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Original Research

Effects of Moderate Exercise Training on ApoE and ApoCIII in Metabolic Syndrome

Kutluhan Ertekin[1], Metin Baştuğ[2], Asena Gökçay Canpolat[3]

1 Ufuk University, School of Nursing, Ankara, Turkey
2 Ankara University, Faculty of Medicine, Department of Physiology, Ankara, Turkey
3 Ankara University, Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey

ABSTRACT

Objective: Metabolic syndrome (MetS) is an endocrinopathy with a combination of cardiovascular and metabolic compounds. In our study, it is expected to obtain results showing that mortality rate, loss of workforce, and treatment costs due to disorders caused by MetS can be reduced by physical exercise. The study analyses the effect of moderate exercise training on this Apolipoprotein E (ApoE), Apolipoprotein CIII (ApoCIII), adiponectin, resistin, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) which are thought to have a role in the deterioration of glucose and lipid metabolism in MetS.

Methods: This clinical experimental study consists of 3 groups. The MetS+E (n=24) group, which included the participants who agreed to participate in the exercise program in addition to their medical treatment, the MetS (n=23) group who received medical treatment but did not exercise, and the Control+E (n=25) group, which included healthy volunteers who had the same protocol as MetS+E. ApoE, ApoCIII, adiponectin, resistin, IL-6, and TNF-α plasma levels of all participants were measured both at the beginning of the study and at the end of the protocol.

Results: At the end of the study we reached the following findings; insulin and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) levels decreased in exercise groups (p=0,03). ApoCIII levels are increased all the groups after the study (p<0,01). IL-6 levels decreased in MetS+E (p<0,01) and Control+E (p=0,037). ApoE (p=0,01) and TNF-α (p=0,037) levels decreased only the Control+E group.

Conclusion: Training showed metabolic, anti-inflammatory and physical improvements independent of ApoE and ApoCIII in those with MetS.

Keywords: Adipokines, Apolioprotein CIII, Apolipoprotein E, exercise, metabolic syndrome.

INTRODUCTION

Many adipokines and cytokines with paracrine, endocrine and neural effects are synthesized, and released in adipose tissue. It has been reported that adipose tissue has important roles in inflammation, immunity, cardiovascular and neuronal homeostasis[1].

Metabolic syndrome (MetS), which was named syndrome X for the first time by Reaven[2], according to the World Health Organization (WHO) 1998 definition; Type II diabetes mellitus (DM) is a disease complex accompanied by hypertension, dyslipidemia, abdominal obesity, microalbuminuria, which is the basis of at least one of the disorders of insulin resistance and glucose intolerance. Most of the factors that cause the disease are preventable. The modern sedentary lifestyle is a potential risk factor for the development of MetS. Training programs that include aerobic exercise are involved in the treatment and prevention of MetS.

In this study, we aimed to find the effect of moderate aerobic exercise recommended in addition to medical treatment in patients with MetS, on the levels of Apolipoprotein CIII (ApoCIII) and Apolipoprotein E (ApoE), which are apolipoproteins that are claimed to have a role in the disorder of glucose and fat metabolism. Our hypothesis; was that the training we applied led to an increase in the ApoE / ApoCIII plasma ratio. Another hypothesis is; As a result of the aerobic training program, an increase in adipokine plasma levels and a decrease in resistin, tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) levels. Thus we aimed to contribute to elucidating the mechanisms that have a role in the protective and therapeutic effect of exercise in MetS.

METHODS

Ethics committee approval was obtained from Ankara University Clinical Research Ethics Committee (25 January 2016, approval number 02-57-16) and conformed to the most recent version of the Declaration of Helsinki. All of the volunteers who agreed to

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Corresponding Author: Kutluhan Ertekin **E-mail:** kutluhan.ertekin@ufuk.edu.tr

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participate in the study were given the necessary information before starting the study and their written consent was obtained.

Experimental Design

Participants included in the study were sedentary patients who were diagnosed with MetS (according to WHO 1999 MetS diagnostic criteria) between the ages of 18-40 years from Ankara University Faculty of Medicine, Department of Endocrinology and Metabolism outpatient clinic from 2016-2018. This study, which was designed as experimental clinical longitudinal research, consisted of an MetS intervention group (MetS+E), MetS control (MetS) group and a healthy sedentary control group (Control+E). Among the patients diagnosed with MetS, participants who agreed to participate in the exercise program were included in the MetS+E (n=24) group and those who did not want to exercise were included in the MetS group (n=23). Control+E (n=25) group consisted of healthy sedentaries. The same exercise protocol was applied to this healthy group as the MetS+E group.

Participants

A total of 134 volunteers were included in the study. The number of participants who completed the study was 72. Those participants who did not complete the study either left voluntarily or were removed because they could not adapt to the exercise regime and disrupted the program. All of the participants in our study were asked whether they were sedentary according to the International Physical Activity Questionnaires (IPAQ- short physical activity scale)[3]. Subjects who were not sedentary, and who had cardiovascular and lung diseases, pathological findings in the exercise test in the last two years, malignancies, psychotic disorders, muscle-nervous system disorders that may prevent exercise, hemoglobin level below 10 g/dl in women and 12 g/dl in men, infectious diseases, any chronic inflammatory disease, any hematological disease, history of taking lipid-lowering drugs, and usage of antidepressant drugs were excluded.

The demographic data including age, sex, and clinical data including co-morbidities and smoking habits (current smoker/non-smoker) were recorded and anthropometric data (height, weight, body mass index and waist circumference) were measured for all participants.

Main Points:

- Does a 12-week exercise program cause a change in ApoE and ApoCIII levels in individuals with metabolic syndrome?
- If there is a change, will this be reflected in the lipoprotein metabolism?
- While treadmill exercise caused a decrease in ApoE plasma levels in healthy sedentary people, it did not make a difference in individuals with MetS.
- Pro-inflammatory cytokines, body composition and metabolic improvements were noted in healthy exercisers and individuals with MetS.

Experimental Procedure

The body composition analyzes of participants (fat ratio, body mass index, basal metabolic rate) were determined using a Tanita BC420 MA device 1-3 days at the initiation of the study and the completion of the study. Blood samples were taken from participants in the morning after 12 h of fasting for the parameters to be evaluated in the study, 1-7 days before the initiation of exercise program and 1-3 days after the completion of the 12th weeks exercise program. Blood samples taken for ApoE, ApoCIII, adiponectin, resistin, IL-6 and TNF-α evaluated by ELISA method were centrifuged at 1,000 g x 15 min, and plasmas were separated and stored at -80 °C.

The electrocardiography recordings of the volunteers in the Control+E and Mets+E groups in the exercise program were taken with a Nihon Kodlen 6551-ECG before the exercise protocol and at the end of the 12th week to determine the fitness level of the cardio-circulatory and respiratory systems. In addition to medical treatment, the participants were monitored with the mobile phone application of the same company with Polar brand H7 model heart rate monitors under the supervision of a sports physician. The exercise protocol was performed in the form of aerobic treadmill exercises for 12 weeks, 4 days a week, 30 minutes a day at 50% VO_2max load for the first four weeks, 60% maximal oxygen consumption (VO_2max) load between the fourth and eighth weeks, and 70% VO_2max load for the final four weeks.

Measurements

Total cholesterol, triglyceride, VLDL, LDL, HDL, fasting and postprandial blood glucose levels were measured by autoanalyzers (Beckman Coulter DXI800, Beckman Coulter DXC 800). While calculating the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), the formula HOMA-IR= (Fasting glucose (mmol/L) x serum fasting insulin (mUI/L)/405 was used[4].

The Modified Bruce protocol was used to determine the VO_2max[5].

In ELISA measurements, Elabscience brand E-EL-H0470 for ApoE, Elabscience brand for ApoCIII, E-EL-H0467, ELISA Ebioscience brand for Resistin, BMS2040/BMS2040TEN, Ebioscience brand for Adiponectin, BMS2032-2TEN, Ebioscience brand BMS213 for IL-6- 2- For BMS213-2TEN, TNF-α, we used Ebioscience brand kit with catalog number BMS223/4 / BMS223/4TEN. All ELISA analyses were evaluated at a wavelength of 450 nm. ApoE, ApoCIII, adiponectin results were calculated as ng/mL, resistin, IL-6 and TNF-α results were calculated as pg/mL.

Data and Statistical Analysis

The descriptive statistics on numerical measurements, differences between independent groups from those whose variables did not conform to normal distribution were evaluated using Kruskal Wallis Analysis of Variance. Wilcoxon Sign Rank test was used for those who did not show normal distribution in the comparisons of preprotocol and postprotocol values. SPSS 21.0 package program was used for statistical analysis results (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Type-I error level for testing the two-way hypothesis tests was taken as α=0.05.

Table 1. Characteristics of the participants

	Control+E (n=25)	MetS+E (n=24)	MetS (n=23)	p
Age (years)	26,80±8,30	28,29±7,82	32,83±8,23	0,055
Sex (F/M)	(22/3)	(15/9) *	(12/11) *	*0,019
Dyslipidemic	1	15**	14**	**0,000
DM and/or insulin resistance	4	24**	23**	**0,000
Sedentery (IPAQ (Short))	24	24	23	0,391
Medications				
Metformin	-	6*	4*	*0,036
Statin	-	-	2	0,114
Hypertensive agents	4	11*	11*	*0,036

Control+E; Control + exercise group, MetS+E; metabolic syndrome + exercise group, MetS; metabolic syndrome group, F; female, M;male, DM; diabetes mellitus *Significant difference with Control+E (p<0,05). **Significant difference with Control+E (p<0,01). IPAQ=International Physical Activity Questionnaire

RESULTS

The groups were age-matched, but female predominance was seen in the Control+E group when compared to the MetS groups (p<0,05). All participants were sedentary according to the IPAQ (Table 1).

Data obtained from bioimpedance measurements are given in Table 2. Body mass index (BMI), total body water (TBW), visceral fat rate (VFR). Basal metabolism rate (BMR), BMI, VFR, and fat% values before and after the exercise programme; MetS and MetS+E groups was significantly higher than the Control Group (p<0,001) (Table 2). A significant decrease in BMI, VFR and BMR values was only observed in the MetS+E group (p<0,001).

At the end of the study, an increase in HDL, HOMA-IR and decrease in insulin were observed in the MetS+E Group. A decrease in insulin, HOMA-IR and LDL was observed at the end of the program in the Control+E Group (Table 3). IL-6 levels of the Control+E Group were lower both before and after the program compared to the MetS and MetS+E groups (p=0,048). MetS+E Group showed a decrease in IL-6 (p=0,000) at the end of the program (Table 4). In addition, at the end of the program IL-6 (p=0,014) and TNF-α (p=0,042) values of the MetS+E Group significantly lower than MetS Group (Table 4). When ApoCIII end-of-study data were compared between groups, MetS (p<0,01) and MetS+E (p<0,05) groups were found lower than the Control Group, and there was a significant increase in all groups (p<0,01). The only difference noted in ApoE is the decrease in the Control+E Group (p<0,05) (Table 4).

There was no difference in resistin between the groups before and after the exercise program. In addition, there was no differ-

Table 2. Body compositions (Mean±S.D)

Parameters	Control+E (n=25)		MetS+E(n=24)		MetS(n=23)		p
	Before	After	Before	After	Before	After	
BMI kg/m²	23,71±4,05	23,38±3,91	32,92±6,01**	31,59±6,15** ##	34,91±7,38**	34,21±6,64**	##0,000 **0,000
VFR	3,22±2,60	3,14±2,62	9,33±4,81**	8,52±4,41** ##	9,31±4,35*	9,94±4,21 **	##0,002
TBW %	51,73±5,61	51,06±6,58	45,80±4,38*	46,23±4,72*	47,09±4,66*	47,48±4,68*	*0,04
Muscle %	69,95±7,88	67,52±16, 39#	60,45±6,59 **	61,40±7,45**	62,90±6,07**	63,50±6,34**	**0,009 # 0,014
Fat %	26,41±8,16	26,00±7,39	36,34±6,96**	35,42±7,90**	34,56±7,37**	36,65±7,10 *	*0,02
BMR	1329,40±118,86	1341,8±0125,00	1887,20±347,74**	1870,80±345,58**##	1807,80±279,34**	1811,80±309,60**	##0,000 **0,000
BMR/BMI	61,68±10,15	62,11±9,96#	56,54±10,04	55,29±16,10	56,61±9,29	54,70±8,96	#0,040

Control+E; Control + exercise group, MetS+E; metabolic syndrome + exercise group, MetS; metabolic syndrome group, BMI; body mass index, VFR; visceral fat rate, TBW; total body water, BMR; basal metabolic rate. *Significant difference with Control+E (p<0,05). **Significant difference with Control+E (p<0,01). #Significant difference with before the protocol (p<0,05). ## Significant difference with before the protocol (p<0,01).

Table 3. Blood values and systolic and diastolic arterial blood pressure values of the participants

Parameter		Control+E (n=25)		MetS+E (n=24)		MetS (n=23)		p pairwise
		Before	After	Before	After	Before	After	
Insulin µIU/ml	Mean±S.D	11,00±2,32	9,15± 0,38	21,47±6,10 **	18,19± 5,12**	19,37±8,33**	18,50±13,11**	**0,000
	Median (min-max)	0,964(0,172-2,94)	8,52(3,13-14,79)	1,313(0,11-2,94)	16,445(2,7-34,18)	2,563(0,172-12,356)	12,81(8,99-62,31)	
	p group within	0,030		0,033		0,114		
HOMA-IR	Mean±S.D	2,24±0,96	1,81±0,58	4,79±2,73 **	3,90±1,98 **	5,18±3,44**	4,49±3,06**	**0,000
	Median (min-max)	2,32(0,62-5,37)	1,72(0,68-3,14)	3,93(0,87-13,47)	3,37(0,46-7,09)	3,72(1,53-18,72)	3,05(1,91-11,66)	
	p group within	0,040		0,027		0,028		
FBG mg/dl	Mean±S.D	81,68±8,00	81,08±5,50	88,75±1,00 **	85,17±6,00** δ	105,32±38,87**	99,86±36,58**	δ 0,027 **0,001
	Median (min-max)	82(67-92)	80(69-93)	87(75-141)	84(69-114)	92(76-226)	90(65-287)	
	p group within	0,879		0,034		0,480		
SBP mmHg	Mean±S.D	113,52±12,44	112,08±10,59	125,29±12,82**	123,83±11,09**	124,56±16,23**	123,86±15,44**	**0,001
	Median (min-max)	110 (100-140)	110 (100-140)	122,5 (110-160)	120 (110-155)	120 (99-160)	120 (99-160)	
	p group within	0,493		0,130		0,348		
DBP mmHg	Mean±S.D	71,48±9,75	70,83±8,20	82,38±12,38**	80,50±10,60**	81,70±11,08**	80,30±10,97**	**0,004
	Median (min-max)	70 (60-90)	70 (60-85)	80 (60-120)	80 (60-115)	85 (60-98)	80 (60-95)	
	p group within	0,483		0,077		0,072		

HDL mg/dl	**Mean±S.D**	53,54±10,44	56,04±8,84	45,84±11,30*	47,00±9,14*	47,68±16,45*	46,33±12,46*	*0,04
	Median (min-max)	49(37-74)	57(37-72)	43,5(31-60)	46(31-65)	45(0-92)	44,5(25-69)	
	p group within	0.112		0.036		0.669		
LDL mg/dl	**Mean±S.D**	100,66±25,57	94,45±27,31	120,58±45,95** δ	116,17±46,19** δ	114,05±29,08**	115,66±30,39**	** 0,000 δ 0,000
	Median (min-max)	97(52-147)	87(51-163)	112,5(65-280)	106,5(75-287)	124(41-154)	109,5(67-196)	
	p group within	0.044		0.605		0.548		
VLDL mg/dl	**Mean±S.D**	18,56±7,64	18,54±8,91	29,42±15,01*	26,83±9,98*	45,95±45,35**	32,86±27,19**	*0,06 **0,009
	Median (min-max)	17(8-38)	18(7-38)	25(12-70)	29(11-43)	35(7-224)	21,5(9-123)	
	p group within	0.827		0.513		0.064		
Cholesterol mg/dl	**Mean±S.D**	170,92±26,96	167,95±31,93	185,21±60,87*	190,79±45,62	200,59±27,30**	183,66±34,73	** 0,001
	Median (min-max)	173,5(115-231)	165,5(104-247)	191(124-355)	181,5(131-339)	205(114-246)	193(102-227)	
	p group within	0.175		0.485		0.010		
Triglycerides mg/dl	**Mean±S.D**	92,83±0,97	88,72±0,58	151,13±72,58**	138,13±52,41**	224,82±217,63**	165,86±142,66**	** 0,003
	Median (min-max)	84 (38-190)	78 (33-192)	127 (62-350)	130,5 (57-221)	166,5 (36-1068)	105 (43-637)	
	p group within	0,360		0,074		0,082		

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBG: Fasting blood glucose, Control+E; Control + exercise group, MetS+E; metabolic syndrome + exercise group, MetS; metabolic syndrome group *Significant difference with Control+E (p<0,05). **Significant difference with Control+E (p<0,01), #Significant difference with before the protocol (p<0,05). δ Significant difference with MetS (p<0,01).

Table 4. IL-6, TNF-α, Adiponectin, Resistin, ApoE and ApoCIII values of the participants before and after the study (Mean±S.D).

Parameters		Control+E (n=25)		MetS+E (n=24)		MetS (n=23)		p pairwise
		Before	After	Before	After	Before	After	
Adiponectin ng/ml		26831±18.252	24161±15.519	20168±17.636	17397±14.969	16769±10.490	17274±12.449	>0,05
	Median (min-max)	26450(4825-83825)	21890(2560-59500)	15507(1710-79300)	12325(1585-50970)	15672.5(2560-49380)	14437(1725-45825)	
	p value group within	0.619		0.475		0.864		
Resistin pg/ml		4075,74±2729	2958,06±843	4095,96±867	3737,66±1765	3245,35±1.352	4737,28±3405	>0,05
	Median (min-max)	3209(798-11739)	2367(315-7048)	3567(788-7502)	3476(460-10961)	2977(1468-5737)	3593(1187-13799)	
	p value group within	0.088		0.346		0.130		
ApoE ng/ml		717,76±116	558,66±11,84	812,57±315,24	822,67±164,56	744,40±559,97	988,96±824,62	>0,05
	Median (min-max)	733(104-2645)	450(41-1730)	791(126-2063)	767(11-2346)	724(97-2435)	689(128-2911)	
	p value group within	0.010		0.954		0.346		
ApoCIII ng/ml		58,81±5,18	258,46±88,52	41,87±0,44	229,37±125,96	33,18±50,80	143,34±113,04	**0,002
	Median (min-max)	14.15(8.25-241.88)	192.82(10.18-624) ##	11.16(8.06-241.88)	215(13.56-576) ##*	10.73(8.70-181.06)	114.94(6.88-391.72) ##**	
	p value group within	0.002		<0.001		<0.001		
IL-6 pg/ml		1,60±0,49	1,06±0,27	2,61±0,87	1,40±0,40	3,72±3,86	3,61±3,45	* 0,02 δ 0,014
	Median (min-max)	1.41(0.234-3.774)	0.96(0.172-2.94)	2.45(0.484-8.968) *	1.31(0.110-2.940) δ	2.38(0.696-15.64) *	2.56(0.172-12.356) *	
	p value group within	0.037		<0.001		0.710		
TNF-α pg/ml		6,66±13,22	4,80±9,87	4,35±0,81	3,36±0,21	5,74±5,85	4,19±2,77	δ 0,042
	Median (min-max)	2.99(0.56-64.32)	1.834(0.018-47.394)	2.065(0.332-33.936)	2.214(0.562-25.74) δ	3.453(0.562-19.774)	3.148(0.28-10.334)	
	p value group within	0.037		0.855		0.475		

Control+E; Control + exercise group, MetS+E; metabolic syndrome + exercise group, MetS; without exercise metabolic syndrome group *Significant difference with Control+E (p<0,05). **Significant difference with Control+E (p<0,01), #Significant difference with before the protocol (p<0,05). ##Significant difference with before the protocol (p<0,01). δ Significant difference with MetS (p<0,05). ApoCIII; Apolipoprotein CIII, ApoE; Apolipoprotein E, Interleukin-6; IL-6, Tumor necrosis factor-α; TNF-α.

Table 5. VO2max and total effort time values of the participants before and after the study (Mean±S.D).

Parameters	Control+E (n=25)		MetS+E (n=24)		p
	Before	After	Before	After	
VO_2max (ml/kg/min)	40,33±6,19	56,12±6,38 ##	35,66±7,76	53,57±7,13 ##	##0,000
Total Effort Time (sec)	609,96±94,32	834,52±99,29##	567,58±115,82	821,42±104,59##	##0,000

Control+E; Control + exercise group, MetS+E; metabolic syndrome + exercise group. #Significant difference with before the protocol (p<0,05).
##Significant difference with before the protocol (p<0,01

ence in the initial state of the MetS+E Group in terms of gender, but there was a significant difference in terms of gender after the training group (Table 4). In the MetS+E group, by the end of the program there was a decrease in the resistin in men and an increase in the resistin in women (p=0,03).
In the exercise groups, both VO2max and total effort times increased at the end of 12 weeks (Table-5).

DISCUSSION

This study looks to contribute to the elucidation of of the mechanisms of the protective and therapeutic effect of moderate aerobic training, which is recommended in addition to medical treatment in MetS patients.Our expectation was an increase in the ApoE / ApoCIII ratio and adipokine plasma levels and a decrease in resistin, TNF-α and IL-6 levels at the end of the program. The average muscle percentage of the participants in the MetS+E group increased following the end the training program (p=0,009). One of the study's aims was to see participants lose weight through exercise. Confirming this, there was a significant decrease in BMI and VFR in the MetS+E group. However, no change was observed in MetS and Control+E (Table-2). This may be due to the increased catecholamine synthesis during exercise. Visceral fats are more sensitive to catecholamine-induced lipolysis, while subcutaneous fats are more sensitive to insulin-induced lipolysis[6].

Studies have shown that exercise at 50-60% VO_2max intensity provides the highest fat burning, reduction in body fat ratio, BMI and waist circumference and the same studies have shown that there is a negative relationship between VO_2max and body fat ratio[7,8]. As in the studies mentioned, we programmed our training load as 50% VO_2max for the first 4 weeks, 60% for the next 4 weeks, but we applied it as 70% VO_2max to see the effect of the increased oxygen consumption capacity from the eighth week, and as a result, we saw an increase in effort capacity in our training groups (Table-5). According to the literature, the fat burning rate on the treadmill is higher than on the bicycle[9]. For this reason, we applied the treadmill exercise for 12 weeks as an exercise type.

The significant increase in VO_2max and effort duration in the exercise groups compared to the baseline indicates that this exercise program increased the compliance of the cardiopulmonary system with the exercise (Table-5). This data is consistent with that in the literature that aerobic capacity increases with weight loss, decrease in BMI, and decrease in fat ratio[10].

In our study, a significant decrease was observed in the exercise groups in insulin and HOMA-IR values at the end of the program (Table-3). These findings are consistent with the literature[11]. It was thought that the training might have created an effect that could prevent hyperglycemia and decrease insulin resistance in the MetS+E group. In addition, at the end of the study, the fasting blood glucose (FBG) of the MetS+E group was found to be different from the MetS group. Insulin resistance is a condition that occurs as a result of overnutrition, includes multiple factors, and triggers inflammation[12]. The most important hormones regulating lipoprotein lipase (LPL) activation and expression are insulin and cortisol, and adipose tissue capillaries are rich in LPL[13]. Insulin inhibits lipolysis and stimulates adipocyte differentiation. It causes triglycerides to remain as storage in adipocytes. The training applied in this study appears to have a corrective effect on the impaired fat storage mechanism in patients with insulin resistance.

One of the protective effects of adiponectin from MetS may be that it activates the AMP-activated protein kinase (AMPK) pathway in skeletal muscle and increases GLUT4 translocation in an insulin-independent manner, as well as increasing fatty acid oxidation[14]. Although not significant, the increase in adiponectin recorded in our study may have had positive effects on the metabolism of cytokines and fatty acids. If we had taken a sample at the end of the first week in our study, perhaps we would have seen the increase in adiponectin. The results of some studies suggest that the 12-week exercise program we preferred in our study may be insufficient to show the change in adiponectin[8].
This study showed no observable difference, in terms of ApoE levels between MetS and the control group such as Boiko et al.[15] (Table-4). However, there was a significant decrease in the Control+E group (Table-4). Shiina and Homma[16] found no correlation between ApoE and MetS components. Onat et al.[17] found a relationship between serum ApoE concentration and ApoB, ApoA-I, waist circumference and MetS, excluding genetic factors. Onat et al.[18] suggest that high concentrations of ApoE play a role in making HDL dysfunctional. In other words, high ApoE levels alone are not protective for atherogenic dyslipidemia. Our Control+E group consisted of healthy young individuals. The decrease we observed in ApoE level after the training program in this group is in line with the results of Onat et al.[17]. We could not find any study

showing how ApoE plasma levels are affected by aerobic exercise in people with MetS. Studies that analyse the relationship between ApoE gene polymorphism and MetS have increased in recent years [19,20]. Son et al.[20] state that the polyformism they found in the rs769450 region of the single nucleotide ApoE gene is associated with MetS. In addition, they note that the triglyceride change caused by the same polymorphism is affected by physical activity. However, Reas et al.[21] could not determine a relationship between carrying the ε4 allele and exercise. There is no consensus in the literature between ApoE and MetS. In a case study involving a 10-week exercise program, a 38-year-old male Apoε4 carrier with MetS had significant improvements in MetS criteria at the end of the exercise program[22]. The closest findings ours are in this study; however, this study include data from only one individual and do not provide information about the plasma ApoE level.

While it is known that ApoCIII also inhibits hepatic lipase, there are publications stating

that it increases the hepatic uptake of VLDLs via cholesteryl ester transfer protein (CETP)[23]. There is a study that show the ratio of ApoE/ApoCIII to be lower in individuals with hyperlipidemic and hypertriglyceridemia when compared with the healthy control group[24]. In addition, Boiko et al[15]. found ApoCIII to be higher in MetS patients than in the healthy control group. We hypothesized that ApoCIII would decrease as a result of exercise and could increase triglyceride hydrolysis by improving the LPL function. Surprisingly we found a significant increase in ApoCIII levels in all groups. ApoCIII gene expression was found to be negatively correlated with insulin and positively correlated with glucose[24]. Caron et al.[25] argue that this increase may also suppress lipolysis and therefore peripheral fatty acid intake may remain low. However, there is a also study stating that insulin does not affect ApoCIII gene regulation[26]. This may be because the promoter regions of the ApoCIII gene for insulin and glucose are different. In addition, the relationship between ApoCIII and MetS may be due to DM[27]. The reason we could not find a difference between groups may be that most of the participants with MetS had insulin resistance, not DM. The lack of correlation between the increase ApoCIII and the baseline indicates that our exercise protocol affects ApoCIII through pathways independent of LPL, CETP, or hepatic lisape (HL).

Prior to the study, we observed that IL-6 levels were higher in MetS groups than in the control group and IL-6 level decreased significantly after the training program in the both exercise groups (Table-5). In addition, a moderate correlation was found between IL-6 and HOMA-IR (r=0.298). Subcutaneous adipose tissue and visceral adipose tissues can synthesize proinflammatory cytokines like IL-6 under stress[28]. IL-6 is a proinflammatory cytokine known to reduce insulin-dependent sugar intake, affect fat oxidation and lipid conversion[29]. Balducci et al.[29] showed that inflammatory biomarkers such as IL-6 were decreased as a result of long-term training in individuals with metabolic syndrome. IL-6 is also an inhibitor of LPL, which is an important element of fat metabolism. Due to the high level of IL-6, blood fats cannot be broken down. Fats cannot pass to the tissues where they will perform lipolysis and remain at high levels in the blood, and increased blood fats increase IL-6 synthesis. Thus, IL-6 causes a vicious circle in obese humans. Antioxidant capacity is low in with visceral obesity and fatty liver disease. One of the significant reasons for the decrease in IL-6 level in our results may be decreased visceral adipose tissue and BMI. The decrease in IL-6 level, especially with the effect of training consisting of aerobic exercise, is in line with our findings.

In obese individuals, hypertrophic adipocyte cells are hypoxic because their diffusion distances for oxygen are increased[13]. In addition, since the oxidative capacity of the muscles of sedentary individuals is lower, the breakdown of fats is also low. The increased exercise capacity and VO_2max with the training program suppressed oxidative stress and decreased IL-6 secretion from adipose tissue, thus the inhibitory effect on LPL may have been weakened.

There was no difference in TNF-α plasma levels between groups at the start of the study (Table-4). The Control+E group was the only group in which we found a significant difference compared to the pre-training program (Table-4). TNF-α, like IL-6, is an important proinflammatory cytokine that is an inhibitor of LPL. Another study found this cytokine to be significantly higher in patients with MetS than in healthy controls[30]. Giannopoulou et al.[11] found no difference in the resistin, adiponectin and TNF-α data obtained as a result of the diet+exercise and diet-only program. The exercise protocol they applied (the walking exercise they performed at a VO_2max level of 65-70% for 60 minutes a day 3-4 days a week) is a similar protocol to the treadmill exercise we chose.

In this study, we have obtained results such as increase in anti-inflammatory agents, weight loss, decrease in BMI and visceral obesity, decrease in insulin resistance and increase in oxygen consumption capacity. Some of the limitations we identified in our study are as follows; Most of the participants were housewives, students, and the unemployed, and the majority of the Control+E group consisted of women. The fact that women show more interest in the determination of health status and health promotion studies than men can be the subject of a separate behavioral study. Extending the training program to 16-24 weeks by making intermediate measurements may contribute to the findings of this study. In addition to the dietary recommendations in national and international health programs to build the bridge between our biological evolution and our cultural evolution, increasing the amount of physical activity should become an important goal.

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