Turkish Journal of Diabetes and Obesity / *Türkiye Diyabet ve Obezite Dergisi*
Original Article / Özgün Araştırma

Effect of Low Fat and Low Cholesterol Diet Intervention on LDL Subgroups in Dyslipidemic Patients: Epidemiological Observational Study

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Cite this article as: Kaçar Mutlutürk Ü et al. Effect of low fat and low cholesterol diet intervention on LDL subgroups in dyslipidemic patients: Epidemiological observational study. Turk J Diab Obes 2023;2: 145-151.

ABSTRACT

Aim: According to studies, the individual cardiovascular disease (CVD) risk is predicted and low density lipoprotein cholesterol (LDL cholesterol) sub-group concentration better than LDL cholesterol. High fat and cholesterol intakes are generally considered to pose a risk on CVD. The purpose of this study is to analogize LDL sub-group concentration pre and post a diet with LowFat and LowCholesterol written a prescription to dyslipidemic sicks along 3 months.

Material and Methods: Diagnosticated dyslipidemia sicks (n=47) on the part of the endocrinologist were pursued along 3 months via a LowFat, LowCholesterol diet upon a lasting a month basis, on condition that they were proper for each. Before and after dietary intervention periods, biochemical parameters and anthropometric measurements were compared.

Results: A sum of 47 participants (15 men and 32 women) with an average age of 48.51±9.86 years were involved. 13 women were at premenopausal and 19 women were at postmenopausal stages of 32 women involved. Small dense LDL (Sd-LDL) decreased from 11.0 (0.0-37.0) mg/dL at the beginning to 7.0 (0.0-68.1) mg/dL after the dietary intervention, but this decline was unimportant (p=0.686). Midbands (MiDC, MidB, MidA) subgroups of intermediate density lipoprotein cholesterol (IDL-cholesterol) declined considerably after dietary interference (p<0.001, p=0.008, p=0.045, respectively).

Conclusion: A LowFat and LowCholesterol diet prescribed to dyslipidemic sicks (without using medicimes influencing lipid profile) along 3 months, had a positive impact on decreasing the sub-groups of IDL-cholesterol and LDL-cholesterol. Also, this dietary intervention induced beneficial impacts on anthropometric indications, tension and blood lipid profiles of the patients.

Keywords: *Dyslipidemia, LDL Sub-groups, IDL Sub-groups , LowFat LowCholesterol Diet*

Dislipidemik Hastalarda Az Yağlı ve Az Kolesterollü Diyet Müdahalesinin LDL Alt Grupları Üzerine Etkisi: Epidemiyolojik Gözlemsel Çalışma

ÖZ

Amaç: Çalışmalara göre, düşük yoğunluklu lipoprotein kolesterol (LDL kolesterol) alt grup konsantrasyonları bireysel kardiyovasküler hastalık (KVH) riskini, LDL kolesterolden daha iyi tahmin etmektedir. Yağ ve kolesterolün fazla alımları genellikle kardiyovasküler hastalık (KVH) için bir risk olarak kabul edilir. Bu çalışmanın amacı, dislipidemik hastalara 3 ay süreyle az yağlı ve az kolesterollü bir diyetin öncesi ve sonrası LDL alt grup konsantrasyonunu karşılaştırmaktır.

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DOI: 10.25048/tudod.1182426

Received / *Geliş tarihi* : 01.10.2022
Revision / *Revizyon tarihi* : 04.07.2023
Accepted / *Kabul tarihi* : 18.07.2023

Gereç ve Yöntemler: Endokrinolog tarafından dislipidemi tanısı konulan hastalar (n=47) aylık olarak her birine özel olmak kaydıyla az yağlı, az kolesterollü diyetle 3 ay izlendi. Diyet müdahale dönemleri öncesi ve sonrası, biyokimyasal parametreler ve antropometrik ölçümler karşılaştırıldı.

Bulgular: Yaş ortalaması 48,51±9,86 olan toplam 47 katılımcı (15 erkek ve 32 kadın) çalışmaya dahil edildi. Dahil edilen 32 kadından 13'ü menopoz öncesi, 19'u menopoz sonrası dönemdeydi. Çalışmanın başında 11,0 (0,0-37,0) mg/dL olan Small dense LDL (Sd-LDL), diyet müdahalesinden sonra 7,0 (0,0-68,1) mg/dL'ye düştü, ancak anlamlı değildi (p=0,686). Orta yoğunluklu lipoprotein kolesterolün (IDL-kolesterol) alt grupları MiDA, MidB, MidC diyet sonrası önemli ölçüde azaldı (sırasıyla, p=0,045, p=0,008, p<0,001).

Sonuç: Dislipidemik hastalara (lipit profilini etkileyen ilaç kullanmayan) 3 ay boyunca verilen az yağlı ve az kolesterollü diyet, LDL-kolesterol ve IDL-kolesterol alt gruplarını düşürmede olumlu etki göstermiştir. Ayrıca bu diyet, hastaların antropometrik ölçümleri, kan basıncı ve kan lipid profilleri üzerinde yararlı etkilere neden olmuştur.

Anahtar Sözcükler: *Dislipidemi, LDL Alt Grupları, IDL Alt Grupları, Düşük Yağlı Düşük Kolesterollü Diyet*

INTRODUCTION

Dyslipidemia refers to; changes in blood lipid distribution due to lipid metabolism disorder, including the numerical excess or deficiency of lipoproteins. Increased LDL-cholesterol, total cholesterol, triglyceride levels and a decline in HDL-cholesterol levels are major risk factors for atherosclerotic diseases (1,2). Dyslipidemia is the main factor in the pathogenesis of atherosclerosis and it is the most significant avoidable hazard consideration which enhances the risk of atherosclerotic cardiovascular diseases (ASCVD) (2).

According to the results of the study conducted to specify the extensity of dyslipidemia and its relationship with cardiovascular hazard elements in Turkish adults, 43.0% had high total cholesterol, 41.5% had low HDL-cholesterol, 36.2% had high LDL-cholesterol and 35.7% had high triglyceride levels (3,4).

Lowering the LDL-cholesterol concentration is the main goal in the prevention of ASCVD. Nevertheless, besides LDL-cholesterol concentrations, a more elaborative assay of LDL physico-chemical features (such as size and oxidation) has been shown to predict individual cardiovascular risk better (5,6). A study showed that small density-LDL-cholesterol (sd-LDL- cholesterol) concentrations are a better marker than total LDL-C in the evaluation of coronary heart disease (CHD) (7-9). Sd-LDL particles have a more pro-atherogenic and lower affinity than large-LDL particles, resulting in long-term circulation of the sd-LDL particles. They enter the arteria wall more handily and tie more ardently to intra-arterial proteoglycans trapped in the artery wall. Furthermore, sd-LDL particles are more susceptible to oxidation, resulting in greater uptake by the macrophages (10).

When fat intake exceeds 35% of energy intake, it is generally considered to be a risk for CVD since it is generally coupled with an increase in saturated fat and energy intakes (11). It should be noted that most cholesterol-rich foods are also high in saturated fatty acids and therefore may grow the hazard of CVD owing to saturated fatty acid substance. In 2019 European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) metadata reported reducing that dietary cholesterol is needed especially for those with high plasma cholesterol levels (<300 mg/day) (11). Studies to specify the impact of a low fat diet on plasma lipids found significant results with a reduction in LDL-cholesterol levels (12,13).

However, the number of studies examining the effect of various dietary interventions on LDL sub-groups are limited. Turkish society has high calorie intake, total fat intake and saturated fat intake. In Turkey, currently there is no study demonstrating the impact of a LowFat, LowCholesterol diet on LDL sub-groups. For this reason, the aim of this study was to assess the impact of a LowFat, LowCholesterol dietary interference on LDL sub-groups among dyslipidemic sicks.

MATERIALS and METHODS

Study Population

Inclusion criteria for the study were the diagnosis of dyslipidemia by an endocrinologist, the absence of any medication affecting the lipid profile (such as oral contraceptives, glucocorticoids), the absence of disease such as diabetes, nephrotic syndrome, Cushing's syndrome, hyperthyroidism and hypothyroidism (including taking hypothyroidism and replacement therapy), smoking three or more times a day, not drinking alcohol, not taking herbal medicine, being nonpregnant or not lactating, having Body Mass Index (BMI) = 25-40 kg/m^2, ages 25-65, and participants to participate. Whole participants took written acknowledgement. Erciyes University Faculty of Medicine Clinical Research Ethics Committee confirmed the study ethically (Approval Number: 2017/550 Date: 08.12.2017).

Study Design and Dietary Intervention

The study was carried out between January 2018-July 2019 in Erciyes University Health Application and Research

Center. This study was arranged as a epidemiological observational study and 47 patients were included. A LowFat (less than 30% of total energy), and LowCholesterol (less than 200 mg/day) diet was designed for the attenders at the outline, in as much as the sex, lifeway, labour conditions, feeding habits, BMI, parallel illnesses and hazard specifications. The sicks were summoned to the controls every month and pursued up for a sum of 3 months. As the sicks accepted at the first and second months, Body Impedance Analyze (BIA) indications were carried out and dietary adherency was checked. Blood samples were received from the sicks at the reference vaue and 3 months later the impacts of a LowFat, LowCholesterol diet on anthropometric and biochemical indications were assessed. Energy limited diet were planned for overweight and obese sicks (~ 500-1000 kcal/day). Moreover, sicks were advised to pace at a moderate velocity minimum 30-40 minutes every day.

Data Collection

A survey involving socio-demographic features, nourishment routines, physical activity situations and concomitant illnesses was filled by the searcher. Nutritional habits of the participants were determined by taking the frequency of food consumption (14). Physical activity was asked by the 'International Physical Activity Questionnaire (short form) (15).

Anthropometric Measurements

Anthropometric assessment contained weight, height, waist and neck circumference gauged with slight dress. We gauged height via a stadiometer to theclosest 0.1 cm, weightiness via a calibrated scale to the closest 0.1 kg. Waist cirumference was gauged via a inelastic tapeline gauging the mid posirion between the lower nervure and the crista iliac crest and scrag circumference was gauged via a inelastic plastic tape from the mid of the neck between the middle jugular backbone and the middle anterior neck finely of 0.1 cm. BIA measurings, Bodily structure of the participators was decided with Tanita BC-418 MA device (16,17).

Biochemical Parameters

In the Endocrinology clinic; the diagnosticated dyslipidemia sicks by an endocrinologist and their preprandial blood glucose (mg/dL), total cholesterol (mg/dL), triglycerides (mg/dL), LDLcholesterol (mg/dL), HDLcholesterol (mg/dL), levels were assessed. Sicks were chosen to the inclusion criteria and blood was drawn after hunger minimum twelve hours. Very low density lipoprotein (VLDL (mg/dL)), smallLDL (mg/dL), largeLDL (mg/dL), medium density lipoprotein (IDL (mg/dL)) (MidA, B, C) values. After centrifugation, blood samples were saved in the refrigerant at -80°C in Erciyes University Endocrinology Service till analysis period. For sicks who were not firstly assessed for insulin (mg/dL), some blood was received and sent to Erciyes University Blood Collection Department and examined at the Central Biochemistry Laboratory of Erciyes University. VLDL, IDL according with 3 midbands (MidA, B, C) and 7 LDL sub assemblies were gauged in serum specimens utilizing a Lipoprint System. This method distinguishes lipoproteins in a non-denaturing gel gradient of polyacrylamide depending on net area charge and magnitude. The paint ties comparatively to the relevant quantity of cholesterol in per lipoprotein. After the electrophoresis, densitometric assays and comparative concentrations of lipoprotein groups and subclasses were figured out on the Lipoware program. LDL1 to 2 (wide, bouyant, patternA); LDL3 to 7 (small, intense; pattern B). The system as well gives the mean LDL particle magnitude. TypeB if particle size was ≤265Å, medium level if particle size was 265-268Å, TypeA if particle size was ≥268Å (18).

Statistical Analysis

The convenience of the information for normal divisionis was assessed via histogram, q-q diagrams and Shapiro-Wilk test. Alteration homogeneity was tested with Levene test. Two classes independent examples t-test and Mann-Whitney U-tests were utilized for amount versions. In the qualified information, two recurring indication comparisons were utilized with McNemar-Bowker test. The double t-test and Wilcoxon tests were utilized in the quantity information for two recurring indications. Spearman's correl assay was utilized to assess the connection between quantitative variables. Data analysis was performed by Turcosa Cloud statistical program. Importance level was admitted as $p<0.05$.

RESULTS

Study Participants

Figure 1 shows the participants in detail. All of 47 participants (15 men and 32 women) with an average age of 48.51±9.86 years, diagnosticated with dyslipidemia, carried out the study. 13 women were at premenopausal and 19 women were at postmenopausal stages among 32 women.

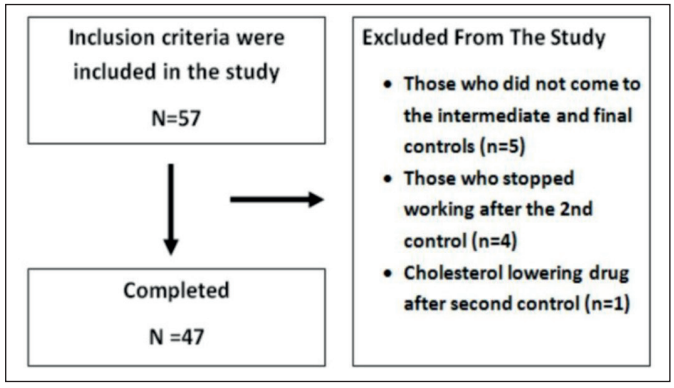

Figure 1. Participant recruitment flow.

When sociodemographic characteristics of individuals are examined, 95.7% live in the province. Of the patients; 38.3% were primary school and 27.7% were high-school graduates. 78.7% of the participants unemployed and 57.4% of their income was less than the minimum wage. According to the marital status, 89.4% were married.

Anthropometric Measurements

As shown in Table 1, after 3 months, mean BMI, body weight, waist-neck circumference and waist-to-height ratio declined at a considerable extent from for two sexes (p<0.001). At the end of 3 months, the mean fat percentage decreased from 26.69±5.47% to 25.36±6.10% in men (p=0.131) and from 39.95±4.38% to 39.65±4.25% in women (p=0.576).

Biochemical Parameters

Biochemical parameters of the patients are given in Table 2. Total cholesterol, preprandial and triglyceride levels were considerably decreased 3 months later with a LowFat, Low-

Table 1: Changes in the anthropometric measurements of participants before and after the dietary intervention.

	Men (n=15)				Women (n=32)			
Variable	**Before Diet**	**After Diet**	**p**	**t**	**Before Diet**	**After Diet**	**p**	**t**
Body weight (kg)	89.8±17. 3	86.6±15.3	0.012	2.884	80.1±12.0	77.3±11.2	0.001	3.662
BMI (kg/m²)	30.6±6.1	29.5±5.5	0.009	3.05	32.3±5.1	31.3±5.1	0.001	3.685
Waist circumference (cm)	106.5±8.9	102.2±8.9	<0.001	5.246	104.6±11.9	100.8±10.4	<0.001	5.178
Waist / Height Ratio	0.6±0.05	0.6±0.06	<0.001	5.339	0.6±0.09	0.6±0.08	<0.001	5.122
Neck circumference (cm)	41.7±2.1	40.5±2.2	<0.001	5.391	36.7±2.4	36.1±2.4	<0.001	4.152
Fat percentage (%)	26.6±5.4	25.3±6.1	0.131	1.606	39.9±4.3	39.6±4.2	0.576	0.566

Data presented as mean±standard deviation or median (min-max). t = Dependent Samples t-test

Table 2: Biochemical parameters of the participants before and after dietary intervention.

Variable		**Reference Values of Variables**	**Before Diet (n=47)**	**After Diet (n=47)**	**Test**	
					p	**statistics**
Fasting blood glucose (mg/dL)		74-106	94.2±9.6	89.7±10.7	0.014	*t*= 2.558
Total cholesterol (mg/dL)		70-200	246.3±31.0	234.2±37.8	0.022	*t*= 2.367
Triglycerides (mg/dL)		40-130	192.0 (153.0-271.5)	143.0 (116.0-228.0)	<0.001	Z= -3.794
HDL Cholesterol (mg/dL)	Men	40-60	39.3±7.2	40.1±6.0	0.584	*t*= -0.560
	Women	40-60	54.3±10.8	54.1±13.1	0.865	*t*= 0.172
LDL Cholesterol (mg/dL)		100-130	153.2±29.6	150.0±29.9	0.459	*t*= 0.746
Insulin (mIU/L)		2.6-24.8	11.8(9.1-15.3)	10.5(8.5-14.5)	0.317	Z= -1.000
VLDL Cholesterol (mg/dL)		≤22	45.6±11.8	49.0±12.1	0.050	*t*= -2.016
MidC (mg/dL)		≤23	28.2±4.7	21.9±4.8	<0.00	*t*= 8.819
MidB (mg/dL)		≤15	17.0 (13-19.5)	14.0	0.008	Z= -2.640
MidA (mg/dL)		≤25	20.0 (16.5-23.0)	17.0	0.045	Z= -1.997
IDL-Cholesterol (mg/dL)		≤63	66.0 (55.0-73.0)	53.0	<0.00	Z= -4.399
LDL1 (mg/dL)		≤57	40.8±10.1	38.4±10.3	0.033	*t*= 2.203
LDL2 (mg/dL)		≤30	33.2±10	29.4±9	0.008	*t*= 2.791
LDL3 (mg/dL) *		≤6	11.0 (5.0-19.0)	7.0 (.5-16.5)	0.759	Z= -0.307
LDL4 (mg/dL) **		≤0	3.0 (2.0-6.0)	2.0 (2.0-6.5)	0.268	Z= -1.108
Large-LDL (LDL1-LDL2) (mg/dL)		≤87	76.0 (66.5-83.6)	67.0 (56.0-78.6)	0.002	Z= -3.111
Small-LDL (LDL3-LDL7) (mg/dL)		≤6	11.0 (0.0-37.0)	7.0 (0.0-68.1)	0.686	Z= -0.465
Small-LDL / Large-LDL (mg/dL)		≤0.07	0.2 (0.0-0.7)	0.1 (0.0-1.4)	0.188	Z= -1.196

Data presented as number (%) or mean±standard deviation or median (min-max).
*Since there are no LDL3 values in the system, LDL3 comparison of 43 participants is given.
** Since there are no LDL4 values in the system, LDL4 comparison of 27 participants is given. t = Dependent Samples t-test
Z = Wilcoxon Signed Rank Test

Cholesterol diet (p=0.014, p=0.022, p<0.001, in turn). There was an increase in HDL- cholesterol at the end of the study, however this increase was not significant (p=0.896). LDL-cholesterol levels decreased from 153.25±29.60 mg/dL to 150.08±29.93 mg/dL (p=0.459).

Although insulin levels decreased after the dietary intervention, it was not significant (p=0.317). MidA, MidB, MidC, also referred to as subgroups of IDL or VLDL residues, declined considerably after the dietary interference (p=0.045, p=0.008, p<0.001 respectively). Similarly, IDL levels declined considerably after dietary intervention (p<0.001).

LDL1 from LDL sub-groups (mean 40.89±10.17 mg/dL to 38.43±10.30 mg/dL, p=0.033) and LDL2 (33.28±10.00 mg/dL to 29.45±9.05 mg/dL, p=0.008) significantly decreased after the dietary intervention. Since the sum of LDL1 and LDL2 yielded large-LDL, a significant reduction was watched in large-LDL after the dietary intervention (p=0.002). Although there was a decrease in LDL3 and LDL4 after the dietary intervention, this decrease was not significant (p=0.759, p=0.268, respectively). Small LDL decreased from 11.0 mg/dL (0.0-37.0 mg/ dL) at the beginning to 7.0 mg/dL (0.0-68.0 mg/dL) after the dietary intervention, but this decline was not important (p=0.686). Although the small-LDL/large-LDL ratio decreased after the dietary intrevention, this reduction was not significant (p=0.188).

The decline in systolic blood pressure (122±10 mmHg vs. 118±9 mmHg, p=0.005) and diastolic blood pressure (78±6 mmHg vs. 75±6 mmHg, p=0.022) of the cases after the nutritional interference was significantly important (p<0.05).

The particle size increased from 266.0 Å (263.0-269.2 Å) to 267.5 Å (263.1-269.2 Å), but this increase was no significant (p=0.412).

DISCUSSION

Dyslipidemia is a component of metabolic syndrome and is a strong indicator of CVD (19). Treatment of dyslipidemia is referred as lifestyle changes, pharmacological and non-pharmacological treatment. Lifestyle changes are accepted as primary care. Among them, the proper dietary intervention is an important part of the treatment (5). LDL-cholesterol is a well-recognized hazard element for the evolvement of cardiovascular events, and lowering LDL-cholesterol is the key for reducing CVD risk (2). LDL cholesterol is composed of sub- groups of particles of different size and density. It is stated that sd-LDL has a greater atherogenic potential than other LDL sub-groups and sd-LDL cholesterol is a better indicator for predicting CVD than total LDL-cholesterol (20). Sd-LDL predominant individuals tend to have higher triglycerides and lower HDL-cholesterol levels (21). In a randomized, doubleblind, cross over study, 12 non-obese men with normal lipid profiles were given a low- (of the energy; 25% fat, 62% CHO) and a high fat diet (of the energy; 37% of fat, 50% CHO) and the changes in plasma lipids and LDL sub-groups at the end of three days were examined. The high-fat diet was additionlly related to an important raise in LDL particle size (255.0 vs 255.9 Å; p=0.01) and an important decline in the rate of smallLDL particle (<255.0 Å) (50.7% vs 44.6%, p=0.01) (11). In our study, we detected decrements in total cholesterol and LDL-cholesterol after the dietary intervention with a LowFat and LowCholesterol diet. Also in our study, the particle size increased from 266.0 (263.0-269.2) to 267.5 (263.1-269.2) (p= 0.412). SdLDL (LDL3 + LDL4) decreased from 11.0 (0.0-37.0) mg at the beginning of the study to 7.0 (0.0-68.0) mg after the dietary intervention (p=0.686). Nevertheles, this difference was unimportant owing to a few patients. This difference would probably be meaningful if more patients were studied. Since the number of individuals with LDL3 cholesterol was 43 and the number of individuals with LDL4 cholesterol was 27, it was thought that this decrease was not significant. In another study, the effect of Mediterranean diet on LDL particle size distribution and oxidation was examined in 37 men and 32 premenopausal women were administered Mediterranean diet for four weeks, and variables were measured before and after the dietary intervention. There was a 10.4% decrease in men and a 7.3% decrease in women in LDL-cholesterol concentrations. There was a decrease in all LDL subgroups for both genders after dietary intervention, however only the decrease in sd LDL-cholesterol in men was significant (5). Similar to this study, we observed an assessment in both men and women in the LDL subgroups. But we only found a significant reduction in LDL1 and LDL2 (p=0.033, p=0.008, respectively). Similarly, decreases in large- LDL (LDL1+LDL2) were significant (76.0 (66.5-83.6) mg/dL-67.0 (56.0-78.6) mg/dL, p=0.002). According to the distribution of LDL subgroups, the dominance of LDL I and II, type A; LDL III and IV are called type B patterns. People of type B have MI risk and generally exhibit atherogenic lipoprotein profiles such as high triglycerides and low HDL- cholesterol levels (22). According to the results of a study comparing 102 individuals with phenotype A and phenotype B undergoing coronary angiographic examination, the incidence of coronary artery disease (CAD) was significantly higher in subjects with phenotype B (n=52) than those with phenotype A. (77% to 44%; p <0.005) (23, 24). Amid the dyslipidemic sicks involved in the study, the number of patients in type B group were decreased and the number of patients in type A and intermediate level group were increased. This resulted in positive changes in the

lipid profiles of the patients after the dietary intervention. Populations with increased levels of IDL include familial combined hyperlipidemia, type III hyperlipoproteinemia, chronic renal failure (CRF), and people with type 2 diabetes. IDL has been associated with the incidence of CAD and progression of CAD in hypercholesterolemic cases (25). In a total of 416 patients, the relationship between IDL and LDL subgroups was determined by other lipids, lipoproteins and markers related to atherosclerosis. In conclusion; while MidB, MidC, LDL2 and LDL3-6 (sdLDL) showed significant and positive correlations with VLDL, MID-A and LDL1 showed significant and inverse correlation with VLDL. MID-A and LDL1 were significantly and positively associated with HDL (26). In our study, after a LowFat and LowCholesterol diet in a short period of 3 months, MidC, MidB and MidA values decreased significantly ($p<0.001$, $p=0.008$, $p=0.045$, respectively). However, contrary to our expectations, VLDL-cholesterol levels were increased at the end of the study (45.68±11.85 mg/dL to 49.06±12.18 mg/dL, $p=0.050$). In our study, we attributed the muscle loss to the weight loss. While young or premenopausal women are preserved from CVD by estrogen-induced cardioprotective mechanisms, considerable alterations in cardiovascular risk factors occur as they age and enter menopause (27). A decrease in estrogen levels in postmenopausal women is related to adverse alterations in lipid profiles, involving total cholesterol, HDLcholesterol, LDLcholesterol triglycerides (28). In this study, 13 out of 32 women were in premenopausal period and 19 were in postmenopausal period. Total cholesterol, MidB, LDL2, small- LDL and systolic tension values of both baseline and last measurements in postmenopausal women as regards premenopausal women were significantly higher. In postmenopausal women, fasting blood glucose and Large-LDL were measured at baseline; in the first measurement, triglyceride, LDL, LDL4, MidC, IDL, levels, SmallLDL/LargeLDL ratio and diastolic blood pressure values were significantly higher than premenopausal women. In conclusion, we have obtained positive results on blood lipid profile in dyslipidemic patients after 3 months of a dietary intervention with a LowFat, and LowCholesterol diet. Especially in LDL sub-groups LDL1, LDL2; we obtained significant reductions in the IDL subgroups MidA, MidB and MidC with a personalized dietary intervention. We also recorded non-significant reductions in sd-LDL-cholesterol levels. Significant and striking results can be obtained in longer studies involving more patients.

Kit purchase is limited due to lack of cost. Therefore, the number of patients included in the study is not sufficient. Evaluation of other metabolic parameters (such as AST, ALT) will also be appropriate for the study.

Acknowledgments

The authors would like to thank the participants for their involvement in the study. Also, thanks to Erciyes University Scientific Research Projects Unit for their support.

Author Contributions

Research design: **Ülger Kaçar Mutlutürk, Betül Çiçek, Fahri Bayram,** Research execution: **Ülger Kaçar Mutlutürk, Betül Çiçek, Fahri Bayram,** Data interpretation and analysis: **Ülger Kaçar Mutlutürk, Betül Çiçek,** Manuscript preparation: **Ülger Kaçar Mutlutürk, Betül Çiçek, Fahri Bayram.**

Conflict of Interest

The author declares that there is no competing interest.

Financial Support

This study was granted by Erciyes University Scientific Research Fund under the code of TYL-2018-8497.

Ethics Approval

The study was evaluated to be ethically appropriate by Erciyes University Faculty of Medicine Clinical Research Ethics Committee (Approval Number: 2017/550 Date: 08.12.2017).

ClinicalTrials.gov ID: NCT04894318. Release Date: May 15, 2021

Peer Review Process

Extremely peer-reviewed and accepted.

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