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RESEARCH

The relationship of energy-restricted diet with FTO and MC4R gene polymorphism in patients with polycystic ovary syndrome

Polikistik over sendromlu hastalarda enerji kısıtlı diyetin FTO ve MC4R gen polimorfizmi ile ilişkisi

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Abstract

Purpose: The aim of this study was to determine whether the effects of an energy-restricted diet on overweight/obese patients with PCOS on body composition and biochemical parameters in groups with MC4R rs17782313 and FTO rs9939609 polymorphisms differ from those without gene polymorphism.

Materials and Methods: A total of 48 women aged 18-45 were accepted. An 8-week diet intervention was applied, and anthropometric measurements, biochemical parameters and food consumption of the patients were determined before and after the intervention. In addition, FTO gene rs9939609 and MC4R gene rs17782313 polymorphisms were determined.

Results: The incidence of FTO and MC4R gene polymorphism was 72.9% and 68.8% respectively. Change in waist/height ratio was found to be higher in the group without FTO gene polymorphism (-0.03±0.015 cm) compared to the group with gene polymorphism (-0.02 ±0.016 cm). There was no statistically significant difference between the groups with and without MC4R gene polymorphism in terms of change (Δ) in anthropometric measurements. Although not statistically significant, there was a greater decrease in body weight (kg) and BMI (kg/m^2) in the group without MC4R gene polymorphism compared to the group with it (without polymorphism group -2.2±1.83 kg; -0.9±0.69 kg/m^2). There was no statistically significant difference between the groups with and without gene polymorphism in terms of biochemical parameters.

Conclusion: We found that the energy-restricted weight loss diet did not detect a statistically significant change in biochemical parameters in the FTO and MC4R gene polymorphism groups, but the presence of gene polymorphism made it difficult to improve in

Öz

Amaç: PKOS'lu aşırı kilolu/obez hastalarda enerji-kısıtlanmış diyetin vücut kompozisyonu ve biyokimyasal parametreler üzerine etkisinin MC4R rs17782313 ve FTO rs9939609 polimorfizmi olan gruplarda, gen polimorfizmi olmayanlardan farklı olup olmadığını belirlemek amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya 18-45 yaş arası (30.4±8.66 yıl) toplam 48 kadın alınmıştır. Hastalara 8 haftalık diyet müdahalesi uygulanmış ve çalışma öncesi ve sonrasında hastaların antropometrik ölçümleri, biyokimyasal parametreleri ve besin tüketimleri belirlenmiştir. Ayrıca FTO geni rs9939609 ve MC4R geni rs17782313 polimorfizmleri saptanmıştır.

Bulgular: FTO ve MC4R gen polimorfizmi insidansı sırasıyla %72.9 ve %68.8 olarak bulunmuştur. Bel/boy oranındaki değişim, FTO gen polimorfizmi olmayan grupta (-0,03±0,015 cm), gen polimorfizmi olan gruba (-0,02 ±0,016 cm) göre daha yüksektir. Antropometrik ölçümlerdeki değişim (Δ) açısından MC4R gen polimorfizmi olan ve olmayan gruplar arasında istatistiksel olarak anlamlı fark yoktur. İstatistiksel olarak anlamlı olmamakla birlikte MC4R gen polimorfizmi olmayan grupta, olan gruba göre vücut ağırlığı (kg) ve BKİ'de (kg/m2) daha fazla azalma vardır (polimorfizm olmayan gruptaki değişimler -2.2±1.83 kg; -0.9±0.69 kg/m2). Gen polimorfizmi olan ve olmayan gruplar arasında biyokimyasal parametreler açısından istatistiksel olarak anlamlı fark bulunmamıştır.

Sonuç: FTO ve MC4R gen polimorfizmi gruplarında enerji kısıtlamalı zayıflama diyetinin biyokimyasal parametrelerde istatistiksel olarak anlamlı bir değişiklik oluşturmadığı, ancak gen polimorfizmi varlığının antropometrik ölçümlerde iyileşmeyi zorlaştırdığı görülmüştür.

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anthropometric measurements.
Keywords:. Polycystic ovary syndrome, obesity, polymorphism, genetic

Anahtar kelimeler: Polikistik over sendromu, obezite, polimorfizm, genetik

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder frequently seen in adolescents and women of reproductive age, associated with irregular menstrual cycle, hyperandrogenism, and polycystic ovary morphology. Although there are different criteria for the diagnosis, the Rotterdam Criteria determined by the Embryology Society / American Society of Reproductive Medicine are mostly used and the incidence of PCOS in women is reported to be 15-20%[1]. According to a study conducted in Turkey, the prevalence of PCOS is 6.1%, 15.3% and 19.9%, respectively, according to NIH, AE-PCOS Society and Rotterdam criteria[2]. Increased in body weight, obesity and insulin resistance are frequently seen in individuals with PCOS. In addition, PCOS is associated with the development of diseases such as hypertension, dyslipidemia, glucose intolerance and diabetes[3].

The increase in the number of gene studies has brought with it the discovery of genes associated with obesity. There are 837,835 and 821 gene loci and 317, 282 and 258 Single Nucleotide Polymorphism (SNPs) identified are associated with obesity[4]. In Genome-wide association studies (GWAS), it was determined that several genes, especially fat mass and obesity-associated gene (FTO) and melanocortin 4 receptor gene (MC4R), are associated with obesity[5,6], and studies have found that FTO and MC4R gene polymorphisms are associated with overweight/obese PCOS patients[7,8]. Obesity related gene polymorphisms were found in women with PCOS and especially the FTO gene rs9939609 and MC4R gene rs17782313 polymorphisms were found to be associated with PCOS[9,10]. Therefore, it is thought that the obesity-related gene risk allele may be a factor that determines the effect of nutritional intervention in patients with PCOS. In some studies, found that in overweight/obese patients with FTO rs9939609 and MC4R rs17782313 gene polymorphism but not diagnosed with PCOS, Mediterranean diet[11], energy-restricted/unrestricted diets with different macronutrients[12,13] and the short- and long-term effects of high-protein weight loss diet[14,15] on body weight loss were examined and it was shown that dietary intervention may be effective/ineffective in risky allele carriers. However, there is no study in the literature examining how risk allele carriers affect anthropometric and biochemical responses to dietary intervention in PCOS patients. Determining this relationship will make a significant contribution to dietary intervention studies in PCOS, where optimal nutritional therapy is not known yet.

To the best of our knowledge, there are no studies on the combined evaluation of 3 factors regarding PCOS, obesity-related gene polymorphisms (FTO and MC4R) and diet effectiveness. Therefore, the aim of this study, to determine whether the effects of nutritional therapy (energy-restricted weight loss diet) on overweight/obese patients with PCOS on body composition and biochemical parameters in groups with MC4R rs17782313 and FTO rs9939609 polymorphisms differ from those without gene polymorphism. The hypotheses of the study were;.

1. There is a significant difference in the amount of change (Δ) in anthropometric measurements before and after the weight loss diet between PCOS patients with (AA+AT) and without (TT) FTO gene polymorphism.
2. There is a significant difference in the amount of biochemical findings change (Δ) before and after the weight loss diet between PCOS patients with (AA+AT) and without (TT) FTO gene polymorphism.
3. There is a significant difference in the amount of change (Δ) in anthropometric measurements before and after the weight loss diet between PCOS patients with (CC+CT) and without (TT) MC4R gene polymorphism.
4. There is a significant difference in the amount of biochemical finding change (Δ) before and after the weight loss diet between patients with PCOS and those with (CC+CT) and without (TT) MC4R gene polymorphism.

MATERIALS AND METHODS

Sample

Patients who applied to Aydın Adnan Menderes University Hospital Endocrinology Polyclinic, were diagnosed with PCOS, aged 18-45 years, BMI ≥25 kg/m^2 and <40 kg/m^2, no diagnosis of chronic organ failure, diabetes and cancer, and did not use corticosteroids are included.

Patients diagnosed with PCOS by doctors who were endocrinologists and worked full-time at Aydın Adnan Menderes University Hospital which working under the ministry of health and located Aydın were referred to a specialist dietitian working as a research assistant at Aydın Adnan Menderes University Faculty of Health Sciences. Patient information is recorded in the system used by the hospital. Nutritional treatments and study follow-up of the patients were carried out by dietitian.

The minimum number of individuals that should be included in the research sample is determined by Wehr et al. (2010) based on their study with women diagnosed with PCOS[16]. (G*Power 3.1. was used). In the analysis made based on the data of this research, the effect size was found to be 0.784 in the calculation made with the assumption that the basic statistics of the research would be done with the t-test. The minimum number of individuals to be included in the sample of this study was calculated according to effect size: 0,784, α=0,05 and power: 0,80 was found to be 42. It was decided to include 10% more individuals in the sample of the study, considering possible case losses, and it was planned to include at least 46 women in the study. 56 women were included in the study, 8 participants (2 of whom were pregnant, 6 of them because they did not want to follow the diet) were excluded from the study and the study was completed with 48 patients.

Procedure

The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Aydın Adnan Menderes University Faculty of Health Sciences (Approval dated 9.1.2019 and numbered 92340882-050.04.04). Informed consent was obtained from all individual participants included in the study.

The study was carried out in 4 stages, following the protocol specified below (Figure 1).

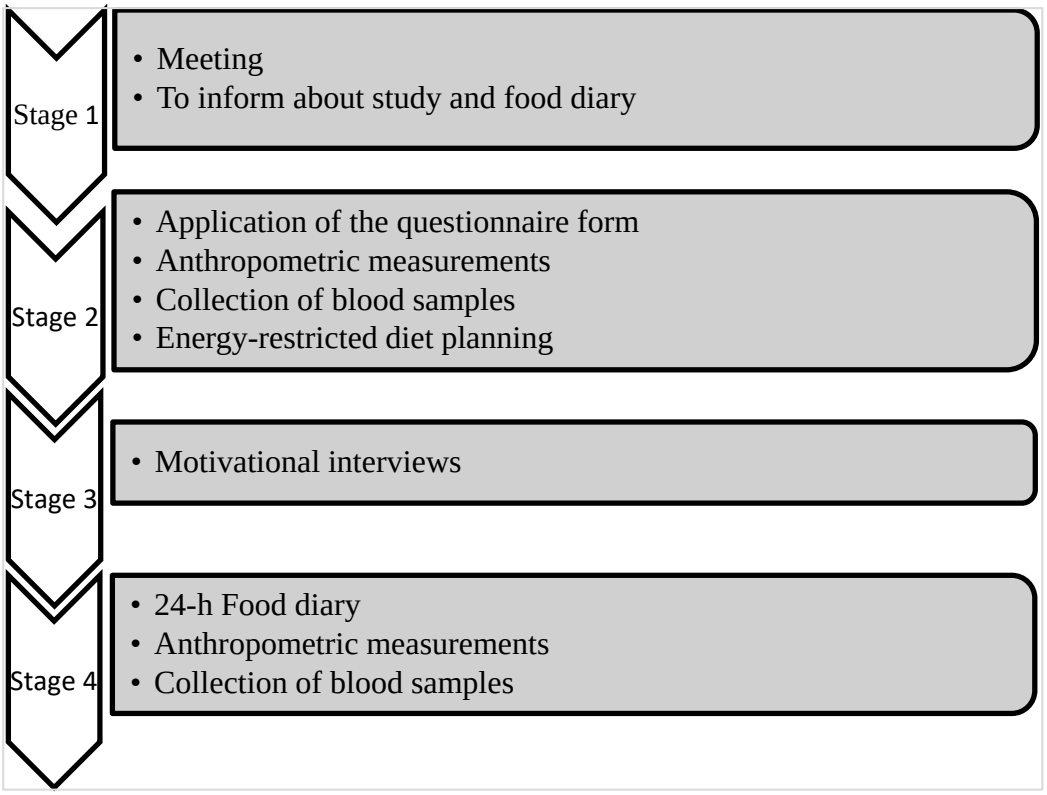

Figure 1. Flow chart of study

Stage 1: Patients diagnosed with PCOS at Aydın Adnan Menderes University Hospital Endocrinology Polyclinic met with the researcher under the direction of the doctor. Once informed of the study, patients were asked to sign an informed consent form and record their food intake for three consecutive days (two weekdays and one weekend) in their food diary. They were then asked to return to the outpatient clinic for a follow-up appointment.

Stage 2: The food diaries of the patients who came to the outpatient clinic for control were checked, their missing or incorrect reports were determined and corrected. With the questionnaire form, the patient's nutritional habits, general health information, food consumption outside of the home, socio-demographic characteristics, smoking and alcohol use habits were questioned, and physical activity information was recorded using the physical activity evaluation form. Anthropometric measurements were completed. Also, blood samples were taken to determine biochemical parameters (sex hormones and routine parameters) and gene polymorphisms. An 8-week energy-restricted weight loss diet was planned for the patients.

Stage 3: 3-5 weeks after the start of the study motivational interviews were conducted face-to-face or over the phone to ensure the compliance and continuity of the patients with the diet between weeks.

Stage 4: After eight weeks of dietary intervention, the patients were called back to the polyclinic, their anthropometric measurements were taken and their compliance with the diet was checked, and blood samples were taken for repetitions of biochemical parameters (sex hormones and routine parameters).

Clinical measurements

The researcher collected general and health information, nutritional habits, physical activity status, and food consumption reports from the patients using a face-to-face interview method and a questionnaire. No exercise recommendations were made to the patients, and they were asked not to make any changes in their physical activities during the study. The patients recorded their food diary data independently.

The researcher employed the Inbody 230 brand body analyzer, Leicester brand stadiometer (height meter), and non-stretchable measuring tape in Aydın Adnan Menderes University Endocrinology polyclinic to obtain anthropometric measurements.

At the beginning of the study and the end of the 8-week dietary intervention, blood samples were taken by the professional health personnel of Aydın Adnan Menderes University Hospital after 8 hours of fasting. Sex hormones and routine blood analyses were performed in Aydın Adnan Menderes University Hospital Biochemistry Laboratory.

Nutrition therapy

For overweight/obese patients with PCOS, personalized weight loss diets with an energy consumption of 500-1000 kcal from the total requirement, prepared by taking into account "TÜBER 2015[17] food consumption recommendations according to age", and with a contribution of saturated fat to energy <10%, are planned.

Mifflin equation was used to determine the basal metabolic rate of the women participating in the study[18].

"BMR =(10 x weight (kg) + 6.25 x height (cm) – 5 x age (h) – 161)"

"Physical activity level (PAL) and lifestyle classification" table in TUBER was used to determine physical activity levels[17]. Dietary energy was determined by reducing the daily energy requirement by 500-1000 kcal from the calculated daily energy requirement after multiplying the basal metabolic rate (BMR) value calculated with the Mifflin equation by the physical activity coefficient. The calculated dietary energy should not be less than the BMR value. Dietary energy was determined by calculated BMR or 0-100 kcal above BMR (Table 1). Considering the TUBER healthy nutrition recommendations to the patients, an individualized weight loss diet plan consists of 15-20% of dietary energy from protein, 25-30% from fat (<10% saturated fat), 50-55% from carbohydrates and a total of 6 meals a day was prepared and applied for 8 weeks.

Genotyping

For gene polymorphism analysis, approximately 5 mL of blood was taken by the professional health personnel of Aydın Adnan Menderes University Hospital in a tube containing Ethylenediamine tetra acetic acid (EDTA), and blood samples were stored at -20 ^{0} C until the time of analysis.

In this study, intronic Homo sapiens FTO gene rs9939609 (T/A) polymorphism and MC4R gene rs17782313 (T/C) polymorphism were analysed by Realtime Polymerase Chain Reaction (PCR) method.

Extraction Kit (Vivantis ®, Malaysia) isolation kit was used for whole blood samples collected from individuals in tubes with EDTA. The nucleic acid loads (ng values) of the samples obtained from the total RNA extraction process were measured with the Colibri Microvolume Spectrometer (Titertek-Berthold, Germany) device to be used in the next steps of the study.

Table 1. Average energy requirement of patients, energy content of weight loss diet and negative energy balance (kcal/day)

	$\tilde{x} \pm SS$	M±IQR	Min-Max
BMR	1464 ±185	1464 ±245	1120-2003
Total energy requirement	2096 ±253	2063 ±375	1631-2804
Weight loss diet energy content	1513 ±183	1500 ±200	1200-2000
Negative energy balance	583 ±183	568 ±121	419-817

BMR: basal metabolic rate

The lyophilized primers synthesized for the study were nuclease to be 100 Mm. dissolved with free dH2O. Real time PCR reactions TaqProbe 2X qPCR MasterMix -No Dye (ABM, Canada) was used. 1X TaqProbe 2X qPCR for 20 µl reaction mix Master Mix, 0.3mm forward primer (10 mM) and 0.3 mM reverse primer (10 mM), 0.1 mM probe (10 mM), 3 µl DNA and 3.5 µl nuclease free dH2O was used. Reaction, 7500 Fast Real-Time PCR System (Applied Biosystems, USA) using 8 strip tubes, the first denaturation was done at 95 °C for 5 min, 40 repetitions at 95 °C for 10 sec, 60 °C for 30 sec (read), fragment amplified at 72 °C for 5 sec. Shown based on allele -specific probe data obtained as a result of real-time PCR.

Fluorescent dye-labeled probes for T (FAM) and C (HEX) alleles were used for mutation detection on the MC4R gene region. Genotypes according to these radiations in real time PCR device results were recorded in the table as TT (normal), CC (mutant) and TC (heterozygous).

Fluorescent dye-labeled probes for T (FAM) and A (HEX) alleles were used for mutation detection on the FTO gene region. Genotypes according to these radiations in real time PCR device results were recorded in the table as TT (normal), AA (mutant) and TA (heterozygous).

In the study results; those with the FTO gene A allele (AA+AT) are grouped as polymorphism, and those with the TT genotype are grouped as those without polymorphism. Those with the MC4R gene C allele (CC+CT) are grouped as polymorphism, and those with the TT genotype are grouped as those without polymorphism.

Statistical analysis

Statistical analyses were performed using the SPSS 20.0 Windows (SPSS, Inc.; Chicago, USA) package program. Frequency tables and descriptive statistics were used to comment the findings. Values of the descriptive variables are presented as number (n), percent (%), arithmetic mean ($\bar{x}$), standard deviation (SD), median (median) and IQR (Interquartile range).

In this study, while evaluating quantitative variables, parametric methods were used for measurement values suitable for normal distribution, and non-parametric methods were used for measurement values not suitable for normal distribution. The t-test was used to compare the means of normally distributed data, and the Mann Whitney U test was used to compare data that did not show normal distribution. A p value of <0.05 was considered statistically significant.

RESULTS

In this study, the incidence of polymorphism in the FTO gene rs9939609 variant (AA+AT) was 72.9%, and the incidence of polymorphism in the MC4R gene rs17782313 variant (CC+CT) was 68.8% (Table 2).

Evaluation of individuals' daily dietary intake of energy and nutrients before and after treatment is given in Table 3. Individuals' macro and micronutrient intakes, except for energy, omega 3, vitamin E and vitamin B_{12}, changed statistically significantly after treatment compared to before

Table 2. Distribution of individuals' FTO and MC4R gene polymorphisms (n:48)

	S	%
FTO		
Non-polymorphism (TT)	13	27.1
with polymorphism (AA+AT)	35	72.9
AA	13	27.1
AT	22	45.8
MC4R		
Non-polymorphism (TT)	15	31.2
with polymorphism (CC+CT)	33	68.8
CC	14	29.2
CT	19	39.6

*% is taken over n number.

Table 3. Individuals' daily intake of energy and nutrients before and after nutritional treatment

Energy and nutrients	Before		After		p
	$\tilde{x}$ ±SS	M±IQR	$\tilde{x}$ ±SS	M±IQR	
Energy (kcal)	1316.8±237.13	1320.7±367.75	1350.3±212.25	1362.6±256.59	0.457
Carbohydrate (g)	142.4±28.14	148.7±39.04	162.2±24.80	162.6±34.41	0.000
Carbohydrate (%)	44.5±6.04	45.0±6.00	49.6±3.87	49.0±4.00	0.000*
Dietary fiber (g)	17.3±4.07	16.5±5.54	26.6±5.38	27.4±9.11	0.000
Protein (g)	52.5±12.29	51.4±16.93	66.4±12.65	67.0±20.41	0.000
Protein (%)	16.3±2.89	16±3.00	20.3±3.14	20.0±3	0.000*
Fat (g)	57.9±13.92	57.65±18.4	45.9±10.87	46.8±12.16	0.000*
Fat (%)	39.1±4.92	38.5±5.00	30.1±4.35	31.0±4.00	0.000*
SFA (g)	18.5±5.51	18.0±8.02	14.3±4.38	14.6±4.96	0.000
MUFA (g)	20.6±5.05	20±6.58	17.2±5.51	16.8±7.52	0.006
PUFA (g)	14.8±5.36	13.7±10.42	10.1±4.15	9.7±6.09	0.000*
Omega 3 (mg)	1.2±0.52	1.0±0.68	1.2±0.66	0.9±0.59	0.951*
Omega 6 (mg)	13.6±5.15	13±9.30	8.9±4.13	8.6±5.72	0.000
Omega 6/omega 3	13.4±6.87	11.6±8.46	8.9±5.16	7.5±3.42	0.001*
Vitamin A (µg)	840.6±1115.14	685.2±573.76	1202.4±639.95	1100.4±904.46	0.000*
Vitamin E (mg)	12.9±3.73	12.4±5	11.1±4.39	10.3±5.7	0.057*
Vitamin B_1 (mg)	0.7±0.16	0.7±2.20	1±0.19	1±0.28	0.000
Vitamin B_2 (mg)	1.1±0.34	1.1±0.41	1.5±0.31	1.5±0.40	0.000*
Niacin (mg)	9.7±3.45	9.4±4.43	12±4.03	11.7±4.93	0.005
Vitamin B_{12} (mg)	3.6±3.59	3.3±1.78	3.3±1.74	3.4±2.60	0.731*
Total folate (µg)	242.5±65.35	238±95	369.3±119.98	362.6±196.06	0.000
Vitamin B_6 (µg)	1.1±0.29	1.1±0.36	1.6±0.35	1.6±0.54	0.000
Vitamin C (mg)	97±57.20	86.4±56.86	190.1±78.18	202.2±120.31	0.000*
Potassium (mg)	1932.9±483.33	1867.7±551.55	3037.3±619.00	3072.8±1107.13	0.000
Calcium (mg)	553.7±187.21	541.9±210.44	937.4±225.84	899.1±279.38	0.000*
Magnesium (mg)	226.6±60.26	217.7±86.60	322.4±70.15	307.8±107.57	0.000*
Phosphorus (mg)	935.6±228.25	901.5±309.06	1258.6±249.57	1265.8±444.83	0.000
Iron (mg)	9.5±2.49	9.3±3.55	12.6±3.58	12.4±6.62	0.000
Zinc (mg)	49.6±3.87	49.0±4.00	9.5±2.32	9.2±3.79	0.000*

M±IQR: Median±Interquartile range, SFA:Saturated Fatty Acids, MUFA:Monounsaturated Fatty Acids, PUFA:Polyunsaturated Fatty Acids.; "Paired Sample-t" test was used to compare values with normal distribution.; *"Wilcoxon test" was used to compare values that did not have a normal distribution.

The amount of change (Δ) was determined by giving the difference between the anthropometric measurements before and after the dietary intervention according to the FTO and MC4R gene genotypes of the patients (Table 4).

The amount of change in waist/height ratio was higher in the group without FTO gene polymorphism (-0.03±0.015 cm) compared to the group with gene polymorphism (-0.02±0.016 cm) ($p<0.05$). In addition, although there is no statistically

significant difference, it was shown that there was a greater decrease in body weight (kg), waist circumference, hip circumference (cm) and BMI (kg/m²) values in the group without polymorphism compared to the group with polymorphism.

Table 4. The effect of dietary intervention on anthropometric measurements and biochemical parameters according to the FTO and MC4R genes of the patients (change (Δ))

	FTO gene					MC4R gene				
	with polymorphism (AA+AT)		Non-polymorphism (TT)			with polymorphism (CC+CT)		Non-polymorphism (TT)		
	$\bar{x}$ ±SS	M±IQR	$\bar{x}$ ±SS	M±IQR	p	$\bar{x}$ ±SS	M±IQR	$\bar{x}$±SS	M±IQR	p
Anthropometric measurements										
Body weight (kg)	-1.4±2.25	-1.3±2.00	-2.5±1.95	-2.1±1.90	0.051*	-1.5±2.35	-1.5±2.10	-2.2±1.83	-1.9±1.80	0.258
Waist circumference (cm)	-2.4±2.59	-3.0±3.00	-4.2±2.48	-3.0±2.00	0.110*	-2.9±2.84	-3.0±3.00	-2.9±2.29	-3.0±3.00	0.988
Hip circumference (cm)	-2.0±1.36	-2.0±2.00	-3.1±1.93	-3.0±3.00	0.053*	-2.4±1.76	-2.0±2.50	-2.2±1.15	-2.0±2.00	0.865*
BMI (kg/m²)	-0.5±0.84	-0.5±0.70	-0.9±0.75	-0.7±0.80	0.081	-0.5±0.89	-0.5±0.70	-0.9±0.69	-0.8±0.60	0.179
Waist/hip (cm)	-0.0±0.02	-0.0±0.00	-0.01±0.01	-0.0±0.00	0.119	-0.01±0.02	-0.0±0.00	-0.01±0.02	-0.0±0.00	0.745
Waist/Height (cm)	-0.02±0.016	-0.01±0.02	-0.03±0.015	-0.02±0.01	**0.024***	-0.02±0.02	-0.0±0.00	-0.02±0.01	-0.0±0.00	0.115
Neck circumference (cm)	-0.6±0.74	-0.0±1.00	-0.6±0.77	-0.0±1.00	0.845*	-0.7±0.77	-1.0±1.00	-0.3±0.62	-0.0±1.00	0.105*
Body fat (%)	-0.8±2.26	-0.8±2.30	-1.5±2.50	-0.6±0.60	0.554*	-1.1±1.98	-0.6±2.10	-0.8±3.03	-0.5±0.90	0.789*
Body water (%)	+0.1±1.13	+0.3±1.60	-0.03±0.81	-0.4±1.60	0.822	+0.1±1.07	+0.1±1.50	-0.1±1.01	+0.3±1.60	0.650
Lean body mass (kg)	-0.1±1.49	-0.1±2.00	+0.02±0.66	-0.1±1.00	0.766	+0.1±1.37	-0.1±1.70	-0.4±1.14	-0.4±1.10	0.245
Biochemical findings										
17-OH-prog	+0.1±1.22	-0.0±0.90	+0.5±2.01	-0.0±1.80	0.710*	-0.2±1.24	-0.0±1.00	+0.3±1.91	-0.0±1.70	0.911*
HDL-Cholesterol	-1.5±10.82	+1.5±15.60	-6.5±9.14	-3.8±8.50	0.063*	-3.2±10.17	-1.2±14.00	-2.1±11.66	-1.1±11.40	0.746
LDL-Cholesterol	+2.7±21.72	-1.0±25.00	+15.1±19.99	+10.0±24.50	0.063*	+2.9±22.59	-0.0±25.00	+12.9±18.79	+10.0±29.00	0.145
Cholesterol	+0.1±24.18	-5.0±34.00	+5.1±17.59	+5.0±28.00	0.503	-1.9±21.67	-5.0±31.00	+8.9±23.29	+7.0±31.00	0.126
CRP	+1.4±9.42	-0.0±0.50	-6.1±19.05	-0.0±3.90	0.079*	+1.2±9.65	-0.0±1.10	-4.6±18.09	-0.0±1.80	0.243*
Triglyceride	-5.5±48.63	-3.0±31.00	-11.0±39.00	-4.0±26.50	0.685*	-7.5±45.86	-3.0±23.00	-6.1±47.54	-4.0±35.00	0.859*
Insulin	-1.6±6.77	-0.4±4.20	-2.6±8.27	-0.6±2.50	0.790*	-1.3±4.12	-0.4±3.60	-3.1±11.37	-0.6±4.40	0.764*
E2	+19.8±81.47	-0.0±29.00	+16.7±113.13	+5.0±99.50	0.816*	+14.1±68.54	-1.0±35.00	+29.8±127.19	+11.0±128.00	0.317*
FSH	-1.8±3.13	-1.0±2.80	-0.2±3.72	-0.1±5.30	0.138*	-1.5±2.95	-0.9±3.10	-1.1±4.17	-0.7±4.20	0.374*
LH	-1.9±8.20	-0.6±2.70	+4.1±14.50	-0.1±8.20	0.251*	-2.1±8.59	-0.6±2.50	+3.5±13.31	+0.7±6.20	0.073*
Progesterone	+1.3±4.08	-0.0±1.00	+0.6±6.16	-0.1±3.60	0.345*	+1.1±4.50	-0.0±2.90	+1.3±5.20	-0.0±1.10	0.780*
Prolactin	-0.6±6.03	-0.7±6.40	+2.1±6.22	-0.9±5.50	0.397*	-0.6±5.57	-0.7±5.50	+1.9±7.11	-1.0±7.50	0.764*
SHBG	+1.4±60.91	-2.9±15.50	-4.6±19.85	-1.0±13.80	0.523*	-0.1±57.63	-2.1±13.90	-0.5±42.21	-0.5±18.30	0.689*
Free Testosterone	-0.7±1.32	-0.7±1.30	-0.5±0.66	-0.2±1.10	0.651	-0.7±1.33	-0.7±1.30	-0.5±0.72	-0.3±1.20	0.465
Total Testosterone	-0.1±0.73	-0.0±0.50	-0.1±0.57	-0.0±0.80	0.981*	-0.1±0.70	-0.0±0.50	-0.1±0.66	-0.0±0.70	0.730*
DHEAS	+7.2±66.34	+0.4±40.30	+0.1±55.38	-13.6±44.20	0.296*	+6.9±62.53	-1.3±30.00	+1.6±66.27	-2.0±52.30	0.673*
Glucose	-0.6±8.47	-1.0±9.00	-0.4±8.35	-1.0±7.50	0.946	-1.5±7.72	-1.0±7.00	+1.7±9.50	-1.0±16.00	0.225
HOMA-IR	-0.4±1.65	-0.1±1.10	-0.6±1.57	-0.2±0.80	0.570*	-0.3±1.02	-0.1±0.90	-0.6±2.51	-0.2±1.30	0.422*

BMI: Body Mass Index, M±IQR: Median±Interquartile range, 17-OH-prog:17-hydroxyprogesterone, HDL-C: HDL cholesterol, LDL-C: LDL cholesterol, CRP:C-reactive protein, E2: Estradiol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, SHBG: sex hormone-binding globulin, DHEAS: Dehydroepiandrosterone Sulfate, HOMA-IR: homeostatic model evaluation index for insulin resistance, Independent groups t test was used to compare normally distributed data. *Mann Whitney u test was used to compare data that did not show normal distribution.

There was no statistically significant difference between the groups with and without MC4R gene polymorphism in terms of change (Δ) in anthropometric measurement values ($p>0.05$). However, although there was no statistically significant difference, it was determined that there was a greater decrease in body weight (kg) and BMI (kg/m^2) values in the group without MC4R gene polymorphism compared to the group with polymorphism.

There was no statistically significant difference in the amount of change in biochemical parameters between groups with and without FTO gene polymorphism, and between groups with and without MC4R gene polymorphism ($p>0.05$).

DISCUSSION

It has been suggested that the genes with the strongest association among obesity-related gene polymorphisms are FTO and MC4R[4]. Genotype frequency of FTO gene was observed in 40% for AA and 23.6% for AT of women with PCOS[9]. Also a meta-analysis proved that FTO rs9939609 gene polymorphism is a factor that may cause PCOS, especially for Asians[19]. In a study investigating the MC4R rs12970134 and rs17782313 gene variants in women with PCOS in Saudi Arabia, the incidence of individuals with the rs12970134 variant risk allele was 6.3% for AA, 40% for AG, and 7.4% for CC, 40.1% for CT.[7] In other study, the incidence of the MC4R gene rs17782313 variant C allele was found to be 24.2%[10]. In this study, the incidence of polymorphism in the FTO gene rs9939609 variant (AA+AT) was 72.9%, and the incidence of polymorphism in the MC4R gene rs17782313 variant (CC+CT) was 68.8% (Table 3). Approximately 1 in 3 of the women included in the study (not shown in the table) are obese. In this study, only one variant each for FTO and MC4R was examined, and a ratio of having the A allele or C allele was given. For this reason, polymorphism rates may have been found high in the study.

Obesity is common in PCOS patients. In a study, BMI values were found to be significantly higher in women with PCOS (28.49 kg/m^2) than in healthy women (24.93 kg/m^2)[20].

Improving nutrition and lifestyle after early diagnosis is very important to increase the quality of life and shorten the treatment period of the disease. Also, high protein, moderate carbohydrate and low-fat diets along with an active lifestyle may play a role in reducing symptoms associated with PCOS[21]. The most important aim of treatment in PCOS patients is to reduce body weight, regulate insulin resistance, glucose and lipid profile, regulation of serum androgen levels and the reworking of reproductive functions[22]. Studies are showing that ketogenic diet, high/low protein, high/low carbohydrate diet treatments, mediterranean diet or herbal and supplemental treatments applied to PCOS patients may be effective in improving PCOS symptoms and quality of life[23,24].

Low-carbohydrate, high-protein diets containing carbohydrates with a low glycemic index, also calorie-restricted diets and DASH diet appear to be the most commonly preferred among the nutritional treatments applied to individuals with PCOS to benefit insulin resistance and weight management[25,26]. It has been reported that a high-protein diet provides greater loss of BMI, waist and hip circumference.[27] In studies conducted on obese patients with PCOS on a high-protein diet, weight loss was accompanied by decreased FAI(free androgen index)[27], fasting plasma insulin[28,29], SHBG[28], HOMA-IR[29], free testosterone[27,30], total cholesterol[28] and triglyceride[28] levels.

While the positive metabolic effects of high protein diets are observed, it should not be forgotten that the risk of cardiovascular disease may increase with the increase in red meat consumption. According to a meta-analysis study, it was stated that high-protein diets provided more positive results for fasting insulin levels and HOMA-IR when compared to isocaloric standard diets, while it was stated that they generally had a similar effect on body weight loss, abdominal obesity, blood lipid levels and sex hormones. It can be suggested that short-term, high-protein diets do not cause significant negative effects on cardiovascular markers due to the significant amount of body weight loss in general. For this reason, high-protein diets where total energy is limited can be used in the management of PCOS, but it is recommended to evaluate kidney functions and nephrolithiasis risk before nutritional treatment[31].

In patients with PCOS, in addition to a high protein diet, the use of low-carbohydrate and low-glycemic index and load diets can also be recommended. In one study a low-carbohydrate diet did not significantly change blood pressure and blood lipids[32]. In a study examining diets with low glycemic load (LGL) and different carbohydrate ratios, it was found that, despite difficulties in dietary compliance,

LGL and LF (low fat) diet prescriptions were effective in promoting weight loss and reduction in body fat but had no effect on biochemical hyperandrogenism among overweight and obese adolescents with PCOS[33].

After 12 weeks of ketogenic Mediterranean diet, anthropometric and body composition measurements revealed a signifcant reduction of body weight (−9.43 kg), BMI (−3.35), FBM (8.29 kg) and VAT. A signifcant decrease in glucose and insulin blood levels were observed, in connection with this a signifcant improvement was observed in HOMA-IR. Triglycerides, total cholesterol, LDL, the LH/FSH ratio, LH total and free testosterone, and DHEAS blood levels decreased significantly. Also, estradiol, progesterone, SHBG and HDL levels increased[34].

In a study comparing two diet patterns of low glycemic load and low fat, although positive results were found in terms of body weight loss, no significant changes were found in biochemical parameters[35]. When the efficacy of a low glycemic-loaded energy-restricted diet was examined, a decrease in total testosterone and FAI values and an increase in SHBG values were observed in women with PCOS. It was also reported that menstrual irregularity decreased by 80% and acne development by 32.1%[36].

A study examining the effects of energy-restricted weight loss diets on biochemical findings and anthropometric measurements according to FTO and MC4R gene polymorphism groups in individuals with PCOS could not be found. However, conducted with individuals with a BMI of 25-40 kg/m^2, the relationship between the effectiveness of a two-year weight loss diet and the FTO gene polymorphism was investigated. It has been reported that no significant difference was observed in the low-protein diet group. In the analysis of body composition, it was reported that the amount of total body fat (kg), lean body mass, and fat ratio (%) in the high protein diet group decreased statistically and there was no significant change in the low protein diet group[37]. A high protein diet program has been shown to reduce appetite and hunger pangs in carriers of the rs9939609 variant A allele[38]. In a study examining the effect of a 4-week Mediterranean diet application on body composition and body weight loss in PCOS patients with the FTO rs9939609 variant, it was shown that the decrease in total body fat (kg) was higher in patients without gene polymorphism (TT genotype carriers), but there was no significant difference in other measurements[12]. A low-calorie, high-fat, low-carbohydrate diet has been found to reduce the resting energy expenditure of individuals without the risk allele for obesity (TT) compared to individuals who consume the same type or low-calorie, low-fat diet and have the A allele[12]. It has been reported that calorie restriction does not prevent body weight loss in obese women with the FTO gene polymorphism[39]. However, a meta-analysis study noted that obese individuals with the risk allele (A) showed better body weight loss than those without this allele. It also demonstrated that more significant results were seen in individuals with AA after a lifestyle change that included calorie restriction, participation in physical activity, or a combination of these[40]. In another study, individuals with the TT genotype were shown to have a higher rate of body weight loss than other genotypes[41]. In a study on the MC4R gene polymorphism, it was reported that a high protein diet increased appetite in individuals with the rs72272552 variant A allele[14]. In another study, obese women with the risk allele who followed a low-calorie diet of 600 kcal/day showed similar body weight loss and reduced fat mass compared to women without the risk allele. This study showed that the presence of the risk allele was not affected by body weight loss after caloric restriction[39].

In this study, considering the TUBER healthy nutrition recommendations to the patients, an individualized weight loss diet plan consists of 15-20% of dietary energy from protein, 25-30% from fat (<10% saturated fat), 50-55% from carbohydrates. Table 4 shows that the nutritional contents of the nutrition plan create statistically significant differences compared to the individuals' previous food consumption data. It was found that the energy-restricted weight loss diet did not cause a statistically significant change in biochemical parameters in the FTO and MC4R gene polymorphism groups ($p>0.05$) (Table 5). According to anthropometric measurement values, it was found that the weight loss diet provided a greater reduction in waist/height ratio in the group without FTO gene polymorphism (-0.03±0.015 cm) than in the group with gene polymorphism (-0.02±0.016 cm) ($p<0.05$). In addition, although there was no statistically significant difference, there was a greater decrease in body weight (kg), waist circumference, hip circumference (cm), and BMI (kg/m^2) values in the group without polymorphism compared to the group with polymorphism. Likewise, although there was no statistically significant difference, there was a greater

decrease in body weight (kg) and BMI (kg/m^2) values in the group without MC4R gene polymorphism compared to the group with polymorphism (Table 5). These results show that the presence of gene polymorphism makes it difficult to improve anthropometric measurements. There is no data on the effect of the presence of polymorphism on diet results in patients with PCOS. Since the presence of PCOS is highly associated with obesity, further studies in this patient group will provide more accurate data. Also, planning studies in which the number of samples is increased will provide statistically significant results.

The study has several limitations. The individuals participating in this study have menstrual irregularity, as in many women with PCOS, and it is known that most individuals do not menstruate for several months. The biochemical parameters were analyzed at random times in terms of the menstrual cycle, considering the study period (8 weeks). First, the irregularity in sex hormones that occurs because of menstrual irregularity can affect the results. Therefore, it is recommended to evaluate sex hormones by planning a study with PCOS patients who do not have menstrual irregularities. Secondly, there is no clear dietary recommendation for patients with PCOS, and different dietary patterns are recommended. In this study, only an energy-restricted weight loss diet was planned. Therefore, examining different dietary patterns will be important in evaluating the effects of gene polymorphism on diet in patients with PCOS. Third, in this study, only one variant of the FTO and MC4R genes, out of many genes that are claimed to be associated with obesity, was examined. It is known that different variants of these genes, as well as different genes and gene expression, are important in obese women with PCOS. Gene expression levels were not examined in this study. Apart from limitations, this study will make an important contribution to the literature as it is the first known study to investigate the relationship between weight loss diet and gene polymorphism in patients with PCOS.

In conclusion, an energy-restricted individualized weight loss diet applied to obese patients with PCOS with FTO and MC4R gene polymorphisms for 8 weeks provided a significant decrease in waist/height ratio only in the group without FTO gene polymorphism, but in other parameters (body weight, body composition and biochemical) found no significant change. In addition, although there was no statistically significant difference, there was a greater decrease in body weight (kg), waist circumference, hip circumference (cm), and BMI (kg/m^2) values in the group without polymorphism compared to the group with polymorphism. Although there was no statistically significant difference, it was determined that there was a greater decrease in body weight (kg) and BMI (kg/m^2) values in the group without MC4R gene polymorphism compared to the group with polymorphism. Based on the available data, it can be said that a multidisciplinary approach is essential in achieving body weight loss in overweight and obese women with PCOS, and this approach should include reproductive health specialists, dietitians, behavioral therapists, physiotherapists and family support.

In light of the results of this study, some suggestions have been developed for both dietitians working in the clinic and researchers who will study this issue in the future. It is recommended for dietitians working in the clinic to consider obesity-related gene polymorphisms when planning nutritional interventions for obese patients with PCOS. It is recommended for researchers to follow up more frequently (2-3 times a week), to plan studies with a larger sample size, and to investigate the effects of different dietary patterns to ensure the continuity of patient compliance with the nutritional treatments applied. Studies on gene expression play an important role in explaining the obesity-gene relationship. Therefore, in future studies, different genes and gene expressions associated with obesity can be investigated in individuals with or without PCOS.

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