The Influence of Natural and Surgical Menopause on Cardiovascular Risk Markers Folate and Vitamin B12 Levels

Hakan KIRAN[1], Deniz CEMGİL ARIKAN[1], Gürkan KIRAN[1], Ayhan COŞKUN[1], Semih YANCAR[1], Abdullah TOK[1,2], Hasan Çetin EKERBİÇER[3]

Kahramanmaraş, Turkey

OBJECTIVE: To investigate the influence of both natural and surgical menopause on serum concentrations of lipids, lipoprotein-a, C-reactive protein, homocysteine, folate and vitamin B12 levels.

STUDY DESIGN: The study included 126 healthy women: 20 perimenopausal, 62 natural menopausal, and 44 surgical menopausal women. The serum levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, lipoprotein-a, C-reactive protein, homocysteine, folate and vitamin B12 levels were measured, and comparisons were made between the groups.

RESULTS: The plasma levels of total cholesterol, triglyceride, lipoprotein-a, homocysteine and folate were non-significantly higher in natural menopause group compared to perimenopause group. Also plasma total cholesterol, lipoprotein-a, homocysteine, vitamin B12 levels were higher and high-density lipoprotein cholesterol level was lower in surgical menopause group compared to perimenopause group, the difference was not significant. The plasma level of low-density lipoprotein cholesterol was significantly higher in natural menopausal women than perimenopausal women ($p<0.05$). Surgical menopausal women had higher but non-significant low-density lipoprotein cholesterol levels than perimenopausal women. There was a negative correlation between age and high-density lipoprotein cholesterol in natural menopause group, and there was a positive correlation between age and homocysteine in natural and surgical menopausal groups ($p<0.05$).

CONCLUSION: We did not find any significant difference in studied cardiovascular risk markers, folate and vitamin B12 levels in perimenopausal and postmenopausal women except low-density lipoprotein cholesterol levels.

Key Words: Cardiovascular risk, Folate, Vitamin B12, Menopause

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Introduction

Heart disease represents the most frequent cause of death for women over the age of 60.[1] Calculations have shown that a 50-year-old white women is ten times more likely to die of cardiovascular disease (CVD) than of hip fractures or breast cancer.[2] The frequency of complications from arteriosclerotic vascular disease is much lower in premenopausal women than in men of comparable age, but after the menopause the frequency increases more rapidly in women than in men.[3] Overall, the majority of evidence suggests that bilateral oophorectomy is associated with increased cardiovascular risk and premature death, and that oophorectomy at a younger age further increases this risk.[4]

Changes in lipids and lipoproteins, such as low high-density lipoprotein cholesterol (HDL-C), high low-density lipoprotein cholesterol (LDL-C), lipoprotein-a (Lp(a)) and triglyceride (TG) levels, have been associated epidemiologically with an increased CVD risk.[5,6] While the serum concentrations of total cholesterol (TC), LDL-C and TG increase,[7] HDL-C decreases after menopause.[8] Data from the Heart and Estrogen/progestin Replacement Study indicate that Lp(a) is an independent predictor of the risk of recurrent coronary heart diseases (CHD) in postmenopausal women.[9]

Homocysteine (Hcy) is a thiol-containing amino acid resulting from the demethylation of methionine. The metabolism of Hcy may be disrupted by a deficiency in folate, vita-

[1]*Kahramanmaras Sutcuimam University School of Medicine Department of Obstetrics and Gynecology, Kahramanmaraş*

[2] *Agri State Hospital, Department of Obstetrics and Gynecology, Ağrı*

[3]*Kahramanmaras Sutcuimam University School of Medicine Department of Public Health, Kahramanmaraş*

Address of Correspondence: *Deniz Cemgil Arıkan*
Sütçüimam Üniversitesi Tıp Fakültesi
Kadın Hastalıkları ve Doğum Ana Bilim
Dalı Yörük Selim Mah. Gazi Mustafa
Kuşçu Cad. Kahramanmaraş
drdenizarikan@hotmail.com

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min B6 and B12. Elevated blood levels of Hcy are an established independent risk factor for atherosclerosis, thrombosis, and occlusive arterial disease.[10] Investigations showed a significant increase in Hcy levels during postmenopause.[11,12] but this has not been confirmed by others.[13,14]

C-reactive protein (CRP) is a sensitive marker of inflammation. Elevated levels of CRP predict increased risks of subsequent cardiovascular events in both men and women.[15]

We aimed to investigate the influence of both natural and surgical menopause on serum concentrations of TC, TG, LDL-C, HDL-C, Lp(a), Hcy, CRP, folate and vitamin B12 levels in women.

Material and Method

This cross-sectional study included 126 healthy women with climacteric symptoms, aged 36 to 68 years. They were recruited from among patients treated at the menopause clinics of the Department of Gynecology and Obstetrics of the Medical Faculty of Kahramanmaras Sutcuimam University, Kahramanmaras, Turkey. Research ethics approval was obtained from the Ethics Committee of Kahramanmaras Sutcuimam University before the initiation of the study and signed informed consent was obtained from all women. The study population consisted of 126 women, who were divided into three groups. The first group included 20 normotensive healthy women at perimenopause, aged 36 to 48 years. The second group consisted of 62 women at natural menopause, aged 40 to 68 years. The third group consisted of 44 women at surgical menopause, aged 42 to 59 years.

Climacteric symptoms experienced by women included vasomotor symptoms such as night sweats, hot flashes, and insomnia, as well as mood swings. The diagnosis of menopause was made by at least 6 months of amenorrhea, serum follicle stimulating hormone (FSH) concentration >30 mIU/mL. Surgical menopausal women were selected from the women who had undergone a total-abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy because of benign gynecological disorders. Perimenopause was defined as regular menstrual cycles but duration changes by 7 days or more and as amenorrhea less than 2 months once during a year. All participants were non-smokers, had not received any hormone therapy for at least 6 months or any form of vitamin supplementation before entering the study.

Peri- and post-menopausal women were carefully matched for BMI. The BMI was calculated as weight (kg)/height squared (m^2). Exclusion criteria were confirmed diabetes mellitus, hypertension, occlusive atherosclerotic vascular disease, hyperlipidaemia, acute or chronic inflammatory disease, immunological disease and history or evidence of malignancy, as well as treatment with aspirin, warfarin, lipid-lowering drugs, nonsteroidal anti-inflammatory drugs, antihypertensive drugs, or antibiotics.

Blood sampling

The blood samples, which were obtained from the antecubital area, were collected between the hours of 08:00 and 09:00 following 10-12 h of fasting. Fasting venous blood specimens were drawn from the antecubital vein and collected in no additive vacutainer (Becton-Dickinson, Franklin Lakes, NJ) blood-collecting tubes according to standard hospital guidelines for venipuncture and sample collection. Plasma concentrations of FSH (mIU/mL) and E2 (pg/mL) were measured by Automated Chemiluminescence System (Access, Beckman instr. USA). Serum concentrations of TC (mg/dL), HDL-C (mg/dL), LDL-C (mg/dL) and TG (mg/dL) were measured by the enzymatic assays with the Behring RA biochemical autoanalyser (Germany). LDL-C (mg/dL) levels were calculated by means of the Friedewald formula. Serum concentrations of Lp(a) (mg/dL) were measured by nephelometric assays using Behring BN 100 Nephelometer (Germany). Polysytrene particles coated with antibodies to human Lp(a) are agglutinated when mixed with samples containing Lp(a). The intensity of the scattered light in the nephelometer depends on the Lp(a) content of a sample and therefore the Lp(a) concentrations of a sample can be determined by reference to the solutions of a standard of known concentration. Detection limit is 10 mg/dL. The N latex Lp(a) reagent is designed to measure Lp(a) concentrations within a range of about 10-160 mg/dL a sample dilution of 1/400 automatically. Five Lp(a) concentrations were used to determine the intraassay reproducibility (n:10) and here the coefficient of variation was 1.7-3.2%.

CRP was evaluated by high sensitivity immunonephelometer test with commercially available test (Dade Behring, BM 100, Germany). The intra-assay coefficient of variation was <5%.

Hcy specimens were placed on ice and all specimens were transported to the laboratory within 30 minutes of collection. Serum was obtained after centrifugation at 2,000 x g for 10 minutes, frozen, and stored at -20 ºC until analysis. Serum total Hcy concentrations were measured by using an IMX (Abbott Diagn. USA) Hcy assay. Assay is based on the fluorescence polarization immunoassay (FPIA) technology. Vitamin B12 and folate levels were quantitatively determined by chemiluminescent immunoassay system (Access, Beckman Instr. USA). Vitamin B12 and folate correlation variations (CV) were 4.8% and 5.1%.

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences for Windows version 11.0 (SPSS, Chicago, IL). The data were initially tested for normal distri-

bution by Shapiro-Wilk test and found abnormal ($p < 0.05$). Data were expressed as mean±SD, median (min-max) and analysed using Kruskal Wallis test followed by Mann-Whitney U test for comparisons between two groups whenever appropriate. Chi-square test was used to evaluate categorical variables. Correlations between variables were evaluated using Spearman's rho correlation test. Statistical significance was defined as $p<0.05$.

Results

The clinical characteristics of the groups are given in Table 1. Mean age of the postmenopausal women was significantly higher than the perimenopausal women ($p<0.05$).

The laboratory findings of the groups are shown in Table 2. Although plasma TC, TG, Lp(a), Hcy, and folate levels were higher in natural menopause group compared to perimenopause group, the difference was not significant ($p>0.05$).

Table 1: The clinical characteristics of groups.

Parameters	Groups			p
	Perimenopause (n=20)	Natural menopause (n=62)	Surgical menopause (n=44)	
	Mean±SD	Mean±SD	Mean±SD	
Age (year)	43.39±3.36*	51.00±4.39*	49.33±4.41*	**0.000***
BMI (kg/m^2)	28.87±4.00	30.92±5.52	31.54±3.92	0.123
Menopause duration (months)	-	42.21±45.97	56.31±57.83	0.699
FSH(mIU/mL)	71.14±37.81	74.03±35.64	75.35±33.30	0.698
E2 (pg/mL)	33.37±43.04	26.62±29.95	29.63±60.09	0.979

All results are given mean±standart deviation values in Table 1.
*n: subject number. *; the difference is between these groups.*

Table 2. Laboratory results of groups.

Parameters	Groups Perimenopause (n=20)	Natural menopause (n=62)	Surgical menopause (n=44)	p
	Med (min-max)	Med (min-max)	Med (min-max)	
Total cholesterol (mg/dL)	201.00 (134.00-294.00)	216.00 (132.00-333.00)	205.50 (151.00-278.00)	0.083
Triglyceride (mg/dl)	116.00 (28.00-489.00)	121.50 (45.00-552.00)	116.00 (35.00-334.00)	0.965
LDL (mg/dL)	117.60 (75.00-192.00)*	137.40 (51.00-243.00)*	127.10 (72.00-212.00)	**0.039**
HDL (mg/dL)	52.00 (37.00-88.00)	52.00 (27.00-90.00)	47.00 (33.00-91.00)	0.165
Lp(a) (mg/dL)	11.60 (9.60-70.70)	18.70 (9.60-118.30)	22.25 (9.60-124.50)	0.111
Homocysteine (µmol/L)	12.38 (7.90-16.60)	12,82 (6.00-45.80)	13.02 (6.70-23.60)	0.687
Vitamin B12 (µmol/L)	240 (101.00-453.00)	229.00 (54.00-711.00)	271.50 (123.00-1500.00)	0.270
Folate (pg/ml)	4.59 (3.17-7.13)	4.86 (2.23-11.03)	4.55 (1.97-9.29)	0.503
CRP	3.50 (0.00-36.70)	3.500 (1.00-20.60)	3.50 (0.00-105.00)	0.470

All results are given Med (min-max) (Median (minimum-maximum) in Table 2.
*n: subject number. *; the difference is between these groups.*

Also plasma TC, Lp(a), Hcy, vitamin B12 levels were higher and HDL level was lower in surgical menopause group compared to perimenopause group, the difference was not significant (p>0.05) (Figure 1). The plasma level of LDL-C was significantly higher in natural menopausal women than perimenopausal women (p<0.05). Surgical menopausal women had higher but non-significant LDL-C levels than perimenopausal women (p>0.05). There were no statistically significant differences in the levels of CRP between the study groups. Mild hyperhomocysteinemia (i.e., fasting Hcy plasma levels >15 µmol/L) was present in 10% of the perimenopausal women, in 26% of the natural menopausal women and in 30% of the surgical menopausal women, but this difference was not significant (Figure 2)(p>0.05). Markedly increased CRP (>3 mg/L) values were present in 47% of the perimenopausal women, in 55% of the natural menopausal women and in 46% of the surgical menopausal women, but this difference was not significant (Figure 2).

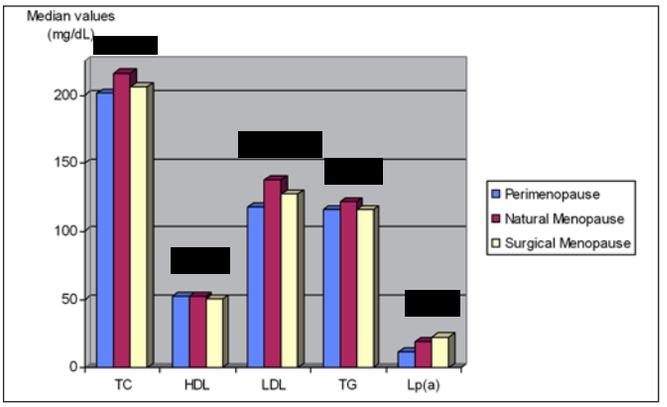

Figure 1: Median values of TC, HDL, LDL, TG and Lp (a) in study groups.

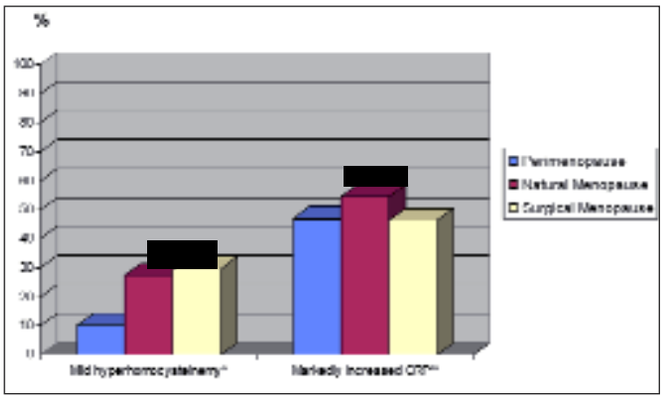

Figure 2: Distributions of women with mild hyperhomocysteinemy and markedly increased CRP in the study groups.

** ; Mild hyperhomocysteinemia means fasting homocysteine plasma levels >15 µmol/L.*
***; Markedly increased CRP means CRP levels >3 mg/L.*

There was no significant correlation between age and TC, LDL-C, Lp (a), folic acid, vitamin B12, CRP levels in all groups (Table 3). There was a negative correlation between age and HDL-C in natural menopause group, and there was a positive correlation between age and Hcy in natural and surgical menopausal groups (p<0.05) (Table 3). there was a positive correlation between age and TG in perimenopause group.

Discussion

Given an average age at menopause of 51.4 years, women in developed countries thus live over one-third of their lives in the postmenopausal state.[16] Approximately 1 in 8 women above age 55 years has undergone bilateral oophorectomy before reaching natural menopause.[17] The menopausal transition

Table 3: Correlations of age with the clinic features of women in groups.

Parameters	Groups					
	Perimenopause (n=20)		Natural menopause (n=62)		Surgical menopause (n=44)	
	Age		Age		Age	
	r	p	r	p	r	p
Total cholesterol	0.322	0.193	0.092	0.502	0.088	0.580
Triglyceride	0.525	0.025*	0.149	0.282	0.088	0.579
LDL	0.251	0.315	0.244	0.085	0.230	0.143
HDL	-0.296	0.234	-0.311	0.023*	0.090	0.575
Lp(a)	0.367	0.197	0.000	0.997	0.051	0.751
Homocysteine	0.396	0.104	0.418	0.001*	0.394	0.010*
Vitamin B12	-0.148	0.558	0.157	0.272	-0.004	0.979
Folate	0.125	0.633	-0.042	0.796	0.032	0.850
CRP	-0.006	0.983	0.087	0.529	-0.029	0.867

*n: subject number. r; Spearman's correlation coefficient. p values statistically evaluated as p<0.05 significant. *; the difference is between these groups.*

has been associated with changes in the lipid concentrations toward an atherogenic profile.[18-20] The evidence for a relationship between changes in CVD morbidity/mortality and menopause is much stronger for women who undergo a hysterectomy with bilateral oophorectomy.[21] In the Nurses' Health Study, bilateral oophorectomy, but not natural menopause, was associated with an increased risk for CHD.[22] A meta-analysis evaluated 11 studies of postmenopausal status and age at menopause in relation to CVD showed that the pooled relative risk of CVD in women who underwent bilateral oophorectomy was 2.62 compared with women who were premenopausal.[23]

There is evidence showing that menopause is accompanied by unfavorable levels of several cardiovascular risk factors. Of all the CVD risk factors, the evidence for a relation with estrogen appears to be the strongest for lipids and lipoproteins.[24] Results from both cross-sectional and longitudinal studies have reported a worse lipid profile in postmenopausal than in pre- or perimenopausal women.[25-27] A previous hamster study has shown hypercholesterolemic changes after bilateral oophorectomy.[28]

The association between cardiovascular events and LDL-C is well established, and abundant evidence shows a reduction in clinical events in both men and women when LDL-C levels are lowered.[29] LDL-C levels are generally lower in women than in men until menopause, then levels increase and LDL particles become smaller, denser, and therefore more atherogenic.[30] Oxidation of LDL-C is believed to be an initiating event in atherogenesis, and estradiol and/or other estrogens may inhibit this process.[31] Verhoeven et al.[32] found higher LDL-C concentrations in postmenopausal compared with premenopausal women after both physiological and surgical menopause. Similarly, we found increased levels of LDL-C both in natural and surgical menopause compared to perimenopausal women, but the only significant difference was between natural and perimenopausal women.

Verhoeven et al.[32] also investigated the influence of natural and surgical menopause on serum lipid levels and found no difference in change in the various lipids investigated except the TC, which was higher in postmenopausal compared with premenopausal women after both physiological and surgical menopause. Again similarly, in our study, no difference in the TC, TG, and HDL-C levels was observed between post- and perimenopausal women. Whether lipid profile change change after menopause is still not clear due to varying reported results of several studies which did not find any influence of menopause on lipids.[33,34] Also there are contrary studies in which some studies reported that changes in weight and lipids observed during the menopausal transition were independent of age,[35,36] but not others.[37,38]

Epidemiological studies have demonstrated a positive association between elevated levels of Lp(a) and the risk of both coronary artery disease and cerebrovascular accident.[39,40] Kim et al.[41] investigated the serial changes in Lp(a) levels with the loss of female sex hormones by surgical menopause and reported that the mean level of Lp(a) was increased by 24.5% 2 months after the surgery. They concluded that the Lp(a) levels appear to be closely associated with female sex hormones. This association might play a pivotal role in postmenopausal increases of atherosclerotic diseases and cardioprotective effect of estrogen in postmenopausal women.[41] Smilarly Bruschi et al. [42] reported that Lp(a) levels rose significantly over the 3 months after hysterectomy with bilateral oophorectomy, from 5.7 +/- 6.1 mg/dL to 10.4 +/- 9.2 mg/dL. In our study, although the difference was not significant there was a prominent increase in Lp(a) levels in natural and especially in surgical menopausal women.

In several studies it has been reported that the Hcy levels increase after menopause and may be related to decreased estrogen concentrations.[11,12,43] Besides Hcy levels did not differ significantly between women with natural and surgical menopause.[12,32] We could not find any significant differences in Hcy levels between the perimenopausal, natural and surgical menopausal groups. Christodoulakos et al.[12] reported that the Hcy levels increased significantly after 60 years and menopause duration increased significantly Hcy levels after >180 months duration. Bruschi et al.[14] reported that age, and not menopausal status, was the main determinant of Hcy levels in women around menopause. Also in our study we found a positive correlation with age and Hcy levels in natural and surgical menopausal women. So, a possible explanation of similar Hcy levels in our study could be the age range, in which our postmenopausal women are not so old and perimenopausal women are not so young. Another cause of this condition could be the short duration of menopause in our study, which was 42.21±45.97 months in natural and 56.31±57.83 months in surgical menopause groups.

We investigated Hcy levels, because the increase in its levels have been associated with increased atherosclerotic disease risk.[12] Also mild hyperhomocysteinemia seems an independent risk factor for vascular diseases localized to the coronary, cerebral, and peripheral vessels.[12] Although we found higher mild hyperhomocysteinemia rates as in 26% of the natural menopausal women and in 30% of the surgical menopausal women compared to the perimenopausal women which was 10%, the difference was not significant. If the postmenopausal women in our study could be older age the difference could be significant.

The metabolism of Hcy may be disrupted by a deficiency in folate, vitamin B6 and B12 and many authors have reported that Hcy levels are inversely related to the plasma concentra-

tions of the above vitamins.[44] Also it has been shown that mild hyperhomocysteinemia may be the consequence of an impairment of the remethylation pathway due to a genetic (e.g., methylen-tetrahydrofolate reductase deficiency) and/or nutritional (deficiencies of folate, vitamin B6, and B12) deficit.[44] Smilarly to Hcy levels it has been reported that vitamin B12 and folate levels shows a decrease trend with age especially after 65 years and suggested that decreased levels also reflect an age-associated inadequate dietary intake and the kind of menopause did not influence their levels.[45,46] There were no significant differences in the levels of folate and vitamin B12 between the perimenopausal and postmenopausal women in our study and the reason of this condition could be again age-specific.

It has been shown that CRP induces adhesion molecule expression in human endothelial cells in the presence of serum. This finding supports the hypothesis that CRP may play a direct role in promoting the inflammatory component of atherosclerosis.[47] Also CRP is an independent marker for the risk of CVD in postmenopusal women without clinically evident CHD.[48] Stefánska et al.[49] found that markedly increased CRP values (>3 mg/L) were found in 25% of late-postmenopausal and 15% of perimenopausal women but this difference was not significant. Recently, in a longitudinal study, CRP levels were not influenced significantly by the menopausal transition. No difference in CRP levels was observed between natural and surgical menopause.[32] In our study, no difference in the CRP levels were observed between perimenopausal, natural and surgical menopausal women. Also markedly increased CRP values were smilar in all groups.

When we made a correlation between age and lipid profile there was a negative correlation between age and HDL-C in natural menopause group, and there was a positive correlation between age and TG in perimenopause group. Zhou et al.[50] reported that aging is associated with increased levels of TC, LDL-C, TG, and TC/HDL-C. They divided perimenopause into early and late menopause and they found the significant increase in lipid profile in the late perimenopause, but not in the early postmenopause. Smilar to them in the Study of Women's Health Across the Nation, it has been demonstrated that TC, LDL-C, TG, and HDL-C levels peak in the late perimenopause.[37] In our study FSH and E2 levels of the perimenopausal and the postmenopausal women were smilar, so we can say that our perimenopausal women were in late perimenopause. Also as previous studies showed that E2 and FSH had effects on serum lipid profile,[51,52] it is not suprising to find smilar lipid profile in our study. So our results supports the hypothesis of Zhou et al.[50] that the changes in lipid profile probably occur in the perimenopausal period but not in the postmenopausal period.

In conclusion, both in natural and in surgical menopause, we could find no change in the CHD risk profile except LDL-C levels. Although we determined high levels of Lp(a) in natural and especially in surgical menopause compared to perimenopause group, the difference was not significant. The perimenopausal women in our study could be accepted as late perimenopause, so it could be one of the reasons why we found similar lipid and vitamin levels. Also the age of women in postmenopausal group were not much older and the menopause duration was short. So if we have chosen early perimenopausal and older postmenopaual women, we could find unfavorable lipid profile which could cause an increase in CHD risk profile among menopausal women. Further investigations with larger numbers and older age of postmenopausal women are necessary to determine the role of this markers on the increased incidence of CVD in menopausal women.

Doğal ve Cerrahi Menopozun Kardiyovasküler Risk Markerları Folat ve Vitamin B12 Düzeylerine Etkisi

AMAÇ: Doğal ve cerrahi menopozun serum lipidleri, lipoprotein-a, C-reaktif protein, homosistein, folat ve vitamin B12 düzeyleri üzerine etkisini araştırmak.

GEREÇ VE YÖNTEM: Çalışmaya 126 sağlıklı kadın dahil edildi. Kadınların 20'si perimenopoz, 62'si doğal menopoz ve 44'ü cerrahi menopozda idi. Total kolesterol düzeyleri, düşük dansiteli lipoprotein-kolesterol, yüksek dansiteli lipoprotein-kolesterol, trigliserid, lipoprotein-a, C-reaktif protein, homosistein, folat ve vitamin B12 düzeyleri ölçüldü ve gruplar arası karşılaştırmalar yapıldı.

BULGULAR: Doğal menopoz grubu ile perimenopozal grup arasında, total kolesterol, trigliserid, lipoprotein-a, homosistein ve folat düzeyleri bakımından anlamlı bir fark saptanmadı. Ayrıca cerrahi menopoz grubunda total kolesterol, lipoprotein-a, homosistein, vitamin B12 düzeyleri perimenopozal gruba göre yüksek, yüksek dansiteli lipoprotein-kolesterol düzeyi ise düşük saptanmasına rağmen bu fark istatistiksel olarak anlamlı değildi. Düşük dansiteli lipoprotein-kolesterol düzeyi doğal menopozal kadınlarda, perimenopozal kadınlara göre anlamlı olarak daha yüksekti ($p<0,05$). Cerrahi menopozal grupta perimenopozal gruba göre düşük dansiteli lipoprotein-kolesterol düzeyleri daha yüksek saptanmasına rağmen bu fark istatistiksel olarak anlamlı değildi. Doğal menopozal grupta yüksek dansiteli lipoprotein-kolesterol ile yaş arasında negatif bir korelasyon vardı ($p<0,05$). Hem cerrahi hem de doğal menopoz grubunda homosistein ile yaş arasında pozitif bir korelasyon saptandı ($p<0,05$).

SONUÇ: Perimenopozal ve postmenopozal kadınlarda düşük dansiteli lipoprotein-kolesterol düzeyleri dışında, incelenen kardiyovasküler risk markerları, folat ve B12 vitamini düzeyleri açısından anlamlı bir fark saptanmamıştır.

Anahtar Kelimeler: Kardiyovasküler risk, Folat, Vitamin B12, Menopoz

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