*
	<35	36-40	41-45	46-50	
Total cholesterol (mmol/L)	4.08±0.56	4.14±0.68	4.22±0.73	3.71±1.09	NS
HDL-C (mmol/L)	1.26±0.19	1.18±0.15	1.23±0.19	1.15±0.22	NS
LDL-C (mmol/L)	2.22±0.39	2.28±0.55	2.34±0.71	1.94±1.01	NS
TG (mmol/L)	1.6±0.34	1.5± 0.42	1.59±0.5	1.38±0.24	NS
Atherogenic Index	3.29±0.55	3.38±0.72	3.49±0.58	3.31±1.0	NS

*One-way ANOVA test

Table (6) shows the lipid profile results for postmenopausal subjects that classified according to menopausal age into

three groups. The differences in results of lipid profile between these menopausal age groups are insignificant.

Table 6: Distribution of postmenopausal women according to menopausal age.

Parameters Mean ± SD	Period (year)			p-value*
	<3 (n=32)	3-6 (n=44)	>6 (n=26)	
Total cholesterol(mmol/L)	4.68 ± 0.97	4.70 ± 0.97	5.01 ± 1.15	NS
HDL-c (mmol/L)	1.19 ± 0.32	1.14 ± 0.37	1.06 ± 0.38	NS
LDL-c (mmol/L)	2.65 ± 0.83	2.71 ± 0.91	3.12 ± 1.06	NS
TG (mmol/L)	1.94 ± 0.57	1.94 ± 0.75	1.81 ± 0.69	NS
Atherogenic Index	4.08 ± 1.00	4.65 ± 2.68	5.09 1.52	NS

*One-way ANOVA test

Discussion

Although women under the age of 50 years infrequently develop CVD, by age 70 years the incidence of CVD becomes similar in men and women, suggested that estrogen deficiency resulted in a rapid increase of rate of CVD risk [14]. Argument is present about whether menopause raises the risk of CVD independently from average aging. Several studies have reported raised risk of CVD post-menopausal, and others have not. For example, Framingham examiners found a 4-times raise in CVD during 10 years following natural menopause. However, the question that if the expected menopause is an independent risk for CVD has not been answered, as it is very complex to design studies that can detach the effect of the usual aging process from menopause. Hyperlipidemia is exceedingly common and occurs in about 33% of developed countries. Furthermore, the relative CVD rise associated with elevated lipid levels is different in males than in females. For example, the relative risk from elevated triglyceride levels is greater in women than in men, and the threshold for increased risk from low levels of HDL-C is higher. HDL-C is athero-protective as evidenced by a strong converse relationship linking HDL-C ranks and cardiovascular risk [14, 15]. To guarantee that the outcomes are due to true relations between natural menopause and risk factors of cardiovascular, bias owing to other factors also has to be considered as a possible explanation. Some other determinants of early menopause were not measured in this study. For example, genetic predisposition, socioeconomic status, or parity, could be correlated to early menopausal time and the variation in lipid levels. This seems unlikely; however, inspite socioeconomic status and parity are associated with raised lipid levels, the documented effects of these factors are inadequate to explain the variation found in our study. Because of our strict exclusion criteria, the consequence of probable misclassification of menopausal status is expected to be little. Misclassification of menopausal age and the postmenopausal years could be noticed, as these evaluations were depend on self-reports. Although it is commonly believed that menopause is associated with weight gain, most studies do not reveal increases in BMI independent of the normal aging process [16, 17]. Although it is estimated that middle-aged women gain approximately 0.55 kg/yr, there does not appear to be an independent effect of menopause on body weight [18, 19]. However, even in the absence of weight gain, body fat distribution changes across menopause. Cross-sectional [20] and longitudinal studies [21, 22] have shown that the menopausal transition is associated with a marked increase in abdominal adiposity, independent of the effect of age and total body adiposity. Menopause is also associated with reduced lean body mass and this appears to be related to decrease physical activity. The reductions in exercise capacity and activity may contribute to the reduced lean body mass and increased central adiposity with menopause. The effects of menopause on BMI remain unclear, but many epidemiological studies have indicated that significant changes in BMI are observed concerning menopause [23]. Several cross-sectional studies have suggested that decreases in resting metabolic rate and physical activity may be accelerated in the postmenopausal years [24, 26]. The decrease in energy expenditure during rest and physical activity may be related to the decreased fat-free mass that has been seen in postmenopausal women [27, 29]. Moreover, the decrease in energy expenditure may result in increased fat mass if daily energy 46 intake is not reduced accordingly. Other researchers, however, have not found that menopause independently affects body weight gain [30, 31]. In this study, the mean for BMI was higher for the postmenopausal compared with premenopausal women, and significant differences in body weight were observed between the postmenopausal and premenopausal women. In the present study, we found that mean levels of serum total cholesterol, LDL, cholesterol, and TG were significantly higher in postmenopausal women than in premenopausal as there is a significant difference in total cholesterol levels between pre and Postmenopausal with $p<0.001$. The observation of an increased total cholesterol level in postmenopausal compared to premenopausal females agrees with most other studies, both cross-sectional [32, 36] and longitudinal [37, 40]. We found that these higher levels were established one year after menopause and did not change significantly thereafter. The results of the presented study reveal a significant difference in serum triglyceride levels between pre and postmenopausal females ($P< 0.001$), and the mean value of postmenopausal females was 24% higher than premenopausal females. This finding of presenting study consistent with results of several cross-sectional studies [37, 41, 43] Lindquist (1982) reported a prospective increase in TG levels in women who became postmenopausal during a 6-yr period, whereas there was no change in TG in the similarly aged women who remained either premenopausal or postmenopausal [43]. While contrary to the present study, other studies showed no significant difference in triglycerides between pre and postmenopausal women [44, 46]. This variability in findings can be explained in 2 ways. First, different definitions of menopausal status were used in the literature, and therefore, variable groups, with conceivably varying differences in plasma lipids, were identified. Likely, those changes in lipids are not instantaneous but rather gradual, expressing the ongoing decline of ovarian function. Second, the distinct possibility should be recognized that regulation of plasma TGs in premenopausal women is different from that in postmenopausal women. There is a significant difference in

total cholesterol levels between pre and Postmenopausal with p<0.001 and the mean of the postmenopausal women was 23.3% higher than premenopausal women. Comparing with other cross-sectional studies was the difference ranged from 10 to 20% [16, 45]. Many studies estimate the LDL particle composition which is also changes after menopause, (LDL are comprised of a spectrum of particles that vary in size, density, chemical composition, and atherogenic potential). The prevalence of small, dense LDL in these studies was low in premenopausal women (10–13%), but increases to 30–49% in postmenopausal women [47, 49]. An increase of small, dense LDL is associated with an increased risk of myocardial infarction [51] as well as the severity of CVD [52]. The risk of CVD is 3-fold higher in women with small dense LDL than in those with large LDL [50]. Several factors including diet, exercise, smoking, alcohol, and medications influence HDL- C level. In this study, the subjects taking the cholesterol-lowering drug or female hormonal preparation and smoker subjects were excluded and other factors were not examined. The results of the presented study reveal a significant difference in serum HDL-C level between pre and postmenopausal women (P< 0.001), and the mean value of premenopausal women was 5.7% higher than postmenopausal women. Most studies show that total HDL levels fall slightly with menopause [16, 45, 52, 53], whereas others reveal no changes [54]. There is a report shows different results (postmenopausal women had significantly higher HDL-C levels than postmenopausal women [55]. Therefore, menopause itself may not associate with the reduction of HDL-C level. Low HDL-C levels in postmenopausal women in most previous reports may not be due to menopause, but due to weight gain, lack of activity, and associated metabolic diseases in old women. The results of the presented study reveal a significant difference in AI value between pre and Postmenopausal women (P< 0.001), and the mean ± SD of postmenopausal women was (4.59 ± 2.02 mmol/L), while it was (3.42 ± 0.66 mmol/L) in premenopausal women. This finding of presenting study consistent with the results of the study [56], the mean ± SD were (3.6±1.2 mmol/L) in premenopausal women compared with (4.35 ± 1.53 mmol/L) in postmenopausal women. The variable most associated with CHD was the total cholesterol to HDL-C ratio. The physicians' Health study showed that the AI was the parameter most predictive of myocardial infarction [57]. AI values above 5 may be considered as a high-risk value for CHD, in both men and women [56]. AI provides a powerful predictive tool independently of other known CHD risk factors [58].

Conclusion

Serum total cholesterol, LDL cholesterol, and TG were significantly higher in postmenopausal women than in premenopausal women, while the level of HDL cholesterol shows contrary results; the HDL-C mean value of premenopausal women was significantly higher than postmenopausal women. Our findings add to epidemiological evidence that menopause adversely affects the lipid and lipoprotein metabolism and thus may increase the risk of coronary heart disease.

Recommendation

1. Lipid profile analysis should be advice for every woman after menopause to reduce the adverse complications of dyslipidemia.
2. Further studies about dyslipidemia in postmenopausal women should be conducted.

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