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Abstract

Background

Obesity is a widespread problem within modern society,serving to increase the risk of cardiovascular, metabolic, and neurodegenerative disorders. Peroxisome proliferator-activated receptor gamma (PPARγ) and PPARγ coactivator 1 α (PGC1α) play a key role in the regulation of cellular energy metabolism and may be implicated in the pathology of these diseases. This study examined the association between polymorphisms of the *PPARG* and *PPARGC1A* genes,*PPARG* gene expression, risk of obesity and efficiency of intervention including physical activity and hypocaloric diet on weight loss.

Methods

Thirty-nineobese Ukrainian women (44.4 ± 7.5 years, BMI > 30.0 kg/m^2) undertook a 3-month fitness programwhilst following a hypocaloric diet (~1500 calories). Anthropometric (BMI, body fat percentage, and visceral fat) and biochemical (high- and low-density lipoproteins, cholesterol, triglyceride) measurements took place before and after the program. Single nucleotide polymorphisms within or near *PPARG* (n=94) and *PPARGC1A*(n=138) were identified and expression of *PPARG* mRNA was measured via reverse transcription and amplification. Theassociation betweenDNApolymorphisms and weight loss, initial body mass, biochemistry and *PPARG* expression was determined using one-way analysis of variance (ANOVA).

Results

The present intervention induced significant fat loss in all participants (total fat: 40.3±5.3 vs 36.4±5.7%; *P*<0.00001). Only one polymorphism (rs17650401 C/T) within the *PPARGC1A* gene was found to be associated with fat loss efficiency after correction for multiple testing, with T allele carriers showing the greatest reduction in body fat percentage (2.5-fold; *P*=0.00013) compared to non-carriers.

Conclusion

PPARGC1A (rs17650401) is associated with fat loss efficiency in obese women. Further studies are warranted to test if this variation affects fat oxidation.

Introduction

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptors demonstrated toplay a keyrole in carbohydrate and lipid metabolism,from the single cell to the whole organism. These receptors are classified into three families; PPARα, PPARδ, and PPARγ. PPARγ controls lipid storage and synthesis[1]. Its activation leads to triacylglycerol production and accumulation in liver, differentiation and proliferation of adipocytes, increased synthesis of both adiponectin and resistin[2], and regulation of the immune system response via areduction in inflammatory activity of lymphocytes[3,4]. Peroxisome proliferator-activated receptor-gamma coactivator (*PPARGC1A)*is a transcriptional coactivator that regulates the genes involved in energy production[5]. Additionally,*PPARGC1A*is involved in NO-induced mitochondrial biogenesis, along with switching of muscle metabolism towards oxidative phosphorylation, thusadapting muscle tissueto endurance training[6].A number of single nucleotide polymorphisms (SNPs) within the *PPAR* gene family are associated with a predisposition to metabolic, cardiovascular, and neurodegenerative disorders, such as obesity, dyslipidemia, hypertension, cancer,type 2 diabetes, and Parkinson's disease[7,8].

Obesity is a major problem withinmodern society, withthe percentage of affected adults in comprising ofup to 40% of the population in many developed countries[9]. Obesity is associated with an increased prevalence of cardiovascular diseases, type 2 diabetes, gastrointestinal and oncological disorders[10,11]. Designinga personalizedweight loss strategy may be an effective tool in reducing the spread of mentioned diseases.

To date, there is a limited data demonstrating the effects of SNPs within the genesof the PPAR family on weight loss through increased physical activity. *PPARG* polymorphismsare known to influence variability ofbody mass index (BMI) independently of sex, age, energy intake, and physical activity[12].However,the effects of these polymorphismson exercise-induced weight loss have not been previously characterized. Thepurpose of this study, therefore, was to identify SNPs within*PPARG* and *PPARGC1A* associated with total and visceral fat percentage, blood lipoprotein and triglyceride concentrations, as well as their modifyinginfluenceon the efficacy of moderate physical exercise in terms ofweight loss.

Materials and methods

Ethic statement

This study was approved by the National Academy of Science of Ukraine Bogomoletz Institute of Physiology Biomedical Ethics Committee, Kyiv, Ukraine (#1/18 05.04.2018). Written informed consent was obtained from the participants,and the study conformed to the guidelines and principles of the Declaration of Helsinki.

Participants

The study participants were 39 Ukrainian middle-aged women (44.4±5.8 years of age),of which 32%had no previous physical activity experience. Inclusion criteria included a BMI ofgreater than 30, and an absence of biochemical signs of severe metabolic syndrome (i.e. normal LDL, HDL, cholesterol and triglycerides). General characteristics of the study participants are shownin the Table 1.

Intervention

All participants were enrolled into a 3-month fitness program, which included 180 minutes of aerobic exercise per week with an average metabolic equivalent (MET) value of 6. Depending on the baseline physical fitness levels of each participant,exercise heart ratedid not exceed 115–125 bpm (low fitness), 125–135 bpm (moderate fitness), or 135–145 bpm (well-adapted).Heart rate was measured usingPolar RC3 GPS with Polar heart rate sensor H7 (Finland).Additionally, throughout the study period, the participants were advised to maintain a healthy hypocaloric diet (~1500 calories), avoid high-sugar, high-fat, and processed food diets, and to include more vegetables and wholemeal products in their diet.

Anthropometric and Blood Measurements

All measurements were done before and after the exercise lifestyle intervention. BMI was calculated as body weight in kilograms divided by the square of the height in meters. Percentage of total and visceral fat was measured by bioelectrical impedance analysiswith "TANITA – BC-418MA" body composition analyser (Japan). For the blood biochemical test, blood samples were collected from the antecubital vein after an overnight fast. Plasma glucose was measured by the standard method. HDL, LDL, and triglycerides were measured via direct methods.

Genotyping

The samples of 39 subjects were sent to the commercial laboratory (Akesogen, UK), where DNA was extracted from the saliva samples using Qiagen chemistry on an automated Kingfisher FLEX instrument (Thermo Fisher Scientific, Waltham, MA, US), following the manufacturer's recommended protocols and standard operating procedures. PicoGreen and Nanodrop measurements were taken to measure the quality and quantity of the DNA. Input to the custom testing array occurs at 200 ng in 20 μl. Amplification, fragmentation, and resuspension was performed using Biomek FXP following Affymetrix's high throughput protocol for Axiom 2.0. Hybridization was performed for 24 hours at 48 °C in a Binder oven, and staining and scanning of the arrays (94*PPARG* and 138 *PPARGC1A*SNPs; DNAFit's custom microchips) was performed

using GeneTitan instrumentation (Thermo Fisher Scientific, Waltham, MA, US), all following the same Affymetrix high throughput Axiom 2.0 protocol. Data analysis was then performed using a raw CEL file data input into the Affymetrix Axiom Analysis Suite (Affymetrix, Santa Clara, CA, US).

Analysis of mRNA expression of*PPARG*

Expression of *PPARG* mRNA was measured via reverse transcription and amplification. Reverse transcription was performed with Random Hexamer primer, Revert Aid RT, Ribo Lock RNAse inhibitor and dNTP mixture on Gene Amp® PCR System 2700, Applied Biosystems, USA. The samples were incubated at 42°C for 1 h, followed by heating at 70°C for 10 min. Amplification was performed on a7500 FastReal-time PCR system (Applied Biosystems, USA). The values were corrected forβ-actin mRNA expression.

Statistical analysis

Statistical analysis was conducted using RStudio software. One-way analysis of variance (ANOVA) was applied to determine statistical significance among different groups. The paired t-test was used to detect the significance of dynamic changes. $P < 0.05$ was considered statistically significant. Bonferroni's correction for multiple testing was performed by dividing the *P* value by the number of tests where appropriate.

Results

Effects of intervention program

The changes in body compositionand biochemical profile induced by the 3-month exercise trainingand hypocaloric diet are summarized in Table 1. As expected, the intervention induced significant improvements of triglycerides, LDL, and cholesterol levels, as well as BMI, waist circumference, hip circumference, total and visceral fat.

Influence of SNPson *PPARG*mRNA expression

Of the 94 analysed*PPARG* SNPs,none were significantly associated with *PPARG* mRNA expression after correction for multiple testing. The most significant SNP,rs6442311A/G,is located in *PPARG* intron.The rs6442311 AG genotype was associated with increased *PPARG* expression (9.01±0.07%; $P = 0.022$).

Associations between *PPARG* and*PPARGC1A*SNPs and adipose tissue mass

We evaluated relationships between 94 *PPARG* and 138 *PPARGC1A* SNPs and baseline values of body fat percentage, visceral fat, and markers of lipid metabolism (HDL, LDL, cholesterol). Of the tested *PPARG* SNPs, only one(rs6442311) of the 94 showed a nominally significant(*P* = 0.016) influence on the initial percentage of body adipose tissue. For individuals with the AG genotype of rs6442311the mean values of body fatpercentage and visceral fat were29.3% and 5.5% respectively. For individuals withthe AA genotype, the results were41.6 %and 10.5 % respectively(Fig. 1). Accordingly, the minor allele of rs6442311 had a negative correlation with the accumulation of white adipose tissue, especially of visceral fat, and with a higher ratio of total to visceral fat mass (5.33 for carriers and 3.96for non-carriers).

Of the 136 tested *PPARGC1A* SNPs,only rs6846769showed a nominally significant association with baseline percentage of adipose tissue (*P*= 0.034). More specifically, the minor allelewas correlated with a lower body fat percentage; 41.4 % and 28 % for major and minor alleles, respectively (Fig.1). Furthermore,the percentage of visceral fat in minor allele carriers was almost two-times lower (9.7 % and 5 %), and the ratio of total adipose fat to visceral fat was higher in carriers (5.6) than in non-carriers (4.3).

Associations between *PPARGC1A*SNPs and blood lipoproteins

None of the 94 tested *PPARG*SNPs showed a statistically significant association with HDL, LDL, cholesterol or triglycerides.One of the 136 tested *PPARGC1A* SNPs showed a nominally significant influence on blood lipoproteins. The minor allele ofrs4458444 (intron variant) was associated with increased HDL(*P* = 0.0081), and total cholesterol (*P* = 0.036).One of the 136 tested *PPARGC1A*SNPs demonstrated correlation with increased triglyceride blood concentrations. A mean triglyceride concentration of 2.38 mM/l was found in carriers of rs2305681 minor allele,whereas the mean of carriers of major allelewas 1.6 mM/l.

Associations between *PPARG* and *PPARGC1A* SNPs and fat mass loss

Only one polymorphism (rs17650401 C/T) within the *PPARGC1A* gene was found to be associated with fat loss efficiency after correction for multiple testing, with T allele carriers showing the greatest exercise-induced reduction in body fat percentage (2.5-fold; *P*=0.00013) compared to non-carriers. As for the 94 analyzed*PPARG* SNPs, rs9833097 (*P*=0.00023) and rs12629751 (*P*=0.0065) have shown nominal associations. Genotypes of rs9833097 (AA, AG, GG) have been shown to be associated with different values of weight loss (14.60 %, 4.71%, and 2.82%, respectively). Presence of the minor allele ofrs12629751was found to correlate witha twofold increase in weight lossafter the three-month moderate exercise program: the percentages ofbodyfat loss were 3.02 % and 6.48 % for CC and TC genotypes, respectively.

Discussion

The effectiveness of physical exercise and diet on fat loss varies considerably between individuals[13]. Our genetic association study was designed to test whether multiple variations in the *PPARG* and *PPARGC1A* genes can modulate changes in body composition and metabolic variables following a3 months supervised fitness program and hypocaloric diet in obese Ukrainian women. We also tested the hypothesis that polymorphisms within *PPARG* gene may influence its expression.

PPARG plays an important role in the control of adipose tissue metabolism, adipocyte division and differentiation, fat storage and oxidation in beige and brown adipose tissue[14]. Exercise is known to increase *PPARG* expression and activity within skeletal muscle, thus promoting mitochondrial biogenesis and aerobic respiration[15]. An increased expression of *PPARG* offers protection against elevated blood glucose levels[16]; as such, the rs6442311 G allele of the *PPARG* gene which has been shown to be associated in our study with increased *PPARG* mRNA levels may decrease the risk of obesity-induced diabetes and cardiovascular diseases. Indeed, we found that *PPARG* rs6442311 G allele was also associated with decreased percentage of the visceral fat at baseline.

Body fat percentage, visceral fat, and markers of lipid metabolism (HDL, LDL, cholesterol)are strongly related to the risk of metabolic syndrome, type 2 diabetes, and cardiovascular diseases[17]. Besides*PPARG* rs6442311, the rs6846769 polymorphism in the *PPARGC1A* gene showed a nominally significant association with baseline percentage of adipose tissue. Thers6846769 SNP may protect against the accumulation of visceral fat in an obese person under the influence of environmental factors via the activation of adaptive thermogenesis in brown adipose tissue[18]. This SNP is located inthe first intron of *PPARGC1A*, prior to the protein coding sequence, and may participate in the control of *PPARGC1A* gene expression. Enhanced *PPARGC1A* expression protects from visceral adipose tissue accumulation, increases total adipose to visceral fat ratio, and reduces total body fat content[19]. Furthermore, the minor allele of the *PPARGC1A* gene rs4458444 polymorphism was associated with increased HDL and total cholesterol. Previously[20,21] it was shown that decreased expression of *PPARGC1A* may upregulate liver lipoprotein synthesis and downregulate systemic utilization of cholesterol lipoproteins. In addition,the *PPARGC1A* rs2305681 SNP was found to be associated with triglyceride concentration. Decreased activity of *PPARGC1A* is associated with increased blood triglyceride levels [7] and risk of cardiovascular disease, especially under the influence of environmental factors which induce obesity. Previously, rs2305681 showed strong correlation with anxiety disorders[22] via

possible activation of the antioxidant system within GABA neurons[23]. Interestingly, *PPARGC1A* rs3774909 (which is in 100% linkage disequilibrium (LD) with rs2305681) has been shown previously to be associated with endurance performance[24], presumably via regulation of oxidative phosphorylation, skeletal muscle mitochondrial biogenesis, and alteration of muscle fiber types.

We have also shown thatrs17650401 C/T within the *PPARGC1A* gene was associated with fat loss efficiency after correction for multiple testing. This is in line with the studies showing that various types of exercises (acute, high intensity interval, and aerobic) induce expression of *PPARGC1A* in the group of overweight people[25], which was accompanied with fatty acid oxidation[26]. Moreover, the increased *PPARGC1A* activity was independent of the glycemic index of the diets[27] and mostly induced by the exercise program.

Furthermore, we found two candidate markers within *PPARG* (rs12629751 and rs9833097) that have shown nominal associations. Interestingly, the minor allele of rs12629751,which correlated with a twofold increase in weight loss, previously demonstrated a protective property against breast cancer[28]. In addition, the polymorphism within rs7626560 (which is in LD with rs9833097) correlated with response to diabetes preventive lifestyle interventions incidence[29], where participants were advised to perform 150 min per week of physical activity (in our study, participants exercised 180 min per week).

All nominally significant SNPsidentified within this researchare located in the intron region. There is no data about the intronic SNPseffects on *PPARGC1A* or *PPARG* expression. Hence, these SNPs may belong to regulatory post-transcriptional sequences producing miRNA. Also, a changing of the nucleotides upstream of promotor region may lead to another nucleosome positioning, thus altering promoter strength and its interaction with transcriptional factors. Altogether, we suggest this leads to a different expression response to the same environmental factors, such as diet, age and physical exercises;this hypothesis is illustrated on Fig 2.

Conclusion

An intervention comprised of physical activity and a hypocaloric diet has a significant impact on fat loss. Individual variability in fat loss efficiency may partly depend on the rs17650401 C/T polymorphism within the *PPARGC1A* gene. The identified SNP,along with many others may be helpfulin designingindividual weight loss programsfocused on exercise and/or nutrition. Further studies are warranted to test if this variation affects fat oxidation and is associated with fat loss efficiency in other ethnicities.

Authors' contributions

IIM contributed to data collection, data analysis, interpretation of results and manuscript writing; SD participated in the design of the study, data analysis, interpretation of results and manuscript writing;

OA, YV, AP and IA contributed to data collection, data analysis and interpretation of results; VD participated in the design of the study, data analysis and interpretation of results; CP participated in the interpretation of results and manuscript writing; IIA participated in the design of the study, contributed to data analysis, interpretation of results and manuscript writing. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competinginterests

CP is a former employee of DNAfit Life Sciences, a genetic testing company. The remaining authors declare no conflicts of interest. The funding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Figure legends

Fig. 1. Associations between *PPARG* rs6442311 and *PPARGC1A* rs6846769 polymorphisms and percentage of total and visceral adipose tissue in obese women (BMI>30 kg/m^2).

Fig. 2. Theoretical model of intron SNPs influence on *PPARG* expression under moderate-exercise environment.

Table 1. Effects of intervention program in 39 obese women

Trait	**Changes (mean±SD)**		***P***
	before	after	
Triglycerides, mM/l	1.58±0.78	1.47±1.04	0.756
LDL, mM/l	3.21±1.16	2.86±0.98	0.016*
HDL, mM/l	1.44±0.3	1.41±0.28	0.549
Cholesterol, mM/l	5.32±1.23	4.81±1.08	0.022*
BMI, kg/m^2	33.2±2.9	30.4±3.7	<0.00001*
Waist circumference, cm	92.4±8.9	85.9±8.9	<0.00001*
Hip circumference, cm	115.3±7.1	107.9±7.7	<0.00001*
Total fat, %	40.3±5.3	36.4±5.7	<0.00001*
Visceral fat, %	9.5±2.4	8.1±2.2	<0.00001*

*$P < 0.05$, statistically significant differences (paired *t*-test).