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ORIGINAL ARTICLE

Body fat, cardiovascular risk factors and polymorphism in the FTO gene: randomized clinical trial and different physical exercise for adolescents

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Abstract
Objective: To investigate the effects of different physical exercise programs and polymorphisms of the FTO (fat mass and obesity-associated gene) on body composition and cardiovascular risk factors in adolescents with overweight and obesity.
Methods: A randomized, parallel, double-blind clinical trial consisting of the adolescent overweight from the state public network, in a simple representative random sample, who participated in an aerobic exercise or weight training intervention for 10 weeks. Anthropometry, body composition, biochemical markers, sexual maturation, and rs9939609 polymorphism in the FTO gene were assessed. 347 adolescents had their characterization of nutritional status. 72 individuals with overweight and obesity were invited to participate. 39 remained for the start of the program and were randomly allocated to both types of intervention. In the end, 26 subjects participated in the intervention programs, with 12 and 14 in the aerobic and weight training programs, respectively.

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Results: Heterozygous and homozygous bearers of risk allele A participating in the aerobic program showed improvements in glycemia (p = 0.002) and total cholesterol (p = 0.023) and a reduction in body fat mass (p = 0.041). The weight training program reduced glycemia in patients with the risk allele A (p = 0.027). Cameron's stage four sexual maturation participants were 2.1 times more likely to improve their body fat (CI = 1.31-3.39).
Conclusion: Aerobic exercises produced exclusively a significant decrease in fat mass and total cholesterol in patients with risk allele A. Distinct physical exercise programs may cause diverse changes in risk variables related to the health of adolescents.

Introduction

Obesity is progressively affecting an epidemic percentage of adults, children, and especially young adults. Cardiovascular diseases (CVD) are even the leading cause of death from chronic non-communicable diseases (NCDs), whose most commonly reported risk factors for CVD are changes in total and fractional cholesterol levels, triglycerides, insulinemia, fasting glucose, systolic, diastolic and mean blood pressure, body mass index (BMI), percentage of body fat (%BF), aerobic physical fitness and physical activity levels (PAL).[1] An enhanced risk of obesity is a result of genetic susceptibility to variants of the fat mass and obesity-associated (FTO) gene, which can be lessened through physical activity. Single nucleotide polymorphisms (SNPs) grouped in the first *intron* of the FTO exhibit associations with obesity and are more investigated than any other genetic variant common in human obesity.[2] rs9939609 represents the SNP with the largest association with the characteristics of obesity and type II diabetes, and those with risk allele A exhibit a higher intake of highly delectable foods.[3]

The purpose of this study was to evaluate the effects of different exercise programs and polymorphisms on the FTO gene and body composition as well as on cardiovascular risk factors in overweight and obese adolescents.

Methods

Randomized, parallel clinical trial survey characterized by the diagnostic evaluation, with balanced randomization [1:1], an intervention period, and final evaluation. For allocation of the participants, a computer-generated list of random numbers was used, following simple randomization procedures (computerized random numbers) to 1 of 2 treatment groups by the study coordinator.

The study was previously approved by the Human Research Ethics Committee of the Federal University of São João del Rei- Campus Centro Oeste and recorded RBR-7hsjfjk in the ReBEC (Brazilian Registry of Clinical Trials). Full details of the trial protocol are available at https://ensaiosclinicos.gov.br/rg/RBR-7hsjfjk.

The informed consent form (ICF) was written and signed by each participant.

Diagnosis of the nutritional status of 7001 high school students from state public schools (aged between 15 and 19 years in the municipality of Divinopolis, Minas Gerais, Brazil) was conducted through a simple random sample representative of the population, taking into consideration the proportionality in each school. The classification of nutritional status using BMI was acquired by using the free software Who Anthro Plus, based on proposals from the World Health Organization.[4] The diagnosis of Metabolic Syndrome used the criteria of the International Diabetes Federation (IDF).[5]

All 72 adolescents classified as overweight (49) and obese (23) were invited to engage in this clinical trial (Fig. 1 – supplementary material).

Individuals who were unavailable to take part in the assessments, those who were not able to attend physical education classes at school, and those who had any injury or illness (before or during the intervention program) that permanently disabled them from practicing the exercises were excluded. An upper limit of consecutive absences of 20% was set for the intervention program.

Body mass and height

A digital electronic TANITA® brand scale, model BF-683 W (Tanita Corporation, Japan), was utilized. Height was measured by using an ALTUREXATA® brand mobile vertical anthropometer (Alturexata, Brazil).

Waist circumference (WC)

Flexible and inelastic anthropometric tape with a length of 2 meters was utilized. Subjects remained in an orthostatic position. The measurement was obtained during normal expiration, using the midpoint between the margin of the last rib and the iliac crest as a reference.[6]

Blood pressure

An OMROM® automatic blood pressure device, model HEM711 (Omron Healthcare, Inc, Bannockburn, Illinois, USA) was used. The first measurement was performed five minutes after the adolescent had assumed a sitting position, and two minutes subsequent to that, between the two other measurements.[7] The arithmetic mean of the measured values was used.

Sexual maturity

The classifications proposed by Tanner and Cameron were used based on self-assessment, in reserved space.[8,9]

Body composition by deuterium oxide (D2O)

The deuterium oxide dilution method (using isotopic mass spectrometry - IRMS) was used for the knowledge of total body water and consequently fat-free mass (FFM) and fat mass (BF).[10,11]

Biochemical tests

Fasting blood glucose and lipid profile analyses were carried out with respect to the 12-hour fast, and 10 mL of blood was collected in a reserved space at the school. The samples were immediately centrifuged at 3000 rpm for 10 minutes, and the serum was stored at −20°C.

Measurement of glucose, triglycerides and total cholesterol (TC) was performed by using an enzymatic colorimetric method with commercial kits: Glucose Liquiform Kit (Labtest Diagnóstica, SA, Brazil), Triglicérides Monorreagente K117-Bioclin Kit (Quibasa Química Básica, Ltda, Brazil), and Monoreagent Cholesterol Kit K083-Bioclin (Quibasa Química Básica, Ltda, Brazil). HDL cholesterol was separated by selective precipitation of low-density and very-low-density lipoproteins (LDL and VLDL), an enzymatic K015-Bioclin HDL cholesterol kit (Quibasa Química Básica, Ltda, Brazil) was utilized and subsequently quantified by an enzymatic colorimetric K083-Bioclin Mono-reagent Cholesterol Kit (Quibasa Química Básica, Ltda, Brazil). LDL and VLDL concentrations were calculated using the Friedewald equation.

Genotyping

Five-milliliter blood samples were collected with EDTA anticoagulant in a reserved space at the school, and 200 μL was utilized for DNA extraction. The genotyping protocol was based on the amplification of the genetic material by polymerase chain reaction (PCR) and detection of the 9939609 polymorphism in the FTO gene by digestion with restriction enzymes. The genomic DNA of all the research participants was stored at −20°C. The extraction of genomic DNA was performed using the salting out method[12] or using the QIAamp DNA Blood Mini Kit in accordance with the manufacturer's protocol (QIAGEN, Germany). The oligonucleotides that were used produced an amplicon of 182 base pairs[13] and were synthesized by Eurofins Genomics of Louisville, USA.[13]

The annealing temperature of the oligonucleotides of 62°C was defined after PCR at different temperatures and assessed by electrophoresis. The digestions of all samples were carried out in a dry bath at 37°C for 20 minutes. The endonuclease applied was ScaI (Jena Bioscience, Germany).

Physical activity level

International Physical Activity Questionnaire (IPAQ-short version) was utilized to assess the level of physical activity of all participants. It consists of eight open questions and its information allows estimating the time spent per week in different dimensions of physical activity, through the product between the duration (minutes/day) and the frequency (days/week) reported by the adolescents in the answers of the questions presented.

The proposed classification is "very active"(vigorous-intensity activity on at least 3 days achieving a minimum total physical activity of at least 1500 MET-minutes/week; or 7 or more days of any combination of walking, moderate-intensity; or vigorous-intensity activities achieving a minimum Total physical activity of at least 3000 MET-minutes/week), "active" (3 or more days of vigorous-intensity activity of at least 20 minutes per day; or 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day; or 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum Total physical activity of at least 600 MET-minutes/week), "irregularly active/sedentary" (those individuals who not meet criteria for previous Categories).[14]

Socioeconomic level

Socioeconomic questionnaire/Brazil Criterion of the Brazilian Association of Research Companies (ABEP) was used,[15] which is an operational rule for the economic classification of households, in strata categorized in letters A to E.

Intervention program

The facilities of a club were used, for the sessions, with a weekly frequency of 3 times, always accompanied by a physical education professional. Aerobic training exercise session had a duration of 40 minutes, with 5 minutes of aerobic warm-up, 30 minutes of specific training, and 5 minutes of cool-down. The exercises included fun, semi-competitive, and recreational activities, with 1-minute recovery intervals between activities. The intensity prescribed utilized the heart rate training equation,[16] using the data collected at the beginning of the program.

Periodization utilized 3 mesocycles with an intensity in the target zone (50-85%). Subjective perception of effort (PSE) was evaluated using the Borg scale.[17]

Bodybuilding work was carried out according to the recommendations established by the American College of Sports Medicine.[18] A linear circuit training periodization was used, varying in volume and intensity. During the adaptation period (2 weeks), the participants were specifically oriented to the exercise techniques, and the maximum repetitions test (TRM) was performed, the result of which was used to calculate the load for each exercise in the program.[19] Participants completed between 10 and 15 repetitions, at a slow speed and a cadence of 1:2, with the period of recovery corresponding to the time required to move from one exercise to the next, with an intensity of 50% to 80% of 1RM.

Statistical analysis

Dependent variables (body composition, BP, WC, lipid profile, and blood glucose) and independent variables (sex, age, sexual maturation, SNP rs9939609, type of exercise program, socioeconomic level, level of physical activity, nutritional status, metabolic syndrome) were organized in the EpiData® spreadsheet model and entered into the statistical program SPSS version 20.

Analytical statistics used a 95% confidence interval, a significance level of 5% (α = 0.05). Shapiro-Wilk test was used to verify the normal distribution of the values of the continuous variables.

Odds ratios of the different characteristics of the groups and the responses to the training models were evaluated. T-tests or the Wilcoxon test were used to compare the means or medians of the variables in the independent groups before and after the intervention.

Results

Initially, 347 adolescents had their data collected and were part of the sample for the characterization of nutritional status. The prevalence of overweight (overweight and obesity) was 20.8% (72 individuals, who were invited to participate in the research).

Genotyping of the rs9939609 was performed and there was a statistically significant association (Pearson's chi-square, p = 0.003) between TT + AT (recessive allele) versus AA, with the presence of the AA genotype being 24% in the overweight group when compared to the eutrophic group, in which the presence was 13%. This means that individuals with a BMI>85 and homozygotes with risk allele A exhibited an association, consequently being more susceptible to problems resulting from obesity, whose population showed balance in relation to rs9939609 polymorphism genotyping, according to the Hardy-Weinberg equilibrium (EHW) assessment.

Due to the losses related to non-initiation of activities due to a lack of interest (20 individuals, 27.8%), pre-intervention clinical conditions (three participants, 4.2%), and other pre-intervention commitments (10 individuals, 13.9%), 39 individuals remained for the start of the program and were randomly allocated to both types of intervention.

During the planned 10-week training, there were losses due to absenteeism and/or other commitments (13 losses, 33.3%), of which seven (53.8%) corresponded to the aerobic program and six (46.2%) to the weight training program. In the end, 26 subjects participated in the intervention programs, including 12 and 14 adolescents in the aerobic and weight training programs, respectively, whose characteristics are shown in Table 1.

The mean %BF of the group showed a non-parametric distribution ($p < 0.05$), with an average of 34.8 $\pm$ 9.8%BF, with 28.5 $\pm$ 11.3%BF among boys and 39.4%BF $\pm$ 5.1 among girls, as well as a median of 37.5 (28.3-42.3)%BF, with 24.5 (20.9-42.2)%BF among boys and 38.8 (36.4-42.4)%BF among girls.

Significant differences between the means and medians in the parameters %BF, WC, systolic arterial pressure, diastolic arterial pressure, glycemia, lipid profile, and physical conditioning variables were evaluated in participants of both types of programs, especially related to the polymorphic characterizations of the participants. The results are shown in Tables 2 and 3.

In patients with risk allele A, the intervention program produced significant reductions in blood pressure (systolic and diastolic), fasting blood glucose, lipid profiles (TC and LDL), and systolic blood pressure in wild-type homozygotes.

Table 1 Descriptive statistics and characterization of the sample of adolescents, who were high school students from state public schools, aged 15 to 19 years, participating in the intervention program. Divinopolis, Minas Gerais, Brazil, 2019. n = 26.

	n (%)		
Variable	Male	Female	Total
Sex			
	11(42.3%)	15 (57.7%)	26 (100%)
Program type			
Aerobic	8 (30.8%)	4 (15.4%)	12 (46.2%)
Weight Training	3 (11.5%)	11 (42.3%)	14 (53.8%)
Genotyping			
Presence of the risk allele A	8 (30.8%)	8 (30.8%)	16 (61.6%)
Non-risk allele A	3 (11.5%)	7 (26.9%)	10 (48.4%)
MS			
IDF	2 (8.3%)	0 (0.0%)	2 (8.3%)
Race			
White	5 (19.2%)	2 (7.7%)	7 (26.9%)
Brown	2 (7.7%)	8 (30.8%)	10 (38.5%)
Black	4 (15.4%)	5 (19.2%)	9 (34.6%)
Socioeconomic level			
A	0 (0.0%)	1 (3.8%)	1 (3.8%)
B1	0 (0.0%)	1 (3.8%)	1 (3.8%)
B2	3 (11.5%)	3 (11.5%	6 (23.1%
C1	4 (15.4%)	7 (26.9%)	11 (42.3%)
C2	2 (7.7%)	1 (3.8%)	3 (11.5%)
D-E	2 (7,7%)	2 (7.7%)	4 (15.4%)
Physical activity level			
Sedentary / Irregularly active	8 (30.8%)	5 (19.2%)	13 (50.0%)
Active/Very active	3 (11.5%)	10 (38.5%)	13 (50.0%)

IDF, international diabetes federation; MS, metabolic syndrome.

Table 2 Measures of central tendency and dispersion of body composition and blood pressure variables before and after intervention with different physical exercise programs in overweight and obese adolescents. Divinopolis, Minas Gerais, Brazil, 2019. n = 26.

Variable	Median		p-value
	Pre	Post	
Intervention (risk allele A)			
Body fat percentage	34.6 (23–42)	32.8 (23–38)	0.211
Fat mass (kg)	25.1 (18–38)	24.0 (18–28)	0.232
Waist circumference (cm)	81.6 (76–89)	82.4 (77–88)	0.295
Systolic blood pressure (mmHg)	116 (109–130)	115 (106–123)	0.042[a]
Diastolic blood pressure (mmHg)	68 (66–74)	65 (58–72)	0.017[a]
Intervention (non–risk allele A)			
Body fat percentage	38.3 (36–44)	39.5 (36–43)	0.753
Fat mass (kg)	27.7 (23–32)	28.3 (23–31)	0.753
Waist circumference (cm)	76.7 (76–80)	76.1 (74–79)	0.612
Systolic blood pressure (mmHg)	115 (110–122)	106 (105–112)	0.018[a]
Diastolic blood pressure (mmHg)	62 (57–73)	62 (58–65)	0.398
Aerobic (risk allele A)			
Body fat percentage	36.4 (23–42)	32.8 (23–40)	0.077
Fat mass (kg)	24.0 (18–42)	23 (18–36)	0.041[a]
Waist circumference (cm)	82.8 (78–95)	82.4 (78–91)	0.346
Systolic blood pressure (mmHg)	118 (113–130)	115 (109–122)	0.071
Diastolic blood pressure (mmHg)	67 (65–72)	65 (60–71)	0.147
Aerobic (non–risk allele A)[b]			
Body fat percentage	-	-	-
Fat mass (kg)	-	-	-
Waist circumference (cm)	-	-	-
Systolic blood pressure (mmHg)	-	-	-
Diastolic blood pressure (mmHg)	-	-	-
Weight training *(risk allele A)*			
Body fat percentage	31.9 (21–38)	29.9 (22–38)	0.866
Fat mass (kg)	25.0 (14–28)	24.3 (18–27)	1.000
Waist circumference (cm)	81.6 (75–87)	82.4 (75–87)	0.502
Systolic blood pressure (mmHg)	112 (106–123)	108 (99–127)	0.310
Diastolic blood pressure (mmHg)	70 (66–76)	64 (57–73)	0.063
Weight training *(non-risk allele A)*			
Body fat percentage	38.8 (37–43)	39.8 (37–42)	0.735
Fat mass (kg)	28·2 (24–29)	28·8 (24–30)	0.735
Waist circumference (cm)	76.7 (76–80)	76.1 (74–79)	0.612
Systolic blood pressure (mmHg)	115 (110–122)	106 (105–112)	0.018[a]
Diastolic blood pressure (mmHg)	62 (57–73)	62 (58–65)	0.398

[a] $p < 0.05$- Wilcoxon test.
[b] Insufficient sample due to losses during the study.

There was a reduction in glycemia in patients with risk allele A who practiced both types of training. In participants of the aerobic program with risk allele A, other changes were also noted, such as in the TC and especially in the reduction of fat mass. Significant reductions in systolic blood pressure for non-risk allele A were observed.

The measures of effect linked to the independent variables related to the reduction in the % BF are shown in Table 4.

Discussion

The intervention program for patients with allele A produced reductions in blood pressure, fasting blood glucose, lipid profile, and a reduction in systolic blood pressure in wild-type homozygotes.

Lower glucose levels were observed in the participants who were homozygous for the risk allele A after the exercise program (including ground aerobic exercise programs, water walking, high-intensity interval training, and combined training) compared to those non-risk allele A, in a study of 432 Brazilian children and adolescents.[20]

Another program for weight loss with a minimum duration of 8 weeks, based on aerobic exercise, lifestyle exercise and decreasing sedentary behavior, nutritional guidance, and behavioral therapy, concluded that there was no significant association in its sample between the presence of the risk allele A and weight loss,[21] revealing that not all intervention

Table 3 Measures of central tendency and dispersion of the lipid profile and blood glucose variables, pre- and post-intervention, with different physical exercise programs in overweight and obese adolescents. Divinopolis, Minas Gerais, Brazil, 2019. n = 26.

Variable	Median		p-value
	Pre	Post	
Intervention (risk allele A)			
Glucose (mg/dL)	76 (69–78)	60 (59–62)	0.000[a]
Total cholesterol (mg/dL)	159 (136–175)	137 (122–164)	0.006[a]
Triglycerides (mg/dL)	92 (52–121)	73 (54–93)	0.327
HDL cholesterol (mg/dL)	37 (33–45)	38 (35–45)	0.320
LDL cholesterol (mg/dL)	101 (83–118)	83 (73–106)	0.018[a]
VLDL cholesterol (mg/dL)	19 (11–24)	15 (11–19)	0.327
Intervention (non–risk allele A)			
Glucose (mg/dL)	71 (65–77)	60 (56–62)	0.116
Total cholesterol (mg/dL)	148 (140–163)	139 (123–151)	0.249
Triglycerides (mg/dL)	51 (33–100)	69 (53–86)	0.600
HDL cholesterol (mg/dL)	38 (35–49)	40 (35–47)	0.892
LDL cholesterol (mg/dL)	96 (81–108)	81 (78–93)	0.116
VLDL cholesterol (mg/dL)	10 (7–20)	14 (11–17)	0.528
Aerobic (risk allele A)			
Glucose (mg/dL)	76 (70–77)	61 (59–62)	0.002[a]
Total cholesterol (mg/dL)	161 (136–182)	142 (119–175)	0.023[a]
Triglycerides (mg/dL)	105 (57–146)	75 (56–92)	0.071
HDL cholesterol (mg/dL)	37 (32–44)	40 (35–45)	0.157
LDL cholesterol (mg/dL)	108 (83–123)	82 (64–112)	0.091
VLDL cholesterol (mg/dL)	21 (12–30)	15 (11–19)	0.065
Weight training (risk allele A)			
Glucose (mg/dL)	74 (62–82)	60 (55–62)	0.027[a]
Total cholesterol (mg/dL)	146 (136–173)	136 (135–157)	0.093
Triglycerides (mg/dL)	78 (36–89)	73 (51–118)	0.173
HDL cholesterol (mg/dL)	37 (35–48)	35 (30–51)	0.893
LDL cholesterol (mg/dL)	94 (81–121)	88 (74–91)	0.074
VLDL cholesterol (mg/dL)	16 (7–18)	15 (10–24)	0.172
Aerobic (non–risk allele A)[b]			
Glucose (mg/dL)	-	-	-
Total cholesterol (mg/dL)	-	-	-
Triglycerides (mg/dL)	-	-	-
HDL cholesterol (mg/dL)	-	-	-
LDL cholesterol (mg/dL)	-	-	-
VLDL cholesterol (mg/dL)	-	-	-
Weight training (non–risk allele A)			
Glucose (mg/dL)	71 (65–77)	60 (56–62)	0.116
Total cholesterol (mg/dL)	148 (140–163)	136 (111–156)	0.249
Triglycerides (mg/dL)	51 (33–100)	69 (53–86)	0.600
HDL cholesterol (mg/dL)	38 (35–49)	40 (35–47)	0.892
LDL cholesterol (mg/dL)	96 (81–108)	81 (78–93)	0.116
VLDL cholesterol (mg/dL)	10 (7–20)	14 (11–17)	0.528

[a] $p < 0.05$- Wilcoxon Test.
[b] Insufficient sample due to losses during the study.

models produce a reduction in overweight, especially in patients with risk allele A.

In the present study, there was a reduction in glycemia in participants with risk allele A who participated in both training sessions (aerobic and weight training). Reduction in adiponectin levels would impair glucose metabolism, that is, the rs9939609 SNP in the FTO gene can contribute to the modulation of adiponectin and, consequently, glucose metabolism.[20]

In those who participated in the aerobic program, changes were also observed in the TC levels and especially in the reduction of fat mass. Data indicate that risk allele A does not influence weight loss, regardless of the program/diet,[21] and carriers of the homozygous for the risk allele A do not have impaired weight loss.[22] Variations in FTO appear to have an effect on the development of obesity, such as the SNP of risk allele A of rs9939609, and in this respect, physical activity can

Table 4 Prevalence of a % BF reduction and odds ratios of variables among adolescent students from state public schools, aged 15 to 19 years, who participated in a physical exercise program. Divinopolis, Minas Gerais, Brazil, 2019. n = 26.

Variable	Improvement	Odds ratio	CI (95%)
Presence of the risk allele A	63.2%	1.286	0.22–7.50
Aerobic Program	75.0%	3.000	0.56–16.01
Extra physical activity	77.8%	3.111	0.49–19.54
Physical activity level-IPAQ	69.2%	1.929	0.39–9.60
Socioeconomic Level[a]	62.5%	1.061	0.19–5.90
Sexual maturity-Tanner[b]	83.3%	4.091	0.40–41.66
Sexual maturity-Tanner[c]	66.7%	1.500	0.30–7.43
Sexual maturity–Cameron[d]	47.4%	2.111	1.31–3.39[g]
Female	60.0%	0.857	0.17–4.27
Race[e]	30.0%	0.099	0.02–0.63
Nutritional status[f]	80.0%	3.000	0.29–31.63

% BF, body fat percentage; CI, confidence interval; IPAQ, international physical activity questionnaire.
[a] Dichotomized into classes A/B versus classes C/D/E.
[b] Breasts/genitals dichotomized at levels 5 versus $^{3}/_{4}$.
[c] Pubic hair dichotomized at levels 5 versus $^{3}/_{4}$.
[d] Dichotomized at 4 versus 2/3.
[e] Dichotomized in brown versus others.
[f] Dichotomized in obese versus overweight.
[g] Statistically significant ($\alpha = 0.05$).

improve the deleterious effect of this polymorphism on body fat estimates in adolescents.[23] Physical activity reduces the influence of genetic factors on the development of high BMI and WC, which suggests that individuals with a higher genetic risk of obesity would be the ones who would benefit most from physical activity, decreasing the additive genetic component on BMI and WC.[24]

A study with Chinese children and adolescents demonstrated a greater reduction in the levels of TC and LDL in patients with risk allele A in relation to TT after intervention with diet and aerobic exercises, indicating that the FTO polymorphism rs9939609 may be a factor that affects the therapeutic effect on obesity in the sample.[25]

There are possible explanations related to the regulatory transcriptional role linked to FTO, either to increase or decrease the expression of FTO and the fact that the enzyme expressed by the gene is involved in the level of alternative splicing, metabolism, and physiological processes, such as the control of energy homeostasis and adipogenesis.[2]

FTO encodes the alpha-ketoglutarate-dependent enzyme dioxygenase (2-oxoglutarate),[26] and the alternative splicing site can occur positively or negatively, that is, either activating or inhibiting the mechanism.[27] 2-oxoglutarate (2-OG) is an intermediate of the citric acid cycle (one of the components of aerobic metabolism), formed from isocitrate and subsequently decarboxylated to succinyl-CoA.[3] A possible mechanism by which FTO may be linked to the energy balance is related to the levels of 2-oxoglutarate and, therefore, to citric acid cycle activity.[26]

Carriers who are homozygous for the risk allele A of rs9939609 have higher FTO expression than carriers of the homozygote's non-allele risk A, indicating that obesity results from increased expression of the FTO gene.[22] In contrast, FTO deletion promotes increased sympathetic activity and consequent energy expenditure by the organism or even a reduction in hyperphagia.[28] Naturally, patients with the risk allele A have a greater loss of behavioral food control than non-carriers, and the reduction in FTO activity in other studies has resulted in an increase in thinness.[26] The aerobic activity could be linked to the lower expression of FTO in individuals with the risk allele, reducing hyperphagia or even potentiating the greater caloric expenditure in these individuals by means of greater availability of 2-OG synthesized in the aerobic metabolic pathway, especially in the citric acid cycle.

Common obesity probably has a "polygenic" etiology, with multiple variables, each having a subtle effect; that is, a better understanding of the function and identity of the circuits that depend on FTO is essential,[28] contributing to the selection of other polygenic risk factors allegedly acting synergistically or opposite to FTO in a combined investigation.[3]

Participants who are in stage four of sexual maturation as proposed by Cameron[29] have an approximately 2.1 times greater chance of improving their % BF in relation to those who are in stages two and three. Adolescents in different maturation stages had different growth and motor performance indicators, that is, maturation is an important tool to be used in conjunction with growth and motor performance indicators to provide more appropriate interpretations for adolescents.[30]

Aerobic exercises promoted an important reduction in fat mass and TC in patients with risk allele A, and blood glucose was reduced in both the aerobic exercise and weight training groups. The lipid profile of the group as a whole was improved after 10 weeks of exercise, especially with regard to TC and its LDL fraction. Individuals who are in stage four of sexual maturation, as proposed by Cameron, have twice the chance of reducing the % BF in relation to those who are in stages two and three.

The number of participants in the intervention program, as a larger number participants, could produce other statistical significance and there was a low amount of adherence at the beginning of the program. The establishment of the minimum level of physical activity for participation and the requirement of exclusively practicing physical exercises for research purposes should be implemented in future studies,

especially multicentric studies, to increase the sample size and enhance the provision of more responses to cardiovascular risk factors in the adolescent population.

Aerobic exercises produced exclusively a significant decrease in fat mass and total cholesterol in patients with risk allele A. Distinct physical exercise programs may cause diverse changes in risk variables related to the health of adolescents.

Conflicts of interest

The authors declare no conflicts of interest

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jped.2022.07.004.

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