ADRB2 GLN27GLU POLYMORPHISM ASSOCIATED WITH ADIPOSITY INDICATORS AND IL-10 IN ADOLESCENTS

POLIMORFISMO ADRB2 GLN27GLU ASSOCIADO A INDICADORES DE ADIPOSIDADE E IL-10 EM ADOLESCENTES

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ABSTRACT

Introduction: Studies of association between obesity and genetic factors have demonstrated a significant contribution of polymorphisms related to body fat distribution and subclinical inflammatory process. Objective: To investigate the association between genotypes of the Gln27Glu polymorphism of the *ADRB2* gene and indicators of adiposity, inflammatory markers, metabolic parameters and parameters of physical fitness in overweight adolescents. Methods: A total of 44 male and female adolescents, aged between 13 and 17 years, with positive clinical diagnosis of overweight, were divided into two groups according to the Gln27Glu polymorphism genotypes of the *ADRB2* gene: a) Group of carriers of the 27Glu allele (Gln27Glu/Glu27Glu) (n = 22); b) Group of non-carriers of the 27Glu allele (Gln27Gln) (n = 22). Both groups were evaluated for body composition, sexual maturation, cardiorespiratory fitness variables and indicators of muscle strength. Basal glycemia and insulin, lipid profile and inflammatory profile were measured. Abdominal subcutaneous and visceral adiposities were evaluated by ultrasonography. Genotyping of the Gln27Glu polymorphism of the *ADRB2* gene was performed by the Taqman allelic discrimination assay. Results: The genotype frequency found was: Gln/Gln (n = 22) (50.0%), Gln/Glu (n = 18) (41.0%) and Glu/Glu (n = 4) %). The frequency of the 27Glu allele was 29.5%. The group of adolescent carriers of the 27Glu allele of the *ADRB2* gene presented higher mean adiposity indicators (abdominal circumference, trunk fat mass and visceral fat), as well as lower IL-10 concentrations when compared to non-carriers. Conclusions: The 27Glu allele was associated with adiposity indicators in overweight adolescents, while subcutaneous abdominal fat exhibited an inverse relationship with inflammatory variables and maximum oxygen uptake, which may result in more damage to health. ***Level of evidence III; Case-control study.***

Keywords: Polymorphism, genetic; Obesity, abdominal; Physical fitness; Overweight; Adolescents.

RESUMO

Introdução: Estudos de associação entre a obesidade e fatores genéticos têm demonstrado a significativa contribuição de polimorfismos relacionados à distribuição de gordura corporal e processo inflamatório subclínico. Objetivo: Investigar a associação entre os genótipos do polimorfismo Gln27Glu do gene ADRB2 e indicadores de adiposidade, marcadores inflamatórios, parâmetros metabólicos e de aptidão física em adolescentes com excesso de peso. Métodos: Participaram 44 adolescentes, de ambos os sexos, com idade entre 13 e 17 anos, com diagnóstico clínico positivo de excesso de peso, divididos em dois grupos conforme os genótipos do polimorfismo Gln27Glu do gene ADRB2: a) Grupo de portadores do alelo 27Glu (Gln27Glu/Glu27Glu) (n=22); b) Grupo de não portadores do alelo 27Glu (Gln27Gln) (n=22). Ambos os grupos foram avaliados quanto à composição corporal, maturação sexual, variáveis de aptidão cardiorrespiratória e indicadores de força muscular. Foram dosados glicemia e insulina basais, perfil lipídico e perfil inflamatório. As adiposidades abdominais subcutânea e visceral foram avaliadas através de ultrassonografia. A genotipagem do polimorfismo Gln27Glu do gene ADRB2 foi realizada através do ensaio de discriminação alélica Taqman. Resultados: A frequência genotípica encontrada foi: Gln/Gln (n=22) (50,0%), Gln/Glu (n=18) (41,0%) e Glu/Glu (n=4) (9,0%). A frequência do alelo do 27Glu foi de 29,5%. O grupo de adolescentes portadores do alelo 27Glu do gene ADRB2 apresentou maiores médias de indicadores de adiposidade (circunferência abdominal, massa gorda troncular e gordura visceral), assim como menores concentrações de IL-10 quando comparados aos não portadores. Conclusões: O alelo 27Glu apresentou associação com os indicadores de adiposidade em adolescentes com excesso de peso, assim como a gordura abdominal subcutânea demonstrou relação inversa com as variáveis inflamatórias e o consumo máximo de oxigênio, podendo resultar em maiores prejuízos à saúde. ***Nível de evidência III; Estudo de caso-controle.***

Descritores: *Polimorfismo genético; Obesidade abdominal; Aptidão física; Sobrepeso; Adolescentes.*

RESUMEN

Introducción: Estudios de asociación entre la obesidad y factores genéticos han demostrado la significativa contribución de polimorfismos relacionados a la distribución de grasa corporal y proceso inflamatorio subclínico. Objetivo: Investigar la asociación entre los genotipos del polimorfismo Gln27Glu del gen ADRB2 e indicadores de adiposidad, marcadores inflamatorios, parámetros metabólicos y de aptitud física en adolescentes con exceso de peso. Métodos: Participaron 44 adolescentes, de ambos sexos, con edad entre 13 y 17 años, con diagnóstico clínico positivo de exceso de peso, divididos en dos grupos según los genotipos del polimorfismo Gln27Glu del gen ADRB2: a) Grupo de portadores

del alelo 27Glu (Gln27Glu/Glu27Glu) (n = 22); b) Grupo de no portadores del alelo 27Glu (Gln27Gln) (n = 22). Ambos grupos fueron evaluados cuanto a la composición corporal, madurez sexual, variables de aptitud cardiorrespiratoria e indicadores de fuerza muscular. Fueron dosificadas glucemia e insulina basales, perfil lipídico y perfil inflamatorio. Las adiposidades abdominales subcutánea y visceral fueron evaluadas a través de ultrasonografía. El genotipado del polimorfismo Gln27Glu del gen ADRB2 fue realizado a través del ensayo de discriminación alélica Taqman. Resultados: La frecuencia genotípica encontrada fue: Gln/Gln (n = 22) (50,0%), Gln/Glu (n = 18) (41,0%) y Glu/Glu (n = 4) (9,0%). La frecuencia del alelo del 27Glu fue del 29,5%. El grupo de adolescentes portadores del alelo 27Glu del gen ADRB2 presentó mayores promedios de indicadores de adiposidad (circunferencia abdominal, masa grasa troncular y grasa visceral), así como menores concentraciones de IL-10, en comparación con los no portadores. Conclusiones: El alelo 27Glu presentó asociación con los indicadores de adiposidad en adolescentes con exceso de peso, así como la grasa abdominal subcutánea demostró relación inversa con las variables inflamatorias y el consumo máximo de oxígeno, lo que puede resultar en mayores perjuicios a la salud. ***Nivel de Evidencia III; Estudio de caso-control.***

Descriptores: *Polimorfismo genético; Obesidad abdominal; Aptitud física; Sobrepeso; Adolescentes.*

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INTRODUCTION

Excess weight is defined by the World Health Organization as the abnormal or excessive accumulation of fat and is considered a major public health problem.[1] In addition to increased death risk and reduced quality of life, overweight contributes to the development of chronic non transmissible diseases, aggravated by some negative effects of the globalization process, sedentary life, genetic factors and high calorie diets.[1,2] The increased presence of these conditions associated with genetic factors have an impact on the main adiposity indicators, cardiovascular diseases and various types of cancers.[3]

Genetic factors are causes of obesity epidemic what is highlighted by the identification of numerous candidate genes associated with nutritional status and unfavorable distribution of body fat.[4] In this sense, the beta 2-adrenergic receptor (*ADRB2*), present in human lipolytic cells, is associated with lipid mobilization, regulation of lipolysis and thermogenesis, and consequently plays an important role in the control of body weight.[5] One common single nucleotide polymorphisms, rs104214(C>G), causes the glutamine (Gln) residue to be replaced by glutamic acid (Glu) at position 27 of the mature protein and changes the *ADRB2* receptor function.[6] The 27Glu allele was associated with several cardiometabolic risk factors, such as overweight and body fat distribution in adolescents [7] and adults[8,9], rates of maximum fat oxidation [10], energy expenditure and exercise.[11,12]

Additionally, a recent study pointed to higher concentrations of leptin in 27Glu allele carriers[13], which suggests a possible association between this adipokine and the Gln27Glu *ADRB2* polymorphism. This relationship may play a key role in proinflammatory states enhancement induced by stressed adipocytes presence in response to lipid overload.[14] However, the influence of the Gln27Glu polymorphism on adiposity indicators and inflammatory parameters in overweight adolescents are scarce. Therefore, the objective of this study is to investigate the influence of the Gln27Glu polymorphism of the *ADRB2* gene on adiposity indicators, inflammatory markers, metabolic parameters and physical fitness in overweight adolescents.

METHODS

A cross-sectional study was conducted, characterized by initial anthropometric screening of adolescents from public schools in Southern Brazil. A total of 1,077 students of both sexes and aged between 11 and 17 years participated in the study. In baseline, participated 106 subjects, after the students were invited to participate in a physical activities program. All participants were evaluated by a pediatric physician consisting in complete anamnesis, anthropometric tests and analysis of sexual maturation, as proposed by *Tanner*[15].

Absence of chronic diseases such as DM2, endocrine diseases, infections and/or use of medications that promote changes in adiposity, inflammatory and metabolic parameters were considered inclusion criteria. The exclusion criterion adopted was the classification of eutrophic nutritional status (n = 37), considered the percentile below 85° by the World Health Organization[16]. All parents and volunteers signed a free and informed consent form, according to a research project approved by the Federal University of Parana Ethics Committee (protocol nº. 2460.067/2011-03-UFPR).

The selection resulted in 69 adolescents who were overweight (32 boys e 37 girls), who were submitted to submaximal treadmill test and blood collection. Of these, twelve did not perform the cardiorespiratory evaluation and maximal strength tests (1 RM), six did not attend to the blood collection and for seven blood samples it was not possible to perform genotyping of the Gln27Glu polymorphism, resulting in 44 adolescents with excess weight (21 boys e 23 girls).

Body mass (MC) was obtained on a platform-type scale, Filizola® brand with an accuracy of 0.1 kilograms (kg) and a maximum capacity of 150 kg, and the stature was measured in a stadiometer fixed to the wall, with precision of 0.1cm and amplitude of 220 cm. Abdominal circumference (AC) was measured with the help of flexible and inextensible anthropometric tape (0.1 cm resolution), following recommendations of the *Centers for Disease Control and Prevention*.[17]

Body fat composition evaluation was performed with dual energy X-ray absorptiometry (DEXA), with LunarTM Prodigy device, according to protocol previously described.[18] Fat mass (FM), obtained globally and in the subgroups arm (FM-a), trunk (FM-t) and legs (FM-l), was described in kilograms (kg). To reconstruct the image of total fat mass, the software enCore 2008 version 12.30 was used.

The subcutaneous (SAF) and visceral abdominal fat (VAF) measurement (centimeters) was performed by the GE portable, Logiq Book XP model for high-resolution ultrasonic examination with 8MHz linear transduction, according to a methodology described by *Vlachos et al*.[19] and protocol previously described.[18] Body mass index Z-score (BMI-z), abdominal circumference (AC), FM, FM-a, FM-t, FM-l, SAF and VAF were considered as indicators of adiposity.

The maximal oxygen consumption (VO_{2max}) and the maximum peak oxygen consumption (VO_{2peak}) were measured on the X-Fit 7 Power treadmill using the portable gas analyzer K4b2® (Cosmed, Italy) and a ramp protocol previously described.[12] The test was considered maximum when two of the following criteria were observed: a) exhaustion or inability to maintain required speed; b) R ≥ 1,09; c) maximum heart rate (HR) predicted by the formula 208 - (0.7 x age), proposed by *Tanaka*.[20]

The muscle strength was estimated based on the load obtained in the test of a maximum repetition (1RM), conducted according to the protocol proposed by *Brown & Weir*.[21] Bench Press (BP), Direct thread (DT) and Leg Press (LP), respectively, according to a protocol previously used.[22] The muscular strength estimated by the 1RM test was expressed in absolute terms (absolute load, in kg).

Blood samples were collected in the morning, after 12 hours of fasting and packed in appropriate tubes. Plasma concentrations of total cholesterol, HDL cholesterol and triglycerides were determined in mg/dL by enzymatic colorimetric assay. LDL cholesterol was calculated by the Friedewald equation in mg/dL.[23] Glucose values were determined by the enzymatic method (Glucose Oxidase - Labtest) and insulin measured by the chemiluminescence technique by immunometric immunoassay in uU/L in automated equipment, using as reference 11.9 uU/ml. Insulin resistance was calculated by the HOMA - IR (Homeostasis Model Assessment - Insulin Resistance).

For the determination of serum levels of interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP) and leptin, adiponectin and resistin, the ELISA method was used (solid phase immunoenzymatic assay), according to the specifications of the high sensitivity kits (R&D Systems, Minneapolis, USA).

DNA extraction from the blood samples was performed by the *QIAamp DNA Mini Kit* (QIAGEN). Genotyping of the Gln27Glu polymorphism of the *ADRB2* gene was performed by the *TaqMan* allelic discrimination assay using the 7500 ™ real time PCR system (Applied Biosystems) following the conditions: 1 step of 2 minutes at 50ºC; 2nd step of 10 minutes at 95°C; and 50 cycles of 15 seconds at 95°C interspersed for 1 minute at 62°C.

The distribution of the genotypes among the adolescents who composed the study was: Gln/Gln (n=22) (50%), Gln/Glu (n=18) (41,0%) and Glu/Glu (n=4) (9,0%). The frequency of the 27Glu allele was 29.5%, and genotypes are in *Hardy-Weinberg* equilibrium, that is, the observed values are similar to those expected (p = 0.909). The recessive, dominant and codominant allele interaction models were tested, and considering that the dominant model was more consistent with our results, individuals were grouped into carriers (Glu/Glu + Gln/Glu) and non-carriers (Gln/Gln) of the 27Glu allele.

Normality and homogeneity of variances were verified using the *Shapiro-Wilk* and *Levene* tests, respectively. *Student's* t-test was used for variables with normal distribution (mean and standard deviation) and *U-Mann Whitney* test for variables without the assumption of normality (medians and interquartile ranges). For between groups proportions comparisons, Fisher's exact test was used for the maturational stage and the Chi-square test (x^2) for sex and genotype frequencies (*Hardy-Weinberg* equilibrium). The correlation between the adiposity indicators and the studied variables was estimated by *Pearson's* correlation (parametric data) or by *Spearman's* (non-parametric) correlation. The significance level adopted was p<0.05.

RESULTS

The anthropometric, blood pressure and physical fitness variables of adolescents, carriers and non-carriers of the 27Glu allele of the *ADRB2* gene were similar (Table 1).

Figure 1 presents the comparisons of adiposity indicators mean values between the groups, stratified in carriers and non-carriers of the 27Glu allele. The carrier group presented higher mean values of AC (p = 0.032), FM-t (p = 0.040) and VAF (p = 0.018), when compared to the non-carrier group. The other indicators of adiposity were similar.

Table 2 presents the comparisons of metabolic parameters and inflammatory markers between groups. Carriers of the 27Glu allele exhibited lower values of the anti-inflammatory cytokine interleukin 10 (p = 0.038). The other metabolic and inflammatory variables were similar.

Table 1. Anthropometric variables, body composition and physical fitness according to 27Glu allele presence.

Variables	Gln27Gln (n=22)	Gln27Glu + Glu27Glu (n=22)	*p*
Tanner (4/5)	2/20	3/19	0,500[b]
Gender (M/F)	11/11	10/12	0,317[c]
Age (years)	14.78 ± 0.90	14.87 ± 1.10	0.766
BM (kg)	76.70 ± 15.56	81.78 ± 14.51	0.270
Height (m)	1.65 ± 0.07	1.67 ± 0.09	0.424
BMI (kg/m^2)	27.93 ± 4.35	29.02 ± 3.24	0.349
SBP (mmHg)	104.64 ± 12.73	111.27 ± 9.43	0.056
DBP (mmHg)[a]	63.91(7.52)	67.36 (7.31)	0.121
LM (kg)	44.00 ± 8.19	46.19 ± 9.00	0.404
VO_{2peak} (L/min)	2.57 ± 0.48	2.77 ± 0.86	0.300
VO_{2max} (Kg/ml/min)	33.80 ± 5.09	34.03 ± 8.68	0.334
Leg Press (kg)	177.95 ± 40.02	193.50 ± 56.74	0.300
Supine[a] (kg)	36.19 (8.71)	39.15 (11.20)	0.389
Direct thread (kg)	20.09 ± 4.01	21.77 ± 6.32	0.298

Note: BM = body mass; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; LM = lean mass; VO_{2peak} = peak of maximum oxygen consumption; VO_{2max} = maximum oxygen consumption relative to weight. Statistic: proportions or averages and standard deviation; p relative to comparison of proportions or averages between carriers and non-carriers of 27Glu allele. [a]Non-parametric data; [b]Fisher exact test; [c]Chi-square test.

The correlation values between the adiposity indicators and the study variables in non-carriers of the 27Glu allele are presented in Table 3. SAF indicated direct correlation with leptin and inverse with QUICKI, while VAF correlated inversely with baseline glycemia. FM-t showed direct correlation with SBP and VO_{2peak}, whereas FM-a correlated directly with Leg Press and inversely with VO_{2max}. FM-l was inversely correlated with VO_{2max}, and, directly with leptin and Leg press. AC correlated directly with VO_{2peak} and muscle strength variables, whereas BMI-z showed direct correlation with metabolic variables (SBP, DBP, INS and HOMA-IR), VO_{2peak} and leg press.

Table 4 presents the correlation values for the adolescents bearing the 27Glu allele. The SAF presented a direct correlation with the inflammatory (IL-6 and leptin) and metabolic (INS and HOMA-IR) variables, however an inverse correlation was observed with QUICKI and VO_{2max}. VAF inversely correlated with IL-10. The FM-t variable presented an inverse correlation with adiponectin, whereas FM-a correlated directly with IL-6 and LDL. FM-a directly correlated with CRP, IL-6, INS and HOMA-IR, and, inversely with QUICKI. AC showed an inverse correlation with adiponectin and a direct correlation with IL-6 and VO_{2peak}. BMI-z was directly correlated with IL-6, INS, HOMA-IR and Leg press, and, indirectly with QUICKI and adiponectin.

DISCUSSION

This work investigated the influence of the Gln27Glu polymorphism on the indicators of adiposity, inflammatory markers, metabolic parameters and physical fitness in overweight adolescents. The results indicated that the group carrying the 27Glu allele had higher values of abdominal circumference, trunk fat mass and visceral abdominal fat when compared to adolescents with absence of the allele, as well as lower concentrations of the anti-inflammatory cytokine IL-10. Our results are in line with findings in other studies, in which associations were found between the 27Glu allele, lower rates of maximum fat oxidation in obese adults [10,11] and higher risk of obesity in obese adolescents.[7,8]

Therefore, the β2-adrenergic receptor, which is coded by the *ADRB2* gene, is distributed through various organs and adipose tissue, in addition

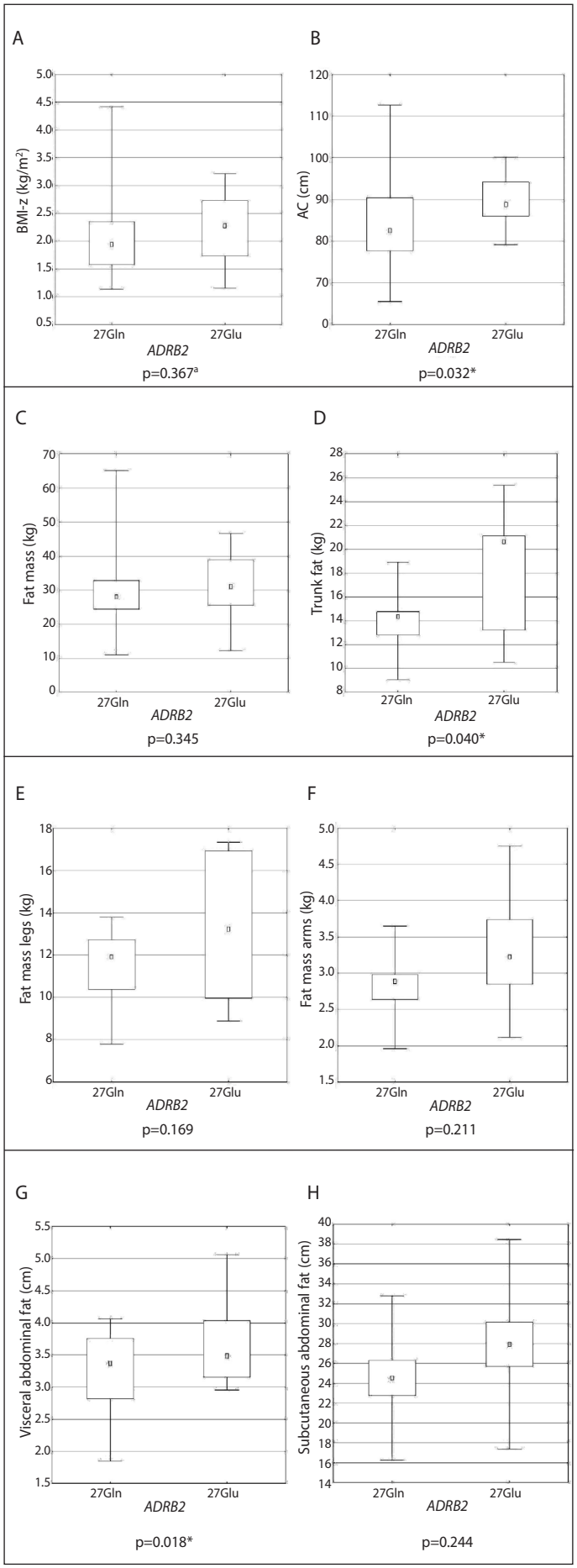

Figure 1. Box plot of adiposity parameters in carriers of Gln27Gln genotype and Gln27Glu and Glu27Glu genotypes. ªNon-parametric data; *p<0.05.

Table 2. Metabolic and inflammatory variables according to 27Glu allele presence.

Variable	Gln27Gln (n=22)	Gln27Glu + Glu27Glu (n=22)	*P*
INS (μU/L)[a]	16.02 (9.16)	15.61 (7.38)	0.963
GLIC (mg/dL)	86.38 ± 8.13	87.64 ± 9.9)	0.649
HOMA-IR	3.36 ± 1.77	3.39 ± 1.66	0.945
QUICKI[a]	0.33 (0.02)	0.33 (0.02)	0.925
CT (mg/dL)	162.85 ± 32.08	153.14 ± 34.68	0.340
HDL-c (mg/dL)	54.75 ± 11.77	52.81 ± 11.36	0.581
LDL-c (mg/dL)	86.87 ± 18.19	78.49 ± 20.97	0.165
TG (mg/dL)[a]	106.21 (51.93)	109.21 (76.99)	0.707
CRP (ng/mL)[a]	2.16 (2.09)	2.02 (1.91)	0.763
IL-6 (pg/mL)[a]	1.62 (0.95)	2.10 (0.82)	0.132
TNF-α (pg/mL)[a]	3.17 (3.82)	3.55 (4.55)	0.771
Resistin (ng/mL)	8.18 ± 2.62	7.55 ± 2.82	0.440
Leptin (pg/mL)[a]	35.15 (23.63)	39.74 (28.62)	0.757
Adiponectin (ng/mL)[a]	7.81 (4.05)	7.59 (3.27)	0.840
IL-10 (pg/mL)	0.52 ± 0.20	0.39 ± 0.20	0.038*

Note: INS = basal insulin; GLIC = basal glycaemia; CT = total cholesterol; HDL-c = high density lipoprotein; LDL-c = low density lipoprotein; TG = triglycerides; CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-α, IL-10 = interleukin-10; Statistic: averages and standard deviation; p relative to comparison of averages between carriers and non-carriers of 27Glu allele. ªNon-parametric data.

Table 3. Correlation coefficients between pairs of inflammatory, metabolic and physical fitness indicators in carriers of Gln27Gln genotype.

	BMI-z[a]	AC	TF	FM-I	FM-a	VAF	SAF
CRP[a]	-0.171	-0.343	-0.076	0.018	0.026	0.095	0.237
IL-6[a]	-0.201	-0.335	-0.105	-0.101	-0.058	0.057	0.009
TNF-α[a]	-0.135	-0.055	-0.281	-0.147	-0.041	0.079	-0.232
Leptin[a]	0.277	-0.139	0.348	0.575**	0.281	0.190	0.595**
Resistin	0.042	0.040	0.217	-0.030	0.128	0.054	0.237
Adiponectin[a]	-0.234	-0.332	-0.037	-0.159	-0.359	-0.340	-0.128
IL-10	-0.009	-0.096	-0.162	0.124	0.077	-0.167	-0.040
SBP	0.515*	0.361	0.642*	0.078	0.364	-0.150	0.153
DBP[a]	0.544**	0.339	0.589	0.124	0.292	-0.054	0.308
INS[a]	0.489*	0.315	0.385	0.148	0.536	0.232	0.290
GLIC	-0.249	-0.134	0.425	0.310	0.324	-0.428*	-0.041
HOMA-IR	0.472*	0.303	0.445	0.153	0.559	0.201	0.330
QUICKI[a]	-0.460*	-0.325	-0.420	-0.234	-0.580	-0.233	-0.444*
TC	0.136	-0.035	0.369	0.338	0.616	0.202	0.261
HDL	-0.030	-0.277	0.497	0.386	0.596	-0.094	0.166
LDL	0.135	0.069	0.362	0.314	0.456	0.363	0.248
TG	0.219	0.086	-0.014	0.094	0.486	0.095	0.183
VO_{2peak}	0.539**	0.711**	0.437*	0.194	0.318	0.354	0.289
VO_{2max}	-0.162	-0.088	-0.413	-0.636**	-0.540**	0.312	-0.308
Leg Press	0.461*	0.650**	0.388	0.469*	0.464*	-0.015	0.233
Supine[a]	0.212	0.549**	0.092	-0.061	0.032	-0.002	-0.199
Direct thread	0.415	0.597**	0.204	0.096	0.139	-0.009	-0.025

Note: BMI-z= body mass index z score; AC= abdominal circumference; TF= trunk fat, in kg; FM-I= fat mass leg, in kg; FM-a= fat mass arm, in kg; VAF= visceral abdominal fat; SAF= subcutaneous abdominal fat; INS= basal insulin; GLIC= basal glycemia; TC= total cholesterol; HDL-c= high density lipoprotein; LDL-c= low density lipoprotein; TG= triglycerides; CRP= C-reactive protein; IL-6= interleukin-6; TNF-α= tumor necrosis factor-α, IL-10= interleukin-10; SBP= systolic blood pressure; DBP= diastolic blood pressure; LM= lean mass; VO_{2peak}= peak of maximum oxygen consumption; VO_{2max}= maximum oxygen consumption relative to weight. Statistic: Pearson or Spearman correlations coefficients. ªNon-parametric data;*p <0.05; **p <0.01.

Table 4. Correlation coefficients between pairs of inflammatory, metabolic and physical fitness indicators in carriers of Gln27Glu and Glu27Glu genotypes.

	BMI-z[a]	AC	TF	FM-I	FM-a	VAF	SAF
CRP[a]	0.397	0.121	0.336	0.277	0.518*	-0.084	0.379
IL-6[a]	0.447*	0.441*	0.403	0.628**	0.482*	-0.254	0.522*
TNF-alfa[a]	0.361	0.201	0.198	0.148	0.030	-0.079	0.074
Leptin[a]	0.356	0.188	0.363	0.421	0.350	-0.369	0.768**
Resistin	0.107	0.080	-0.052	-0.052	-0.068	0.200	0.162
Adiponectin[a]	-0.440*	-0.469*	-0.564**	-0.093	-0.402	0.250	-0.302
IL-10	-0.136	0.070	0.299	-0.091	-0.126	-0.465*	0.238
SBP	-0.243	-0.036	-0.414	-0.279	-0.135	0.299	-0.379
DBP[a]	0.041	0.027	0.092	0.006	0.450	0.419	-0.087
INS[a]	0.443*	0.252	0.424	0.376	0.844**	-0.211	0.504*
GLIC	0.155	-0.120	0.205	-0.104	-0.043	-0.257	0.381
HOMA-IR	0.455*	0.225	0.463	0.370	0.857**	-0.281	0.538**
QUICKI[a]	-0.429*	-0.158	-0.426	-0.249	-0.747*	0.216	-0.497*
CT	0.049	0.075	0.152	0.591	0.635	-0.166	0.398
HDL	-0.073	-0.111	-0.081	0.399	0.489	-0.086	0.393
LDL	0.007	0.127	0.295	0.675*	0.659	-0.118	0.235
TG	0.155	0.078	0.052	0.345	0.445	-0.151	0.286
VO_{2peak}	0.348	0.468*	0.218	0.179	0.109	0.041	-0.259
VO_{2max}	-0.225	-0.049	-0.262	-0.353	-0.406	0.228	-0.594**
Leg Press	0.460*	0.390	0.269	0.238	0.139	-0.071	-0.199
Supine[a]	0.124	0.276	0.085	0.118	-0.149	-0.032	-0.293
Direct thread	0.339	0.376	0.250	0.122	0.032	-0.142	-0.324

Note: BMI-z= body mass index z score; AC= abdominal circumference; TF= trunk fat, in kg; FM-I= fat mass leg, in kg; FM-a= fat mass arm, in kg; VAF= visceral abdominal fat; SAF= subcutaneous abdominal fat; INS= basal insulin; GLIC= basal glycemia; TC= total cholesterol; HDL-c= high density lipoprotein; LDL-c= low density lipoprotein; TG= triglycerides; PCR= C-reactive protein; IL-6= interleukin-6; TNF-α= tumor necrosis factor-α, IL-10= interleukin-10; SBP= systolic blood pressure; DBP= diastolic blood pressure; LM= lean mass; VO_{2peak}= peak of maximum oxygen consumption; VO_{2max}= maximum oxygen consumption relative to weight. Statistic: Pearson or Spearman correlations coefficients. [a]Non-parametric data;*p <0.05; **p <0.01.

to the blood vessels and heart, playing an important role in the regulation of energy homeostasis, lipid mobilization through the activation of lipolysis.[5] Surveys performed with both premenopausal and obese women[9], and in children and adolescents[7], suggested an association of the 27Glu allele with the distribution of body fat, greater percentage of fat mass, higher values of hip circumference and increased risk for obesity. Our results corroborate these findings, in which 27Glu allele carriers presented higher values of body adiposity, reinforcing the hypothesis of the interaction of this polymorphism and the negative stimulus of lipolytic activity in adipose tissue.[24]

It is also known that the associations between visceral and subcutaneous fat with cardiometabolic risk factors and insulin resistance are well established in the adult population[25] and in adolescents[26]. Our results indicate that among the homozygotes for the 27Gln allele, the subcutaneous abdominal fat presented an inverse correlation with the glycemia, whereas among the carriers of the 27Glu allele, a direct correlation with the metabolic variables was observed for this adiposity indicator (INS, HOMA-IR), despite an inverse correlation with QUICKI. These correlations suggested that subcutaneous abdominal fat may be closely related to the Gln27Glu polymorphism, which may reinforce the hypothesis of the influence of body fat distribution on the risk of metabolic syndrome[8]. In addition, excess fat promotes changes in adipose tissue such as hypertrophy and dysfunctions in the secretory profile of adipocytes, acting directly on the inflammatory response.[27]

The relationship between excess weight and inflammatory profile is evidenced in adolescents [28] and adults[27], however the role of the Gln27Glu polymorphism is not well understood. Our results showed that IL-10 concentrations were higher among adolescents, non-carriers of the 27Glu allele. In addition, 27Glu allele carriers showed a direct correlation between subcutaneous abdominal fat and the inflammatory variables CRP, IL-6 and leptin, thus suggesting that the circulating level of cytokines and proteins released by adipocytes that are associated with inflammation may have direct relationship with the Gln27Glu polymorphism of the *ADRB2* gene.

Some studies have associated a higher frequency of the 27Glu allele with metabolic alterations[5,6,8], but it was not observed in our findings. Studies conducted with overweight adults and adolescents indicated higher total cholesterol values for 27Glu allele carriers and suggested a contribution of the 27Glu allele to the development of obesity and asthma.[9,29] The interaction between Gln27Glu polymorphism, physical activity and body adiposity has been suggested. In both sedentary[6,11] and active groups[5], as well as in the rates of fat oxidation in adults.[10,11] Thus, the group of adolescents with the 27Glu allele had an inverse correlation between subcutaneous abdominal fat and VO_{2max}.

It is known that the frequency of the 27Glu allele varies among ethnicities, for example it is found in 8.51% in the Taiwanese population[30] and 45% among euro-american.[8] In the present study, we observed 29.5%, similar to the one described previously for the Brazilian population (32%).[5]

The present study has some limitations, such as the reduced sample size (n = 44) made it impossible to perform individualized analysis by gender and the generalization of the results obtained should be used with caution. However, the method used for the analysis of body fat composition (DXA) is considered *gold standard* and all adolescents were classified in stage 4 or 5 of Tanner, final stages of sexual maturation that suffer less influence in the study variables.

The group of adolescents' carriers of the 27Glu allele had higher values of adiposity indicators (abdominal circumference, trunk fat mass, and visceral abdominal fat) and lower concentrations of IL-10, when compared to non-carriers. In conclusion, the Gln27Glu polymorphism possibly influences abdominal adipose tissue and may be related to the inflammatory processes underlying obesity.

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REFERÊNCIAS

1. World Health Organization. Fact sheet: obesity and overweight [Internet]. 2016 [acesso em 2018 sep 20). Disponível em: http://www.who.int/mediacentre/factsheets /fs311/en/
2. Garver WS, Newman SB, Gonzales-Pacheco DM, Castillo JJ, Jelinek D, Heidenreich RA, et al. The genetics of childhood obesity and interaction with dietary macronutrients. Genes Nutr. 2013;8(3):271-87.
3. Mahmood T, Arulkumaran S. Worldwide Epidemic of Obesity. Obesity: A Ticking Time Bomb for Reproductive Health. Elsevier: London. 2012.
4. Coletta A, Kreider RB. Genetic profiling for weight loss: Potential Candidate Genes. Bioenergetics. 2015;4(2):1-14.
5. Mattevi SV, Zembrzuski VM, Hutz R. Impact of variation in *ADRB2*, ADRB3, and GNB3 genes on body mass index and waist circumference in a Brazilian population. Am J Hum Biol. 2006;18(2):182-86.
6. Zhang H, Wu J, Yu L. Association of Gln27Glu and Arg16Gly polymorphisms in Beta2-adrenergic receptor gene with obesity susceptibility: a meta-analysis. PloS One. 2014;9(6):e100489.
7. Ochoa MC, Moreno-Aliaga MJ, Martinez-Gonzalez MA, Martinez JA, Marti A, GENOI Members. TV watching modifies obesity risk linked to the 27Glu polymorphism of the *ADRB2* gene in girls. Int J Pediatr Obes. 2006;1:83-8.
8. Podolsky RH, Barbeau P, Kang HS, Zhu H, Treiber FA, Snieder H. Candidate genes and growth curves for adiposity in African- and European American youth. Int J Obes. 2007;31:1491-9.
9. Rauhio A, Uusi-Rasi K, Nikkari ST, Kannus P, Sievänen H, Kunnas T. Association of the FTO and *ADRB2* genes with body composition and fat distribution in obese women. Maturitas. 2013;76(2):165-71.
10. Macho-Azcarate T, Marti A, González A, Martinez JA, Ibañez J. Gln27Glu polymorphism in the beta2 adrenergic receptor gene and lipid metabolism during exercise in obese women. Int J Obes Relat Metab Disord. 2002;26(11):1434-41.
11. Rosado EL, Bressan J, Martínez JA. Environmental factors and beta2-adrenergic receptor polymorphism: influence on the energy expenditure and nutritional status of obese women. Lipids. 2015;50(5):459-67.
12. Leite N, Silva LR, Jesus IC, Lopes WA, Cavaglieri CR, Consentino CL, et al. *ADRB2* Gln27Glu polymorphism influenced changes in leptin but not body composition or metabolic and other inflammatory parameters after twelve weeks of combined training in overweight adolescents. Motriz: Rev Educ Fis. 2017;23(2):1-13.
13. Cipolletta E, Carillo A, Annunziata R, Trimarco B, Franco A, Iaccarino G. The impact of β2 adrenergic receptor polymorphisms on the outcomes in cardiovascular diseases. Cardiogetics. 2014;4(1):10-21.
14. Rodrigues KF, Pietrani NT, Bosco AA, Campos FMF, Sandrim VC, Gomes KB. IL-6, TNF-α, and IL-10 levels / polymorphisms and their association with type 2 diabetes mellitus and obesity in Brazilian individuals. Arch Endocrinol Metab. 2017;61(5):438-46.
15. Tanner JM. Normal growth and techniques of growth assessment. Clin Endocrinol Metab. 1986;15(3):411-45.
16. World Health Organization (WHO). Growth reference data for 5-19 years. Geneva: WHO, 2007.
17. National Health and Nutrition Examination Survey. Anthropometry Procedures Manual, 2002. Available online at: http://www.cdc.gov/nchs/data/nhanes/bm.pdf.
18. Coutinho PR, Leite N, Lopes WA, da Silva LR, Consentino CM, Araújo CT, et al. Association between adiposity indicators, metabolic parameters and inflammatory markers in a sample of female adolescents. Arch Endocrinol Metabol. 2015;59(4):325-34.
19. 19. Vlachos IS, Hatziioannou A, Perelas A, Perrea DN. Sonographic assessment of regional adiposity. American Journal of Roentgenol. 2007;189(6):1545-53.
20. Tanaka H, Monahan KD, Seals DR. Age - predicted maximal heart rate revisited. J Am Coll Cardiol. 2001;37(1):153-6.
21. Brown LE, Weir JP. Asep procedures recommendation I: Accurate assessment of muscular strength and power. J Exerc Physiol Online. 2001;4(3):1-21.
22. Moraes Jr FB, Lopes WA, Silva LR, Araújo CT, Jesus IC, Coutinho PR, et al. Localized fat-free mass does not influence muscle strength in obese and non-obese boys. Rev Bras Med Esporte. 2018;24(5):361-5.
23. Friedewald ET, Levy RI, Fredrickson DS. Estimation of the concentration of Low-Density Lipoprotein cholesterolin plasma without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502.
24. Enoksson S, Talbot M, Rife F, Tamborlane WV, Sherwin RS, Caprio S. Impaired in vivo stimulation of lipolysis in adipose tissue by selective β2-adrenergic agonist in obese adolescent girls. Diabetes. 2000;49(12):2149-53.
25. Kranendonk ME, Van Herwaarden JA, Stupkova T, de Jager W, Vink A, Moll F, et al. Inflammatory characteristics of distinct abdominal adipose tissue depots relate differently to metabolic risk factors for cardiovascular disease: Distinct fat depots and vascular risk factors. Atherosclerosis. 2015;239(2):419-27.
26. Oliveira RP, Remor JM, Matsuo AR, Dada RP, Mendes AA, et al. Visceral adiposity index as a predictor of cardiometabolic risk in children and adolescentes. Rev Bras Med Esporte. 2017;23(3):222-6.
27. Gealekman O, Guseva N, Hartigan C, Apotheker S, Gorgoglione M, Gurav K, et al. Depot-specific differences and insufficient subcutaneous adipose tissue angiogenesis in human obesity. Circulation. 2011;123(2):186-94.
28. Mahassni SH, Sebaa RB. Obesity and CRP, Adiponectin, Leptin, and Lipid Profile in Saudi Arabian Adolescent Females. J Basic Appl Sci. 2013;9:500-9.
29. Leite N, Lazarotto L, Milano GE, Titski AC, Consentino CL, Mattos F, et al. Beta 2-adrenergic receptor gene association with overweight and asthma in children and adolescents and its relationship with physical fitness. Rev Paul Pediatr. 2015;33(4):381-6.
30. Chou YC, Tsai CN, Lee YS, Pei JS. Association of adrenergic receptor gene polymorphisms with adolescent obesity in Taiwan. Pediatr Int. 2012;54(1):111-6.