

Association of the *TNF- α* -308G/A polymorphism with lipid profile changes in response to aerobic training program

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ABSTRACT: Promoter polymorphism of the tumor necrosis factor- α (*TNF- α*) gene is associated with obesity-related traits, although the role of its potential modifying effect on changes in obesity-related parameters achieved through a training program is still unknown. The aim of the present study was to examine whether the *TNF- α* -308G/A polymorphism (rs1800629) influences the effects of a training program. Accordingly, we studied the alleles and genotypes distribution in a group of 168 Polish Caucasian women measured for selected body mass and composition, as well as biochemical parameters before and after the realization of a 12-week aerobic training program. Our results showed that *TNF- α* genotypes can modulate training-induced biochemical parameter changes such as lipid profile. We demonstrated that carriers of the GG genotype are associated with decreases in post-training high-density lipoprotein cholesterol (HDL-C) levels ($p < 0.001$). Additionally, we revealed that participants with the GG genotype had a higher low-density lipoprotein cholesterol (LDL-C) level ($p = 0.046$) during the entire study period. It could be concluded that harboring the GG genotype of rs1800629 may be considered to be a disadvantageous factor in the context of training-induced effects on lipid profile changes in young female participants.

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INTRODUCTION

Regular physical activity is a major component of total daily energy expenditure and as such, contributes to improved body composition and helps control weight. Currently, the number of people who are overweight or obese is increasing rapidly worldwide and is described as an epidemic; consequently, the prevention of weight gain is a very important health issue [1–3].

Obesity is now considered to be a state of chronic low-level inflammation. Adipose tissue, apart from its classical role as an energy storage depot, is also a major endocrine organ secreting many factors, whose local and circulating levels are affected by the level of obesity. Among these “adipokines” are cytokines such as a tumor necrosis factor- α (*TNF- α*), which is a pleiotropic pro-inflammatory protein [4]. *TNF- α* is involved in the regulation of a wide spectrum of biological processes, including cell proliferation, differentiation, apoptosis, angiogenesis, cytotoxicity, inflammation, immunomodulation, lipid metabolism and coagulation, and has been implicated in a variety of diseases, including autoimmune diseases, insulin resistance and obesity, cancer, coronary heart disease, and asthma [5–9].

The human *TNF- α* gene is located within the class III region of the major histocompatibility complex region on chromosome 6p21.3,

which codes for a 157-amino acid polypeptide processed from a 233-amino acid precursor. Among several single nucleotide polymorphisms (SNPs), the substitution of guanine (G) for adenine (A) at position -308 in the promoter region of the *TNF- α* gene (-308G/A, rs1800629) has been most well characterized. This polymorphic variant has been shown to affect the promoter region of the *TNF- α* gene leading to increased transcriptional activation of the protein compared to the wild allele [10,11]. Some previous studies have evaluated the influence of the -308G/A polymorphism of *TNF- α* on obesity-related traits and have reported a significant association of the A allele with insulin resistance, higher body mass index (BMI), leptin, plasma triglycerides (TGL), and low-density lipoprotein cholesterol (LDL-C) levels, as well as lower high-density lipoprotein cholesterol (HDL-C) levels [10,12]. However, not all studies have replicated these associations [13–15].

Although, acute bouts of exercise are well known to increase concentration of pro-inflammatory cytokines and acute-phase reactants, regular physical activity may reduce basal concentrations of inflammatory markers such as *TNF- α* [16,17]. Most of the weight-loss studies including diet and physical activity showed the magnitude of decrease in inflammatory markers to be linearly related to the

amount of weight loss [9,16]. The physiological effects of these changes are determined by the volume, intensity and frequency of physical activity. However, it is well known that individuals vary in their responses to similar training: from a lack of adaptive response to extreme overload. Recent studies have shown that people with the same genotypes respond similarly to exercise in comparison to those with different genotypes, indicating that some genes such as the *TNF- α* play a significant role in determination of individual differences in response to physical activities [3].

Taken together, the aforementioned findings suggest that the *TNF- α* gene is engaged in developing obesity-related traits and specific training-induced physiological reactions. We examined whether the *TNF- α* -308G/A polymorphism would influence the effects of a training program. Accordingly, we studied the allele and genotype distribution in female participants measured for selected body mass and composition, as well as biochemical parameters before and after the realization of a 12-week aerobic training program to see if there is an interaction between genotype and training.

MATERIALS AND METHODS

Ethics Statement

The procedures followed in the study were conducted ethically according to the principles of the World Medical Association Declaration of Helsinki and ethical standards in sport and exercise science research. The study was approved by the Ethics Committee of the Regional Medical Chamber in Szczecin (Approval number 09/KB/IV/2011). All participants were given a consent form and a written information sheet concerning the study, providing all pertinent information (purpose, procedures, risks, and benefits of participation). The experimental procedures were conducted in accordance with the set of guiding principles for reporting the results of genetic association studies defined by the Strengthening the Reporting of Genetic Association studies (STREGA) Statement.

Participants

168 Polish Caucasian women aged 21 ± 1 years (range 19–24) were included in the study. None of these individuals had engaged in regular physical activity in the previous 6 months. They had no history of any metabolic or cardiovascular diseases. Participants were nonsmokers and refrained from taking any medications or supplements known to affect metabolism. Participants were included in a dietary program and on the basis of an individual dietary plan, were asked to keep a balanced diet. The nutritional appointment included a prescription of an adequate diet for individual energy needs and nutritional status, with a food replacement list, in addition to orientation on a healthy diet. The share of macronutrients in the energy pool of the average food rations was as follows: 45–65% of total calories coming from carbohydrates, 10–20% from protein, and 20–35% from fat (increase the intake of unsaturated fats and decrease the intake of saturated fats). Daily cholesterol intake < 300 mg and dietary fiber intake > 25 g were recommended. The participants kept

a food diary every day. Weekly consultations were held during which the quality and quantity of meals were analyzed and, if necessary, minor adjustments were made.

Body Composition Measurements

Before and after the completion of a 12-week training period, all participants were measured for selected body mass and body composition variables, which were assessed with the bioimpedance method using a Tanita TBF 300M electronic scale (Arlington Heights, Illinois, USA). The measurements taken with the use of the “Tanita” electronic scale are as follows: total body mass (kg), fat free mass (FFM, kg), fat mass (FM, kg), fat mass percentage (FM%, %), BMI (kg/m^2), total body water (TBW, kg), and basal metabolic rate (BMR, kJ or kcal) [18].

Biochemical and Hematological Analyses

Fasting blood samples were obtained in the morning from the elbow vein before the start of the aerobic fitness training program and repeated at the 12th week of this training program (after the 36th training unit). The analyses were performed immediately after the blood collection, as described earlier [19]. Parameters received using the Random Access Automatic Biochemical Analyzer for Clinical Chemistry and Turbidimetry A15 (BIO- SYSTEMS S.A., Barcelona, Spain) are as follows: total cholesterol (TC, mg/dL), triglycerides (TGL, mg/dL), high density lipoprotein cholesterol (HDL-C, mg/dL), low density lipoprotein cholesterol (LDL-C, mg/dL), and glucose (mg/dL).

Training Phase

The training stage was preceded by a week-long familiarization stage, when the examined women exercised 3 times a week for 30 minutes at an intensity of about 50% of their maximum heart rate (HR_{max}). After the week-long familiarization stage, the proper training started. Each training unit consisted of a warm-up routine (10 minutes), the main aerobic routine (43 minutes), and stretching and breathing exercises (7 minutes). The main aerobic routine was a combination of two alternating styles - low and high impact, as described by Leońska-Duniec *et al.* [20].

Genetic Analyses

DNA was extracted from the buccal cells using a GenElute Mammalian Genomic DNA Miniprep Kit (Sigma, Germany) according to the manufacturer’s protocol. All samples were genotyped in duplicate using an allelic discrimination assay on a C1000 Touch Thermal Cycler (Bio-Rad, Germany) instrument with TaqMan® probes. To discriminate the *TNF- α* rs1800629 alleles, TaqMan® Pre-Designed SNP Genotyping Assays were used (Applied Biosystems, USA) (assay ID: C__7514879_10), including primers and fluorescently labelled (FAM and VIC) MGBTM probes to detect alleles.

Statistical Analyses

A chi-square test was used to test the Hardy-Weinberg equilibrium. To test the influence of the -308G/A polymorphism of the *TNF- α* gene on training response, the 3 x 2 and 2 x 2 mixed-design ANOVA tests were used. Additionally, the Kolmogorov-Smirnov test was used to check for data normality. The level of statistical significance was set at $p < 0.05$.

RESULTS

TNF- α genotype frequencies were consistent with the Hardy-Weinberg theorem ($\chi^2 = 0.11$, $p = 0.740$). Results of the two-way ANOVA with repeated measures are presented in Table 1. We found a significant genotype x training interaction for tissue impedance ($F_{(2,165)} = 4.80$, $p = 0.009$) and HDL-C ($F_{(2,165)} = 6.05$, $p = 0.003$). For tissue impedance, post-hoc analysis showed that the post-train-

ing values were significantly lower compared with pre-training for the AA and GG genotypes (604 ± 53 vs 551 ± 30 , $p < 0.001$ for the AA genotype; 549 ± 57 vs 536 ± 56 , $p = 0.002$ for the GG genotype). Planned comparison revealed that the change during training was greater in the AA group than in the GG group ($F_{(1,165)} = 7.37$, $p = 0.007$). Post-hoc tests demonstrated that the HDL-C only decreased significantly during training (65 ± 13 vs 60 ± 13 , $p < 0.001$) in the carriers of the GG genotype.

Owing to the low number of AA homozygotes ($n = 6$), we repeated the analysis with AA homozygotes paired with AG heterozygotes (Table 2). We found only one genotype x training interaction ($F_{(1,166)} = 8.9$, $p = 0.003$) for the HDL-C. Post-hoc test revealed that the HDL-C decreased significantly only in the GG genotype (65 ± 13 vs 60 ± 12 , $p < 0.001$). Additionally, this statistical analysis showed the effect of genotype for LDL-C, $p = 0.046$ (Table 2).

TABLE 1. The *TNF- α* genotypes and response to training

Parameter	AA (n=6)		AG (n=48)		GG (n=114)		Genotype	Training	Genotype x Training
	Before training	After training	Before training	After training	Before training	After training			
Body mass (kg)	57.55 ± 9.08	56.07 ± 8.24	60.46 ± 7.79	59.65 ± 7.53	60.81 ± 7.54	60.13 ± 7.40	0.506	<0.001	0.452
BMI (kg/m ²)	21.28 ± 2.65	20.85 ± 2.31	21.72 ± 2.67	21.47 ± 2.71	21.55 ± 2.34	21.34 ± 2.26	0.858	<0.001	0.538
BMR (kJ)	1420.00 ± 98.25	1403.00 ± 90.80	1445.10 ± 78.35	1439.17 ± 77.37	1450.28 ± 77.36	1446.49 ± 77.73	0.498	0.002	0.249
Tissue independence (Ohm)	604.00 ± 53.12	551.33 ± 29.69	544.29 ± 76.27	537.15 ± 77.78	549.41 ± 57.38	535.51 ± 56.48	0.364	<0.001	0.009
%FM (%)	23.60 ± 5.69	20.38 ± 6.57	23.51 ± 5.56	22.55 ± 5.83	24.03 ± 5.43	22.64 ± 5.50	0.815	<0.001	0.058
FM (kg)	13.92 ± 5.41	11.57 ± 5.29	14.60 ± 5.19	13.80 ± 5.36	14.94 ± 5.031	14.00 ± 5.00	0.698	<0.001	0.084
FFM (kg)	43.12 ± 3.75	44.20 ± 3.20	45.83 ± 3.38	45.99 ± 3.37	45.77 ± 3.05	46.27 ± 3.19	0.203	0.002	0.127
TBW (kg)	31.62 ± 2.79	32.35 ± 2.35	33.37 ± 2.90	33.73 ± 2.42	33.59 ± 2.42	33.90 ± 2.40	0.208	0.026	0.761
TC (mg/dL)	161.00 ± 13.13	142.33 ± 24.50	166.31 ± 21.15	167.06 ± 20.44	171.98 ± 26.40	170.36 ± 29.25	0.102	0.035	0.100
TGL (mg/dL)	77.50 ± 26.72	75.50 ± 22.82	74.50 ± 22.71	83.88 ± 29.92	82.76 ± 35.55	84.02 ± 37.50	0.637	0.556	0.332
HDL-C (mg/dL)	57.28 ± 12.55	49.78 ± 14.21	65.24 ± 13.23	65.69 ± 13.96	65.45 ± 13.43	59.82 ± 12.74	0.061	0.007	0.003
LDL-C (mg/dL)	88.22 ± 15.01	77.38 ± 15.38	86.10 ± 21.15	84.62 ± 16.94	89.90 ± 22.64	93.72 ± 25.60	0.132	0.332	0.085
Glucose (mg/dL)	85.67 ± 4.32	77.83 ± 12.16	79.29 ± 9.78	75.77 ± 9.81	77.28 ± 9.87	75.30 ± 10.14	0.253	0.003	0.298

Mean \pm SD; *geometric mean (antilogged mean of the log data), in brackets - antilog of the log mean + log SD and log mean - log SD; BMI - body mass index; BMR - basal metabolic rate; %FM - fat mass percentage; FM - fat mass; FFM - fat free mass; TBW - total body water; TC - total cholesterol; TGL - triglycerides; HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol

TABLE 2. The *TNF- α* genotypes and response to training (AA homozygotes combined with the AG heterozygotes)

Parameter	AA +AG (n=54)		GG (n=114)		Genotype	Training	Genotype x Training
	Before training	After training	Before training	After training			
Body mass (kg)	60.13 ± 7.91	59.25 ± 7.83	60.81 ± 7.54	60.13 ± 7.40	0.534	<0.001	0.426
BMI (kg/m ²)	21.67 ± 2.65	21.40 ± 2.66	21.55 ± 2.34	21.34 ± 2.26	0.819	<0.001	0.454
BMR (kJ)	1442.32 ± 80.12	1435.15 ± 78.85	1450.28 ± 77.36	1446.49 ± 77.73	0.452	0.001	0.298
Tissue impedance (Ohm)	550.93 ± 76.05	538.72 ± 73.94	549.41 ± 57.38	535.51 ± 56.48	0.814	<0.001	0.769
%FM	23.52 ± 5.52	22.31 ± 5.89	24.03 ± 5.43	22.64 ± 5.50	0.641	<0.001	0.634
FM (kg)	14.52 ± 5.17	13.56 ± 5.35	14.94 ± 5.03	14.00 ± 5.00	0.601	<0.001	0.927
FFM (kg)	45.53 ± 3.49	45.79 ± 3.37	45.77 ± 3.05	46.28 ± 3.19	0.489	<0.001	0.253
TBW (kg)	33.18 ± 2.91	33.58 ± 2.43	33.59 ± 2.42	33.90 ± 2.40	0.355	0.003	0.679
TC (mg/dL)	165.72 ± 20.39	164.32 ± 22.10	171.98 ± 26.40	170.36 ± 29.25	0.118	0.384	0.951
TGL (mg/dL)	74.83 ± 22.93	82.94 ± 29.16	82.76 ± 35.55	84.02 ± 37.49	0.353	0.087	0.209
HDL-C (mg/dL)	64.35 ± 13.28	63.92 ± 14.74	65.45 ± 13.43	59.82 ± 12.74	0.461	0.001	0.003
LDL-C (mg/dL)	86.33 ± 20.45	83.81 ± 16.79	89.90 ± 22.64	93.72 ± 25.60	0.046	0.689	0.053
Glucose (mg/dL)	80.00 ± 9.53	76.00 ± 9.99	77.28 ± 9.87	75.30 ± 10.14	0.228	<0.001	0.228

Mean±SD; *geometric mean (antilogged mean of the log data), in brackets - antilog of the log mean+log SD and log mean-log SD; BMI – body mass index; BMR – basal metabolic rate; %FM – fat mass percentage; FM – fat mass; FFM – fat free mass; TBW – total body water; TC – total cholesterol; TGL – triglycerides; HDL-C – high density lipoprotein cholesterol, LDL-C – low density lipoprotein cholesterol

DISCUSSION

To address the question of whether the functional *TNF- α* polymorphism influences selected body composition measurements as well as glucose, lipid, and lipoprotein phenotypes, we chose to correlate the distribution of genotypes and alleles described in the *TNF- α* rs1800629 polymorphism in female participants engaged in a 12-week aerobic training program. The changes in body mass/composition and biochemical parameters measured before and after training have been analyzed in the context of carrying specific *TNF- α* genotypes and alleles. The results provide some further evidence that *TNF- α* plays a role in human lipid metabolism. Our major concern was whether the *TNF- α* polymorphism is involved in the modulation of lipid profile, and if so, to what extent.

Parameters such as body mass, BMI, BMR, tissue impedance, %FM, FM, FFM, TBW, TC, and glucose changed significantly during

the 12-week training program. We also observed a significant decrease in HDL-C concentration, which could be explained by an increase in energy consumption and achieving an “energy expenditure threshold” during physical effort by participants [21]. Additionally, our statistical analyses revealed that harboring a specific *TNF- α* genotype may be associated with different post-training changes of measured biochemical parameters. There were two significant genotype × training interactions (for tissue impedance and HDL-C) in which a significant decrease of tissue impedance over training was observed in the AA carriers and HDL-C levels in the GG homozygotes. However, owing to low numbers of AA homozygotes, we repeated the analysis with the AA homozygotes in combination with the AG heterozygotes to obtain more reliable results. The second analysis revealed only one significant genotype x training interaction. The carriers of the GG genotype exhibited a significant decrease in post-training HDL-C

levels, indicating that harboring this specific genotype is unfavorable for achieving the desired training-induced HDL-C level changes. Additionally, we identified a statistically significant association between LDL-C level and genotype. Participants with the GG genotype had higher LDL-C level during the entire study period compared with the AA and AG genotypes, suggesting that the G allele is a risk allele.

Up to now, a lot of experimental studies have assessed the role of TNF- α in human lipid metabolism [7,12,14,15]. In adipose tissue, TNF- α inhibits lipoprotein lipase synthesis as well as the synthesis of acetyl-CoA carboxylase, fatty acid synthase, fatty acid-binding protein and glycerol phosphate dehydrogenase, all these enzymes being involved in fat synthesis. This cytokine also stimulates TGL degradation in the adipocyte by activating the hormone-sensitive lipase. Partly as a result of these metabolic changes in adipose tissue and partly because it stimulates liver lipogenesis and hepatic very low density lipoprotein (VLDL) production, TNF- α causes severe hypertriglyceridaemia [5]. Many authors have reported the polymorphism in the promotor region of *TNF- α* to cause the modification of the binding sites of certain transcription factors, and therefore affect the regulation of transcription and modulate their secretion [10,11]. The minor A allele was associated with increased *TNF- α* expression and as a result, it is described as a risk allele linked with insulin resistance, higher BMI, leptin, TGL, and LDL-C levels, as well as lower HDL-C levels [6,10,12,14]. On the other hand, our study indicated that carriers of the GG genotype had significantly higher LDL-C level during the entire study and experienced decreases in post-training HDL-C levels, suggesting that the G allele is the risk allele. Phillips et al. [14] also revealed unfavorable effects of the G allele, showing that GG homozygotes had increased risk of metabolic syndrome (MetS). These individuals had elevated plasma complement component 3 (C3) and LDL-C levels and were hypertensive relative to the A allele carriers.

Little is known about the *TNF- α* gene x physical activity interactions. Nicklas et al. [22] showed that walking distance and stair-climb time were better in individuals homozygous for the major G allele of the *TNF- α* polymorphism compared to those with at least one minor A allele. The less common allele of the *TNF- α* is a stronger activator of *TNF- α* transcription and is associated with higher protein production, higher circulating concentrations, and greater expression in skeletal muscle. All of these effects may provide a microenvironment in which the A allele could affect skeletal muscle and/or cartilage function resulting in slower walking speed [11,22,23]. However, in response to regular physical activity, there was a significant interaction between the *TNF- α* genotype and exercise treatment with respect to 6-month changes in stair-climb time and 18-month changes in self-reported physical disability, such that individuals with the A allele showed greater improvement in response to exercise [22]. In our study, we observed that harboring the specific *TNF- α* genotype may be associated with different post-training changes of measured

biochemical parameters. Carriers of the GG genotype exhibited a significant decrease in post-training HDL-C levels, indicating that harboring this genotype is unfavorable for achieving the desired training-induced HDL-C level changes.

The inconsistency of these results might be explained by the fact that as cytokines act in a complex network, single gene activity does not provide full insight into the role of different genetic markers in the human metabolism, as their combined action could result in different biological effects [14,24]. The genes regulating the inflammatory process can contribute to the individual variability of plasma cytokine levels, physical performance, as well as to the response of these variabilities to physical activity [24]. It has also been suggested that eating habits might influence these genes' effects on obesity-related traits. Few studies have described the impact of different hypocaloric diets on weight loss and metabolic parameters, analyzing the rs1800629 polymorphism of *TNF- α* in obese participants [25,26]. Therefore, analyzing and understanding the influence of genetic markers on the effects of training protocols, as proposed by our study, may support the development of new perspectives not only on individualization of exercise programs to make them more efficient and safer, but also on improved recovery, traumatology, medical care, diet, supplementation and many other areas [3].

CONCLUSIONS

The results of our experiment suggest that *TNF- α* genotypes can modulate training-induced biochemical parameters such as lipid profile changes. We have demonstrated that carriers of the GG genotype are associated with decreases in post-training HDL-C levels. Additionally, we showed that participants with the GG genotype had higher LDL-C levels during the entire study period. From this evidence, it could be concluded that harboring this specific genotype of the rs1800629 polymorphism may be considered to be a disadvantageous factor in the context of training-induced effects on lipid profile changes in Polish Caucasian women. However, more experimental studies are needed to establish this complicated association between the *TNF- α* gene, obesity-related traits, and physical activity across different study populations.

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Conflict of interest declaration

The authors declare that there is no conflict of interests regarding the publication of this paper.

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