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Impact of *APOE2* allele on lipid profile change after a weight loss program

Impacto del alelo APOE2 *en el cambio del perfil lipídico después de un programa de pérdida de peso*

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ABSTRACT

Background: Apolipoprotein E (ApoE) polymorphism is a genetic determinant of lipid and lipoprotein levels and the risk for coronary heart disease.

Objective: To evaluate the impact of *ApoE2* allele in lipid plasma levels and the influence of a healthy hypocaloric diet plus a controlled physical activity on the lipid profile, we performed a study in a cohort of overweight and obese healthy subjects (Body Mass Index (BMI) between 25 and 34.9 kg·m^{-2}).

Methods: One hundred eighty participants (96 women), aged 18-50 years participated in a 22 weeks weight loss intervention based on same dietary treatment and different controlled exercise programs. All subjects followed a hypocaloric diet (25-30% less energy intake than the daily energy expenditure). Blood samples were obtained for lipids measurements at the beginning and end of the study.

Results: After intervention, men of the E2 group showed the greatest decreases in low-density lipoprotein (LDL), triglycerides (TG) and total cholesterol (TC) values (p = 0.039; p = 0.001; p = 0.001; respectively). For high-density lipoprotein (HDL), E2 group had significant differences compared with E4 at pre- (p = 0.020) and post-intervention values (p = 0.024).

Conclusion: Our results show great changes in men carrying *ApoE2*, mainly in TG and TC concentrations after treatment with hypocaloric diet and controlled exercise. Therefore, adding supervised training to nutritional intervention seems to be a good alternative for the reinforcement of the effect of the treatment.

Key words: *ApoE* genotype. Lipoprotein. Overweight. Obese. Weight loss program.

RESUMEN

Antecedentes: el polimorfismo de la apolipoproteína E (ApoE) es un determinante genético de los niveles de lípidos y lipoproteínas y el riesgo de enfermedad coronaria.

Objetivo: para evaluar el impacto del alelo ApoE2 en los niveles de lípidos plasmáticos y la influencia de una dieta hipocalórica sana más una actividad física controlada en el perfil lipídico, se realizó un estudio en una cohorte de sujetos sanos con sobrepeso y obesidad (índice de masa corporal entre 25-34,9 kg·m^{-2}).

Métodos: ciento ochenta participantes (96 mujeres), de 18-50 años participaron en una intervención de pérdida de peso de 22 semanas basada en el mismo tratamiento dietético y diferentes programas de ejercicios controlados. Todos los sujetos siguieron una dieta hipocalórica (consumo de energía entre 25-30% inferior que el gasto energético total diario). Se obtuvieron muestras de sangre para las mediciones de lípidos al inicio y al final del estudio.

Resultados: después de la intervención, los hombres del grupo E2 mostraron las mayores disminuciones en los valores de lipoproteína de baja densidad (LDL), triglicéridos (TG) y colesterol total (TC) (p = 0,039; p = 0,001; p = 0,001). Para las lipoproteínas de alta densidad (HDL), el grupo E2 presentó diferencias significativas en comparación con E4 en los valores previos (p = 0,020) y postintervención (p = 0,024).

Conclusión: nuestros resultados muestran grandes cambios en los hombres que portan ApoE2, principalmente en las concentraciones de TG y TC después del tratamiento con dieta hipocalórica y ejercicio controlado. Por lo tanto, la adición de entrenamiento supervisado a la intervención nutricional parece ser una buena alternativa para el refuerzo del efecto del tratamiento.

Palabras clave: Genotipo ApoE. Lipoproteína. Sobrepeso. Obesidad. Programa de pérdida de peso.

INTRODUCTION

Atherosclerosis is a multifactorial disease involving environmental and genetic factors and their interactions (1). The lipoprotein concentrations are modulated by different apolipoproteins, mainly by the multifunctional apolipoprotein E (ApoE), that plays a key role in the metabolism of cholesterol and triglycerides by binding to hepatic ApoE receptor or LDLR in the liver to help mediate clearance of chylomicrons and very low-density lipoproteins from the plasma (1-3). So, ApoE plays a crucial role in transport and redistribution of lipids in peripheral tissues such as brain peripheral nerves, and arterial wall (4). The phenotype of severe hyperlipidemia and spontaneous development of atherosclerosis in mice lacking ApoE clearly demonstrates the central role of ApoE in mammalian lipid metabolism (5,6).

The *ApoE* gene locus is polymorphic with 3 common alleles, designated as *ApoE2*, *ApoE3* and *ApoE4*. The corresponding protein isoform for each allele has different affinity for the cellular apolipoprotein receptor (7). Hence, the presence of at least one *ApoE4* allele is associated with lower plasma ApoE (8) and increased plasma cholesterol, LDL cholesterol, and ApoB levels (2). The presence of at least one copy of the *ApoE2* allele has been associated with higher plasma ApoE (8) and lower plasma cholesterol, LDL cholesterol, and ApoB levels (2) when compared with *ApoE3* homozygotes. The *ApoE2* allele is also associated with lower risk of coronary artery disease (9), except in 5-10% of *ApoE2* homozygotes who develop type III hyperlipoproteinemia and premature atherosclerosis (10). Under an obesogenic environment (sedentarism, hypercaloric and cholesterol-enriched diets), the presence of the *ApoE4* allele is associated with a significant risk of coronary artery disease (9), when compared with *ApoE3* homozygotes. Low-cholesterol diets normalize lipid profile and minimize cardiovascular risk in subjects with at least one *ApoE4* allele. In addition, clinical trials and longitudinal studies indicate that after supervised exercise carriers of the *ApoE2* allele and homozygotes for the *ApoE3* allele have greater improvements in plasma lipoprotein lipid than *ApoE4* carriers (11-13). However, the impact of a strict hypocaloric and equilibrated diet plus controlled physical activity program in *ApoE2* and *ApoE4* carriers it is less established.

Therefore, in order to investigate the impact of *ApoE2* allele in triglycerides plasma levels, and the influence of a healthy hypocaloric-diet plus a controlled physical activity program on lipid profile, we performed a study with overweight and obese healthy subjects in which the hyper caloric-sedentary conditions were presumed.

MATERIAL AND METHODS

Design

The present RCT (ClinicalTrials.gov ID: NCT01116856) was conducted from January, 2010, through June, 2011, and followed the ethical guidelines of the Declaration of Helsinki. The Institutional Review Board of the Hospital Universitario La Paz (PI-643) reviewed and approved the study design and research protocol. Details of the study's theoretical rationale, protocol, and intervention are described elsewhere (14).

Participants

Participants were sought via advertisements in newspapers and on the radio, internet and TV. The sample population consisted of 180 subjects (96 women and 84 men, weight: 80.44 ± 10.1, 96.40 ± 9.43 kg; height: 1.63 ± 0.06, 1.76 ± 0.7 m; BMI: 30.29 ± 1.22, age; 38.01 ± 7.8, 38.3 ± 8.01 years) overweight (n = 84, 48 women and 36 men; BMI 25-29.9 kg/m^2) and obese participants (n = 96, 48 women and 48 men; BMI 30-34.9 kg/m^2). All subjects were healthy, normoglycaemic, non-smokers, but led sedentary lifestyles. All female subjects had regular menstrual cycles. The exclusion criteria covered all physical and psychological diseases that may have precluded the performance of the requested strength or endurance training, and the taking of any medication known to influence physical performance or the interpretation of the results. Subjects with a background of systematic strength or endurance training (moderate to high intensity training more than once a week) in the year before the study started were also excluded. Before starting, all participants signed an institutionally approved document of informed consent.

Procedures

A 6-months diet and exercise-based intervention, focusing on a behavior change. Participants entered into the study in two waves, one of overweight participants and the other of obese participants. Each wave was split into four randomly assigned groups, stratified by age and sex: strength group (S), endurance group (E), combined strength and endurance group (SE) and the control group, who follow the physical activity recommendations. The measurements took place in the first week (pre-intervention values) for all participants before starting and after 22 weeks of intervention, in week 24 (post-intervention values).

Before the intervention started, physical activity was assessed by a SenseWear Pro3 Armband™ accelerometer (Body Media, Pittsburgh, PA). Daily energy expenditure was calculated using the Body Media propriety algorithm (Interview Research Software Version 6.0). In addition, they were required to report the kind, duration, and intensity of any physical activity and the amount of any food undertaken during the intervention period, through a personal diary, to ensure compliance with the recommendations given.

At the beginning of the intervention, the negative energy balance was calculated taking into account the daily energy expenditure, and an estimated 3-day food record, in order to decrease the energy intake of the diet by a 25-30% during the intervention.

Exercise intervention

All exercise training groups (Strength, Endurance and Combined-SE groups) followed an individualized training program, which consisted on three times per week exercise sessions during 22 weeks, carefully supervised by certified personal trainers. Details of the different protocols developed by the groups are described elsewhere (14). An adherence to exercise of 80% was required.

Control group

Participants from the control group followed the dietary intervention and respected the recommendations about physical activity from the American College of Sport Medicine (ACSM) (15). Thus, the C subjects were advised to undertake at least 200-300 min of moderate-intensity physical activity per week (30-60 min on most, if not all, days of the week).

Diet intervention

All groups underwent an individualized and hypocaloric diet (between 1,200 and 3,000 kcal). The diet implied a 25% reduction from the total daily energy expenditure (TDEE) (16) measured using SenseWear Pro Armband™ data. Macronutrient distribution consisted of 29-34% of energy from fat, 12-18% from protein, and 50-55% from carbohydrates, according to recommendations (17). A dietician interviewed each participant at baseline, 3 months, and 6 months and reviewed a 3-day food record diary. An adherence to diet of 80% was elicited and was calculated with 72-hour recall (18).

Outcomes

Blood analysis

All blood samples were taken after 12 h fast between 7:00 and 9:00 a.m. at baseline and post-training intervention (week 1 and week 24). All post-training samples were

obtained 72 hours after the last training day to avoid acute effects of training on blood lipids. All blood samples were drawn from the antecubital vein and handled according to standardized laboratory practice at Hospital Universitario La Paz. Serum biochemicals total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and TG (19) were determined using enzymatic methods with Olympus reagents by automated spectrophotometry performed on Olympus AU 5400 (Olympus Diagnostica, Hamburg, Germany). Menstrual cycle was controlled by diary to define the follicular and luteal phases when blood samples were taken (20).

Genotyping

Genomic DNA was extracted from peripheral blood using a QIAamp DNA Blood Mini kit (QIAGEN, Hilden, Germany). The *ApoE* genotypes for the *ApoE3*, *ApoE4* (rs7412) and *ApoE2* (rs429358) alleles were determined by polymerase chain reaction (PCR) and allele-specific restriction digestion of the amplified products with the restriction enzyme HhaI (21). Samples were analyzed in Metabolism, Genetics and Nutrition Research Group of the Universidad de Cantabria-IDIVAL. Subjects were typed at the *ApoE* locus as previously described (22). To analyse the association of the ApoE phenotype with lipid and apolipoprotein responses and lipoprotein fractions, subjects were grouped as E2 carriers (E2: E3/E2 subjects), E3 homozygotes (E3/E3 subjects) and E4 carriers (E4: E4/E4 and E4/E3 subjects). A single subject with ApoE4/2 phenotype was not included in the study sample.

Body composition

Body composition was assessed by Dual-energy X-ray Absorptiometry DXA (GE Lunar Prodigy; GE Healthcare, Madison, WI, GE Encore 2002, version 6.10.029 software) and was used to measure total body fat (%). Anthropometric measures included height (stadiometer SECA; range 80-200 cm), body mass (BC-420MA. Bio Lógica. Tecnología Médica S.L.) and body mass index (BMI) calculated as [body weight (kg)/(height (m))^2].

Physical fitness

Peak oxygen uptake test (VO$_{2peak}$) was measured using the modified Bruce protocol used elsewhere with overweight and obese population (23,24). The test was conducted on an H/P/COSMOS 3P 4.0 computerised treadmill (H/P/Cosmos Sports & Medical, Nussdorf-Traunstein, Germany). The volume and composition of expired gas measure were measured using a Jaeger Oxycon Pro gas analyser (Erich Jaeger, Viasys Healthcare, Germany) and continuous 12-lead electrocardiographic monitoring. The exercise test was maintained until exhaustion. Peak oxygen uptake (VO$_{2peak)}$ was taken to be the mean of the three largest measurements.

Statistical analyses

SPSS version 15.0 for Windows was used for statistical analyses (SPSS Inc., Chicago, Illinois, USA). Standard statistical methods were used for the calculation of the means and standard deviation (SD).

Three-way analysis of variance (ANOVA) for repeated measures was used to determine any differences between men and women and differences in baseline values and post-training values in each *ApoE* group assessed (E2, E3 and E4). Multivariate analysis of variance (MANOVA) was used to compare *ApoE* group and sex in differences in baseline and post-training values. Bonferroni's *post-hoc* test was employed to locate specific differences. The delta percentage was calculated through the standard formula: change (%) = [(post-test score – pre-test score)/pre-test score] × 100. The significance level was set at α = 0.05.

RESULTS

Due to alterations in data collection final analysed completers were n = 173 (94 women and 79 men). The *ApoE2*, *ApoE3*, and *ApoE4* alleles had frequencies of 0.04, 0.88, and 0.08, respectively. The distribution of the *ApoE* genotypes is E2/E3 7.5%; E2/E4 0.6%; E3/E3 76.4%; E3/E4 14.9%; and E4/E4 0.6%; and did not differ between males and females (p = 0.961). All the genotype frequencies of the analysed gene polymorphism were in agreement with the Hardy-Weinberg equilibrium (chi-square test = 1.60; p = 0.660). The genotype groups were initially similar in terms of age, body weight and composition, VO$_{2max}$, and plasma lipoprotein lipid profiles. After the

intervention, body composition and VO_{2peak} did not differ significantly among groups (Table I).

Blood lipids and lipoproteins

Table II shows the changes in plasma lipid and lipoprotein concentrations in three *APOE* (*APOE* gene) groups before and after the intervention period. At baseline, E2 group had a more adverse lipid profile for the atherogenic variables. Men of the E2 group had significantly higher TG levels compared to E3 and E4 groups (E3 p = 0.001; E4 p = 0.018). However, for HDL, E2 group had healthy values with significant differences with E3 (p = 0.010) and E4 (p = 0.020) groups. After intervention, the men of the E2 group achieved the greatest decrease in both TG (p = 0.001) and TC concentrations (p = 0.001). Furthermore, the E2 group maintained the HDL levels, being significantly higher than the E4 men (p = 0.024).

On the other hand, men of the E3 group decreased LDL, TG and TC concentrations (p = 0.001; p = 0.012; p = 0.001; respectively), and increased HDL levels (p = 0.013) after the intervention.

In contrast, E4 men obtained a reduction only in LDL (p = 0.007) and TC (p = 0.006) levels.

In the group of women who participated in our study no significant differences were observed among genotype groups either baseline or the post-training values. Only women of the E3 group showed a slight improvement in the lipid profile with a significant decrease in the levels of TC (p = 0.008) after the intervention, although their HDL levels also decreased (p = 0.048).

Figure 1 shows the percentage of change in blood lipid profile by *ApoE* and gender groups. There were significant differences between E2 men and E3 men for TG and TC concentrations (p = 0.050; p = 0.022, respectively).

DISCUSSION

The main finding of the present study was that the presence of the allele *ApoE2* in men beneficially affects TG and TC responses. Several studies have demonstrated an association between the ApoE phenotype and lipid levels. This work, to our

knowledge, is the first well controlled clinical trial (14) to examine the effects of *ApoE* genotype on the response to a weight loss program with diet combining exercise.

Based on the review of Hagberg et al. (12) low-fat diet interventions tend to reduce plasma lipoprotein levels more in *ApoE4* carriers than in either *ApoE2* carriers or *ApoE3* homozygotes. Interventions with dietary fat content similarly to our study showed the greatest TC and LDL responses in *ApoE4* carriers (25-27). However, in our results we observed that E4 group had low influence on the change in lipid profile after a treatment combining diet and exercise. These differences could be due to the pre-intervention healthy status (no clinical relevant dyslipemia) of participants required in our intervention, as well as the type of diet (well balanced and hypocaloric maintaining 29-34% energy intake of lipids).

On the other hand, different studies (28,29) showed evidence that plasma lipoprotein-lipid responses to exercise training might be influenced by the *ApoE* genotype. These authors reported that physical activity levels did not affect plasma lipoprotein-lipid levels in E4 men. Furthermore, and in accordance with our results, the E2 men group showed the greatest responses after the exercise intervention program (13,28,29). According to our results, Hagberg et al. found that middle-aged and older *ApoE2* genotype men had larger overall plasma lipoprotein-lipid profile improvements with prolonged endurance exercise training than *ApoE3* homozygotes and *E4* carriers men (22). Therefore, the best treatment to improve lipid profile for the E2 carriers seems to be an exercise program, since diet intervention studies showed no improvements in lipid profile for E2 carriers (25,30).

The most favourable response in all lipid profile variables for men in the E2 group (decrease LDL, TG and TC and increase HDL) can be due to the increase in physical activity through our intervention, since regular exercise is known to increase the amount of lipoprotein lipase (LPL) in adipose and muscle tissue. This may reduce TG concentrations adding the decreased fat intake. However, this better response of the E2 group could be due to the higher initial levels, which can be considered as high values (31). These elevated initial levels of TG in E2 subjects are consistent with impaired clearance of remnant particles containing ApoE2, presumably due to defective receptor recognition of ApoE2 containing particles (32). The work of Taimela et al. (13) found a stronger effect of physical activity on TC in men carrying the E2

allele. The authors of these study (13,22) concluded that plasma lipoprotein profiles of E2 individuals appear to be especially affected by increased physical fitness.

In E3 men, our results showed a greater increase in HDL. This may be related to increased adherence to the HDL particle. HDL is cholesterol enriched in part by the LPL (lipoprotein lipase) mediated transfer of cholesterol from VLDL, and this is one of the postulated mechanisms by which exercise training increases HDL (33).

On the other hand, LDL decreased significantly to values considered as no atherogenic for all *ApoE* groups without differences among groups in men. These results are consistent with other interventions to improve dyslipidemia (33,34). This result suggests that our intervention is appropriate to reduce cardiovascular risk even in men with borderline atherogenic values (31). On the other hand, for the women of our study we observed no significant differences between baseline and final lipid profile levels except for TC in E3 group. The work by Leon et al. (28) reported more favourable changes in TG concentrations for E4/E4 women.

In our study, pre-treatment lipids levels for the *ApoE* genotypes showed values close to non-atherogenic concentrations especially in women. This was due to the inclusion criteria of our study, since all the participants were healthy overweight and obese people. However, it is important to emphasize that the BMI of the participants increased the risk of having metabolism lipid alterations. A point of interest of the present study was to include the randomized-controlled design, the long-supervised training period and the lifestyle changes. Another strength was that it is the first, which combines diet and exercise and includes normoglycemic and borderline or no atherogenic lipid profile according to the guidelines published by the expert panel report (31), young to middle-aged men and women. Furthermore, our participants achieved healthy or non-atherogenic values. In contrast, a limitation of this study is that sample size could be too small to detect significant differences among *ApoE* groups. Another limitation could be that not all the participants followed the same exercise program although the different protocols had the same volume and intensity and they did not show significant differences between intervention groups for lipid profile changes (35,36).

Summarizing, this article explains what type of training is the most appropriate according to the polymorphism of ApoE that the subject has. In conclusion, we

observed greater improvements in lipid profile in men carrying the *ApoE2* allele after a highly-controlled diet and exercise program, mainly due to decreases in TG and TC concentrations. Future research is required in order to confirm this finding and, if confirmed, to define the mechanism for this effect.

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TABLES

Table I. Body composition and peak oxygen uptake (VO$_{2peak}$) changes by ApoE groups and gender

Men									
	E2 carriers (n = 6)			*E3 homozygotes (n = 62)*			*E4 carries (n = 12)*		
	Baseline	*Post-training*	*p-value*	*Baseline*	*Post-training*	*p- value*	*Baseline*	*Post-training*	*p- value*
Age	43.5 ± 6.6	±		37.1 ± 7.9	±		41.8 ± 7.1	±	
Weight (kg)	101.25 ± 7.77	90.47 ± 5.99	0.01*	95.27 ± 11.37	86.57 ± 11.47	0.01*	92.66 ± 7.31	84.90 ± 6.92	0.01*
BMI (kg/m^2)	31.98 ± 4.21	27.63 ± 5.40	0.01*	30.98 ± 2.68	28.21 ± 2.96	0.01*	30.64 ± 2.88	28.12 ± 2.69	0.01*
Body fat (%)	34.48 ± 5.76	28.97 ± 6.87	0.01*	36.87 ± 4.90	31.01 ± 5.87	0.01*	34.25 ± 3.52	28.84 ± 4.58	0.01*
VO$_{2peak}$ rel (mL/kg/min)	34.96 ± 5.84	44.12 ± 5.89	0.01*	36.66 ± 5.88	43.75 ± 7.21	0.01*	37.08 ± 8.46	43.54 ± 4.79	0.01*
Women									
	E2 carriers (n = 7)			*E3 homozygotes (n = 71)*			*E4 carriers (n = 15)*		
	Baseline	*Post-training*	*p-value*	*Baseline*	*Post-training*	*p- value*	*Baseline*	*Post-training*	*p- value*
Age	42.75 ± 7.67	±		38.31 ± 7.62	±		37.00 ± 9.12	±	
Weight (kg)	80.50 ± 10.00	73.76 ± 13.53	0.01*	80.76 ± 10.24	73.86 ± 10.47	0.01*	79.21 ± 10.04	72.19 ± 10.26	0.01*
BMI (kg/m^2)	30.87 ± 3.03	28.45 ± 4.76	0.39	31.56 ± 9.14	28.07 ± 3.13	0.01*	30.97 ± 3.14	28.44 ± 3.29	0.19
Body fat (%)	44.43 ± 3.15	39.70 ± 5.53	0.01*	44.92 ± 4.31	40.39 ± 5.19	0.01*	46.19 ± 3.31	40.81 ± 5.08	0.01*
VO$_{2peak}$ rel (mL/kg/min)	26.28 ± 3.09	31.98 ± 6.26	0.01*	28.16 ± 3.64	32.73 ± 5.05	0.01*	28.11 ± 3.47	31.77 ± 5.62	0.01*

Data are reported as mean ± SD. *Significantly different between baseline and post-training (all p < 0.05).

Table II. Changes in blood lipid profile by Apo E groups and gender

Men												

	E2 carriers (n= 6)			E3 homozygotes (n = 62)			E4 carries (n = 12)		
	Baseline	Post-training	p-value	Baseline	Post-training	p-value	Baseline	Post-training	p-value
HDL (mg/dL)	55.33 ± 18.79	56.67 ± 16.69	0.63	45.19 ± 7.26 a	47.35 ± 8.79	0.01*	43.58 ± 8.60	43.67 ± 7.24 a	0.97
LDL (mg/dL)	145.00 ± 47.73	127.40 ± 53.29	0.04*	138.90 ± 29.59	121.95 ± 25.13	0.01*	146.42 ± 24.32	131.58 ± 26.47	0.01*
TG (mg/dL)	206.33 ± 68.53	133.67 ± 63.50	0.01*	123.11 ± 61.25 a	109.15 ± 45.64	0.01*	132.58 ± 58.37	117.25 ± 60.23	0.22
TC (mg/dL)	235.00 ± 46.90	197.67 ± 67.05	0.01*	209.24 ± 36.08	190.31 ± 28.68	0.00*	215.92 ± 27.88	196.67 ± 28.75	0.01*

Women												

	E2 carriers (n = 7)			E3 homozygotes (n = 71)			E4 carriers (n = 15)		
	Baseline	Post-training	p-value	Baseline	Post-training	p-value	Baseline	Post-training	p-value
HDL (mg/dL)	53.71 ± 14.3	52 ± 13.9	0.50	55.3 ± 10.8	53.70 ± 11.00	0.05*	53.67 ± 10.9	52.60 ± 7.71	0.54
LDL (mg/dL)	109.83 ± 19.10	108.67 ± 34.16	0.88	124.3 ± 25.3	121.71 ± 23.00	0.25	133.73 ± 42.38	128.47 ± 37.83	0.28
TG (mg/dL)	92.71 ± 31.28	80.43 ± 10.85	0.46	102.03 ± 46.76	97.38 ± 47.45	0.37	106.53 ± 35.35	99.33 ± 36.50	0.52
TC (mg/dL)	173.43 ± 43.47	171.00 ± 12.49	0.79	201.00 ± 33.55	193.37 ± 30.47	0.01*	208.33 ± 42.53	200.93 ± 38.96	0.23

Data are reported as mean ± SD. *Significantly different between baseline and post-training; [a]Significantly different from E2 carriers (all p < 0.05).
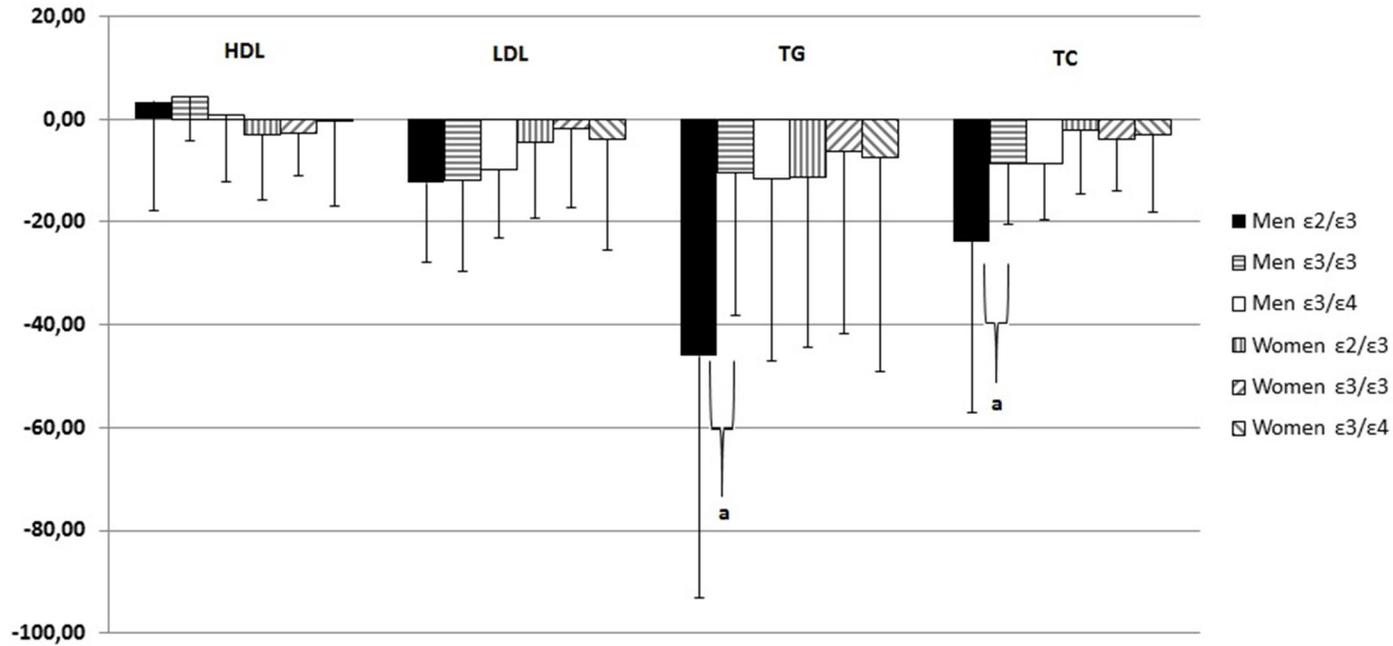
Figure 1. Percentage of change (%) in blood lipid profile by ApoE group and gender ([a]Significantly different from E2 carriers. [b]Significantly different from E3 homozygotes).