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HEALTH SCIENCES

Relationship between the hsa miR 150-5p and FTO gene expression in white subcutaneous adipose tissue with overweight/obesity, lipid profile and glycemia

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Abstract: The overweight population is growing in the world, and the search for obesity-associated mechanisms is important for a better understanding of this disease. Few studies with the FTO gene and miRs show how they associate to obesity and how they can impact this disease. The aim of this study was to verify the relationship between the FTO gene and the hsa-miR-150-5p expression with overweight/obesity, lipid profile, and fast blood glucose. Men and women (18 years older or above), with body mass index ≥ 18.5 kg/m^2, were enrolled in the present study and the FTO gene and hsa-miR-150-5p expression, biochemical parameters of blood and anthropometric measurements were analyzed. The results highlight that the FTO gene expression is associated to obesity (p 0.029), LDL-C (p 0.02) and fasting blood glucose (p 0.02), but not with triglycerides (p 0.69), total cholesterol (p 0.21), and HDL-C (p 0.24). The hsa-miR-150-5p is not associated to obesity (p 0.84), triglycerides (p 0.57), total cholesterol (p 0.51), HDL-C (p 0.75), LDL-C (p 0.32), and fasting blood glucose (p 0.42). The FTO gene expression is related to obesity, LDL-C and blood fasting glucose, representing a good molecular marker for obesity.

Key words: Obesity, miR 150, FTO, adipose tissue, eutrophic.

INTRODUCTION

According to the World Health Organization. (2016), there are more than 1.9 billion adults and more than 340 million children and adolescents with overweight or obesity. In a simple manner, obesity results from the unbalance between energetic intake and energetic spend (Cui & Chen 2017). However, other factors are behind this disease, such as genetics, cultural, and psychologic issues (Upadhyay et al. 2018).

The FTO gene (fat mass and obesity-associated gene) is placed on chromosome 16 (16q12.2) and was first described in a mouse model with fused toes and thymus hyperplasia. It was demonstrated to be highly expressed during embryonic development and was associated with programmed cell death, craniofacial development, and left-right asymmetry (Peters et al. 1999). However, in humans, the trisomy of the 16 chromosome (the region in which the FTO gene is located) was associated with mental retardation, obesity, dysmorphic facies, and several bilateral clinodactyly of some fingers (Stratakis et al. 2000). After the first studies, some more appeared and reported association with humans obesity. It is highly expressed in the brain, but the gene expression in other tissues

and which obesity trait it is related remains unclear (Locke et al. 2015, Gulati et al. 2013).

MiRs are small, endogenous RNAs of approximately 22 nucleotides that act avoiding mRNA translation, mediated by the complementarity of the miR (from nucleotide 2 to 8) with the 3' untranslated region (UTR) of the mRNA target (Treiber et al. 2019). MiRs are conserved in many different species, which suggest that they have an important function in the organism physiology, participating in crucial cellular process and diseases (Liz & Esteller 2016, Mens & Ghanbari 2018, Kinser & Pincus 2019). Among the miRs, the miR-150-5p is known as a circulating miRNA, being involved in inflammatory processes, lipoprotein profile, and vascular system (Ying et al. 2016, Desgagné et al. 2017, Desjarlais et al. 2017). However, the expression of miRs can be tissue-specific. Thus, it is necessary to know how they are associated with metabolic processes and diseases in a tissue-specific manner, to permit their use as diagnostic biomarkers or therapeutic targets in complex diseases in which they have not been used.

Thus, to the best of our knowledge, miRs and the *FTO* gene expression with BMI, lipid profile and glycemia in white adipose tissue from obese individuals have not been well investigated and the few studies in literature present controversial results. Hence, the purpose of the present study was to compare the hsa-miR-150-5p and FTO gene expression between eutrophic and overweight/obesity individuals to investigate the relationship between the hsa-miR-150-5p and FTO gene expression with obesity, lipid profile and glycemia; and verify a possible relationship between the hsa-miR-150-5p and FTO gene expression.

MATERIALS AND METHODS

Study sample

Men and women, above the age of 18 years (42.14 ± 12.29 years) with overweight (25 ≤ BMI ≤ 29.9 kg/m^2) or obesity (BMI ≥ 30 kg/m^2) (n=15) were enrolled in this study. Eutrophic individuals (18.5 ≤ BMI ≤ 24.9 kg/m^2), control group (men and women n=5), were also invited (26.4 ± 2.07 years). Prior to the study beginning, all the procedures were explained and if the participants had any inquiries, they enlightened - all the participants assigned a consent form. The present study was approved by the ethical committee from the School of Physical Education and Sport of Ribeirão Preto (CAAE 37573114.6.0000.5659) and by the Hospital das Clinicas of the Faculty of Medicine of Ribeirão Preto, University of São Paulo (CAAE 37573114.6.3001.5440).

Clinical analyses

The participants were submitted to the following analyses: body mass and height with a balance for the weight (precision of 50g) coupled to a stadiometer (precision of 1mm) (Welmy W200ALCD), waist circumference (umbilicus level) and body fat (bioimpedance - Maltron BF-906). Prior to the analyses, they were informed not to consume alcohol 24h earlier or caffeine 4h before, not exercise, and to consume 2 or 4 glasses of water 2 hours before until the test performance (De Lima Augustemak et al. 2008). Fast blood glucose, triglycerides, total cholesterol, high-density cholesterol (HDL-C), low-density cholesterol (LDL-C) were evaluated from venous blood after 12h fasting (Silva et al. 2007). In addition, the International Physical Activity Questionnaire (IPAQ) and the Food Consumption Markers Questionnaire were utilized to measure the level of physical activity in the last week and the ingestion frequency of 10 groups of foods in the last seven days,

respectively. If the food consumption marker presents a positive result, means that the group ingests health food instead of unhealthy food and if this questionnaire presents negative result, means the opposite (Silva et al. 2007, Damé et al. 2011).

Biopsy

White subcutaneous adipose tissue was collected with a supraumbilical incision of 2 cm under local anesthesia, by an experienced doctor. Approximately 0.5 g of tissue was collected, immediately stored in liquid nitrogen and taken to the laboratory for posterior analysis. The participants were oriented to not perform physical activities, to have breakfast until 8 a.m., and fasting until this minor surgery time (midday) at the collect day.

Analysis of human FTO mRNA expression

Total RNA was extracted from subcutaneous adipose tissue using TRIzol (cat. n: 15596018, Applied Biosystems, Foster City, CA, USA), and 500 ng RNA was reverse transcribed with the high-capacity cDNA reverse transcription kit (cat.n: 4368814, Applied Biosystems, Foster City, CA, USA). The *FTO* mRNA expression experiment was performed by real time PCR with Power SYBR Green PCR Master Mix (Cat. No: 4367659, Applied Biosystems, Foster City, CA, USA). The emitted fluorescence by the SYBR green at each cycle was measured and the *FTO* mRNA expression was calculated by relative expression to the RPL39 mRNA. The utilized primers were: *FTO* – 5'-CTGGCCAGTGAAAGGGTCTAAT-3' (sense) and 5'-GGCAGCAAGTTCTTCCAAAGC-3' (antisense); RPL39 - 5'- CTCTTCCTTTCTCCGCCATC-3' (sense) and 5'- TCCAGTTTTCATCCGAATCCAC-3' (antisense) (Klöting et al. 2008, Baraldi et al. 2016).

Selection of the microRNA of interest

To select a microRNA to investigate we imputed in the *mirDB* (http://mirdb.org/) the access number of the *FTO* gene from NCBI (ID: 79068) and a list of 78 miRs were generated as output. We considered a score of 80 as a cutting limit and from 17 miRs that attended the criterion score, we selected the hsa-miR-150-5p with a score of 85. To confirm the selection of this miR for posterior analysis we confirmed a hypothetical interaction of this miR with the 3' UTR of the *FTO* mRNA using the *RNAhybrid* (http://bibiserv.techfak.uni-bielefeld.de/rnahybrid) and we observed a hybridization free energy (ΔG) of -28.9 Kcal/mol (Rehmsmeier et al. 2004, Wong & Wang 2014). The hsa-miR-150-5p was select to further study due to their low free energy, as low as better, and to their vestige of relationship with energy metabolism, metabolic associated diseases and lipid metabolism, below mentioned in the discussion.

Analysis of the hsa-miR-150-5p expression

The total RNA was reverse transcribed using the TaqMan MicroRNA Reverse transcription kit (Cat.n: 4366596, Applied Biosystems, Foster City, CA, USA) with specific RT stem loop primers (Cat.n: 4427975, Applied Biosystems, Foster City, CA, USA). The hsa-miR-150-5p expression was performed by real time PCR using the TaqMan MicroRNA Assay (Cat.No: 4427975 – [miR-150-5p #000473; miR-103 #000439], Applied Biosystems, Foster City, CA, USA). The emitted fluorescence was measured and the hsa-miR-150-5p expression was calculated by relative expression to the miR-103.

Statistical analysis

Sample size calculation was calculated considering the FTO gene expression change from 1.0 to 2.0 (arbitrary unit; main variable in the study), a standard deviation of 0.6 (data

from a pilot study), with a power of 80%, and α of 0.05 - the obtained sample size was at least five individuals per group. To reach the proposed objectives we utilized the following statistical tests: The Pearson's correlation coefficient; multiple regression analysis; Student's *t*-test, and linear regression analysis. The utilized software were SAS (version 9.2) and Prism (version 5.0), and the statistical significance value considered was $p \leq 0.05$.

RESULTS

To characterize the differences between the groups, we compared the anthropometrical measures, physical activity level and the food consumption markers between them (Table I). The overweight/obesity group presented higher values compared to the eutrophic group for body mass index (BMI) (34.24 ± 1.46 kg/m^2 vs 21.36 ± 1.05 kg/m^2), higher percentage of body fat (48.44 ± 1.98% vs 28.82 ± 1.43), higher waist circumference (98.58 ± 2.42 cm vs 71.00 ± 3.69 cm) and lower level of high intensity physical activity (0.7 ± 2.67 min/week vs 24.00 ± 53.67 min/week). However, the groups are comparable for walking level, moderate physical activity, and in the food consumption markers.

Aiming to respond how were the *FTO* gene expression and the hsa-miR-150-5p expression profile in eutrophic and obesity individuals, we measured the *FTO* gene expression (Figure 1) and the hsa-miR-150-5p expression (Figure 2) in both groups. We could not observe a difference in *FTO* gene expression between the eutrophic and overweight/obese individuals. When we

Table I. Participants characterization.

	Eutrophic	Overweight/obesity
BMI (kg/m^2)	21.36 ± 1.05 (5)	34.24 ± 1.46* (14)
Body fat (%)	28.82 ± 1.43 (5)	48.44 ± 1.98* (14)
Waist circumference (cm)	71.00 ± 3.69 (5)	98.58 ± 2.42* (12)
Walking (min/week)	80.00 ± 40.00 (5)	39.64 ± 72.97 (14)
Moderate PA (min/week)	42.00 ± 58.48 (5)	36.64 ± 64.34 (14)
Intense PA (min/week)	24.00 ± 53.67 (5)	0.7 ± 2.67* (14)
Food Consumption markers	7.40 ± 9.91 (5)	15.36 ± 6.50 (14)

Data are presented as mean ± standard deviation and number of participants in parenthesis; PA, Physical activity; BMI, Body mass index; *$p \leq 0.05$.

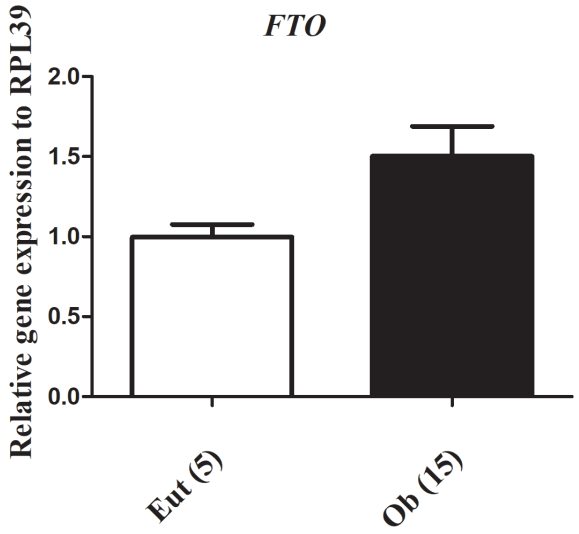

Figure 1. FTO (normalized to RPL39) gene expression profile in eutrophic and overweight/obesity individuals. The graphic is presented as mean ± standard deviation; *p* 0.14. Eut, eutrophic; Ob, overweight/obesity.

performed the comparison between the groups with the hsa-miR-150-5p expression, we did not observe any difference either.

To respond if the *FTO* gene expression and the hsa-miR-150-5p expression were related to obesity, lipid profile, and glycemia, we first performed a Pearson's correlation. We could demonstrate that the *FTO* gene expression was correlated to BMI (r = 0.50, *p* 0.029) and LDL-C (r = -0.54, *p* 0.038) (Table II), but for the hsa-miR-150-5p we did not find any correlation with obesity, lipid profile and glycemia (Table III).

Based on the results obtained in the correlation analysis, we performed a multiple regression analysis with the aim of demonstrating which variables were related to *FTO* gene expression and the hsa-miR-150-5p. We could observe a relationship of the FTO gene expression with LDL-C (β = -0.047 ± 0.016, *p* 0.02) and fasting glucose (β = 0.114 ± 0.04, *p* 0.02) (Table IV). When we performed the same analysis with the miR-150-5p, we could not observe the relationship among the tested variables (Table V).

Lastly, aiming to respond if the FTO was related to the miR-150-5p expression, we performed a linear regression between *FTO* gene expression and hsa-miR-150-5p (Figure 3) - no relationship was found.

DISCUSSION

The present study demonstrated that *FTO* gene expression is related to BMI, LDL-C and fasting glucose, while the hsa-miR-150-5p expression is not related to obesity-related variables. In addition, there were no differences in the *FTO* and hsa-miR-150-5p expression in eutrophic and overweight/obese individuals. No relationship was found between *FTO* and the hsa-miR-150-5p expression.

We demonstrated the relationship of the *FTO* gene expression with BMI, LDL-C and fasting glucose. With a similar propose, Samaras et al. (2010) demonstrated that this gene expression, in white subcutaneous adipose tissue, is related to

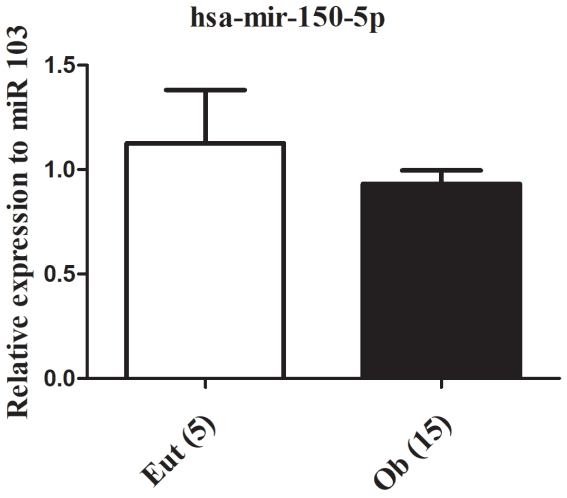

Figure 2. hsa-mir-150-5p (normalized to miR 103) expression profile in eutrophic and overweight/obesity individuals. The graphic is presented as mean ± standard deviation. *p* 0.01. Eut, eutrophic; Ob, overweight/obesity.

fasting glucose and waist circumference. On the other hand, Klöting et al. (2008) and Zabena et al. (2009) demonstrated an inverse relationship between the *FTO* gene expression and BMI and body fat and triglycerides, respectively.

When we compared the FTO gene expression in eutrophic and overweight/obese individuals, we did not found differences between the groups. Zabena et al. (2009) demonstrated a significantly higher expression to this gene in morbidly obese individuals compared to eutrophic individuals, while Samaras et al. (2010) did not show differences in this gene expression studying obese patients. Being the individuals from the last mentioned study most similar to ours, we demonstrated similar results, which suggest that the *FTO* gene expression is proportional to body fat, reinforcing their relationship to obesity.

There is finite information about the FTO metabolic view, however, some mechanisms are proposed. Gulati et al. (2013) proposed that the FTO would act as an amino acid sensor. In embryonic fibroblast cells from *FTO* Knockout mice, they demonstrated reduced mTORC1 (mechanistic target of rapamycin complex 1) activation, a related protein to amino acid availability, suggesting that under low amino acid availability the FTO gene would be negative regulated, making the cell less sensitive to amino acids, which result in mTORC1 metabolic pathway impaired, increasing autophagy. Wu et al. (2010) proposed that FTO would act epigenetically as a transcriptional coactivator, recruiting DNA demethylase, regulating gene expression, while Lin et al. (2014) prosed an increase in CREB (cAMP response element binding) phosphorylation FTO overexpression dependent, positively regulating NPY (neuropeptide Y) and BDNF (Brain-derived neurotrophic factor), which would regulate the food intake.

Concerning the hsa-miR-150-5p expression, we did not observe relationship to any obesity-related variable studied and no differences in the expression level between eutrophic and overweight/obesity individuals. MicroRNAs can regulate several genes, and they can be involved in several cellular processes in a tissue or moment specific way.

Dahlmans et al. (2017), studying mitochondrial metabolism in skeletal muscle, demonstrated that the hsa-miR-150-5p positively regulates the mitochondrial metabolism - once the mitochondrial function is impaired, it is related to diabetes type II and insulin resistance. In addition, the authors compared the expression level of this miRNA in individuals with different levels of physical capacity and demonstrated a higher expression level in athletes when compared to overweight and obese patients. Ying et al. (2016), in a study with knockout mice for the miR-150, demonstrated that this miRNA was involved in the regulation of genes that would act on β-cells receptors modulating macrophages and T cells activation and affecting the adipocyte, with consequent alteration in inflammation, glycemic and insulin profile. On the other hand, Chou et al. (2014) demonstrated that the decrease in the miR-150 processing machinery increased the expression of genes involved in the remodeling of white adipose tissue to brown adipose tissue, suggesting that this microRNA is involved in lipid metabolism.

Finally, an important limitation of our study should be mentioned - the number of participants.

CONCLUSION

The results obtained in our study can corroborate and sum with the finite studies that seek to

Table II. Pearson's correlation between FTO gene expression and obesity, glycemia, and lipid profile.

	***FTO* gene expression**
BMI (kg/m^2)	0.50 0.029* 19
Body fat (%)	0.45 0.051 19
Waist circumference (cm)	0.48 0.053 17
Fasting glucose (mg/dL)	0.11 0.70 15
Triglycerides (mg/dL)	-0.11 0.69 15
Total cholesterol (mg/dL)	-0.34 0.21 15
HDL-C (mg/dL)	0.32 0.24 15
LDL-C (mg/dL)	-0.54 0.038* 15

Data are presented as Pearson's correlation coefficient, *p*-value and number of participants; HDL-C, High-density cholesterol; LDL-C, Low-density cholesterol; * $p \leq 0.05$.

Table III. Pearson's correlation between hsa-mir-150-5p expression and obesity, glycemia, and lipid profile.

	hsa-mir-150 expression
BMI (kg/m^2)	-0.05 0.84 18
Body fat (%)	-0.29 0.24 18
Waist circumference (cm)	0.08 0.78 16
Fasting glucose (mg/dL)	0.23 0.42 14
Triglycerides (mg/dL)	-0.17 0.57 14
Total cholesterol (mg/dL)	0.19 0.51 14
HDL-C (mg/dL)	0.09 0.75 14
LDL-C (mg/dL)	0.29 0.32 14

Data are presented as Pearson's correlation coefficient, *p* value and number of participants; HDL-C, High-density cholesterol; LDL-C, Low-density cholesterol.

Table IV. Multiple regression analysis between *FTO* gene expression and BMI, LDL-C, and fasting glucose.

Variable	Estimative	*p*	Confidence interval	
BMI (kg/m^2)	0.141 ± 0.066	0.07	-0.012	0.294
LDL-C (mg/dL)	-0.047 ± 0.016*	0.02	-0.084	-0.010
Fasting glucose (mg/dL)	0.114 ± 0.04*	0.02	0.021	0.207

Adjusted by the level of physical activity and food ingest quality; Data are presented as estimative ± standard deviation, *p*-value and confidence interval; **p* ≤ 0.05.

Table V. Multiple regression analysis between hsa-mir-150-5p expression and BMI, LDL-C and fasting glucose.

Variable	Estimative	*p*	Confidence interval	
BMI (Kg/m2)	0.017 ± 0.013	0.24	-.0145	0.048
LDL-C (mg/dL)	0.003 ± 0.003	0.45	-.005	0.011
Fasting glucose (mg/dL)	0.004 ± 0.008	0.60	-.014	0.023

Adjusted by the level of physical activity and food ingest quality; Data are presented as estimative ± standard deviation, *p*-value and confidence interval.

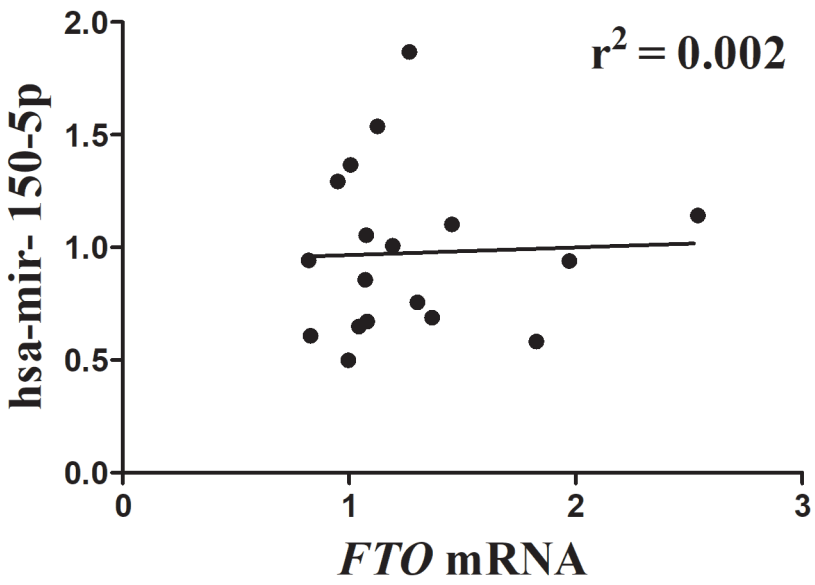

Figure 3. Relationship between FTO gene expression and hsa-mir-150-5p.

find genetic markers related to obesity. Thus, we conclude that the FTO gene expression is moderately related to BMI, LDL, and blood fasting glucose, and we suggest it as a molecular marker for obesity. However, more studies regarding genes and miRs association with obesity seem necessary, since it is a complex disease and results from a vast number of factors.

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Author contribution

ALQ and CRBJ designed the investigation and guided the experiments. VNM performed the experiments, interpreted the data and wrote the manuscript. JALR performed the experiments. DM and WSJ performed the biopsy surgery. MMG performed the statistical analysis. All the authors read and approved the final manuscript.