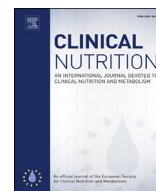




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Original article

Influence of expression of *UCP3*, *PLIN1* and *PPARG2* on the oxidation of substrates after hypocaloric dietary intervention

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SUMMARY

Background & aims: In addition to environmental and psychosocial factors, it is known that genetic factors can also influence the regulation of energy metabolism, body composition and determination of excess weight. The objective of this study was to evaluate the influence of *UCP3*, *PLIN1* and *PPARG2* genes on the substrates oxidation in women with grade III obesity after hypocaloric dietary intervention.

Subjects/methods: This is a longitudinal study with 21 women, divided into two groups: Intervention Group (G1): 11 obese women (Body Mass Index (BMI) ≥ 40 kg/m²), and Control Group (G2): 10 eutrophic women (BMI between 18.5 kg/m² and 24.9 kg/m²). Weight (kg), height (m), BMI (kg/m²), substrate oxidation (by Indirect Calorimetry) and abdominal subcutaneous adipose tissue were collected before and after the intervention. For the dietary intervention, the patients were hospitalized for 6 weeks receiving 1200 kcal/day.

Results: There was a significant weight loss (8.4 ± 4.3 kg – $5.2 \pm 1.8\%$) and reduction of *UCP3* expression after hypocaloric dietary intervention. There was a positive correlation between carbohydrate oxidation and *UCP3* ($r = 0.609$; $p = 0.04$), *PLIN1* ($r = 0.882$; $p = 0.00$) and *PPARG2* ($r = 0.791$; $p = 0.00$) expression before dietary intervention and with *UCP3* ($r = 0.682$; $p = 0.02$) and *PLIN1* ($r = 0.745$; $p = 0.00$) genes after 6 weeks of intervention. There was a negative correlation between lipid oxidation and *PLIN1* ($r = -0.755$; $p = 0.00$) and *PPARG2* ($r = 0.664$; $p = 0.02$) expression before dietary intervention and negative correlation with *PLIN1* ($r = 0.730$; $p = 0.02$) expression after 6 weeks of hypocaloric diet.

Conclusion: Hypocaloric diet reduces *UCP3* expression in individuals with obesity and the *UCP3*, *PLIN1* and *PPARG2* expression correlate positively with carbohydrate oxidation and negatively with lipid oxidation.

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1. Introduction

Several studies have pointed obesity as a significant risk factor for increased morbidity and mortality, mainly because it is associated with several comorbidities, such as cardiovascular diseases, type 2 diabetes mellitus (DM2), hypertension, cancer, and others [17,27].

The adequacy of dietary intake is still one of the most adopted strategies in the obesity treatment [15]. The determination of food intake, macronutrient oxidation and energy expenditure is important to promote a negative energy balance for the weight loss process in obese individuals [33].

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It is also known that genetic factors can also influence the regulation of energy metabolism, body composition and determination of excess weight [13,25]. Among the genes evolved in these pathways, we would like to highlight the peroxisome proliferator-activated receptors (PPARs), perilipins 1 (*PLIN1*), and decoupling protein 3 (*UCP3*).

The PPARs are transcription factors belonging to family of nuclear receptors and may control the expression of genes involved in the differentiation of adipocytes and glucose and lipid homeostasis, being considered one of the genes most related to the development of obesity [22,24,29,35].

The *PLIN1* gene is responsible for producing perilipins, which are very phosphorylated proteins located on the surface of adipocytes, playing a key role in the regulation of triglycerides mobilization and deposition, protecting the lipid nucleus from the action of lipases, promoting the fat droplets formation [10,19,30,32].

The *UCP3* gene plays an important role as a mediator in adaptive thermogenesis, in the regulation of mitochondrial fatty acid oxidation and in the prevention of oxidative damage produced by free radicals [7,9]. It is also known that this gene is involved in the regulation of energy metabolism and control of body weight. Moreover, some studies showed that *UCP3* may modulate the use of lipids and glucose as an energy substrate after weight loss, suggesting possible actions in insulin resistance and DM2 [4,8,11,37].

In this context, the knowledge of influence of genes associated with energy metabolism on weight loss induced by dietary intervention may represent potential clinical utility to predict response to this treatment. Thus, the objective of this study was to evaluate the influence of *UCP3*, *PLIN1* and *PPARG2* expression on the substrates oxidation in women with grade III obesity after hypocaloric dietary intervention.

2. Patients and methods

2.1. Patients

A total of 21 women from mixed population [26], aged between 21 and 50 years were included in the study. The participants were divided into 2 groups: Dietary Intervention Group (GI) composed of 11 women with grade III obesity (body mass index – BMI ≥ 40 kg/m²) and Control Group (GC) composed of 10 eutrophic women (BMI between 18.5 kg/m² and 24.9 kg/m²).

The participants of the GI were selected from the Obesity Outpatient of university hospital and submitted to hypocaloric dietary intervention. For this, they were hospitalized for a period of 6 weeks in this hospital, and the diet protocol of the service was followed, in which a diet containing 1800 kcal was offered on the first day, 1500 kcal on the second day and 1200 kcal from the third day until the sixth week of hospitalization [8]. GC volunteers were selected from a list of patients who underwent a surgical procedure for umbilical hernia (incisional or epigastric) or cholelithiasis without acute cholecystitis.

In both groups, patients with psychiatric disorders, pregnant and lactating women, smokers, drinkers, patients with disease and/or performing some treatment influencing energy metabolism and those who gave up on dietary intervention were excluded from the study.

This study was approved by the Ethics Committee of the hospital (process number 19442213.3.0000.5440) and conducted according to the Helsinki Declaration. All participants provided a written informed consent.

2.2. Phenotypic characteristics

The GI patients were evaluated in two moments: before and after 6 weeks of the dietary intervention. The GC was evaluated in a

single moment. Anthropometric (weight, height, BMI) and substrates oxidation data were collected at each moment.

The QUARK-RMR apparatus (COSMED, Rome, Italy) was used to obtain oxygen consumption (O₂), carbon dioxide (CO₂) production and substrate oxidation. For this, the participants were previously instructed not to exercise, not to drink coffee or black tea 24 h before the exam, and to remain fasting for 6–8 h. The participants remained awake and lying supine throughout the evaluation. Oxygen consumption (VO₂) and carbon dioxide production (VCO₂) were measured during 30 min, with the first 10 min being discarded until the individual reached steady state [39]. The equation of Frayn [14] was used to estimate the glucose and lipid oxidation in the patients evaluated (see Table 1).

2.3. Genetic data

Analysis of *UCP3*, *PLIN1* and *PPARG2* expression was performed on subcutaneous adipose tissue. In the two GI evaluations, the adipose tissue was collected by biopsy procedure. This procedure consisted of a small cut at the level of the umbilical scar in the upper right quadrant under local anesthesia and was performed by a specialized physician. In GC, the material was collected at the beginning of the surgical procedure of umbilical hernia (incisional or epigastric) or cholelithiasis without acute cholecystitis.

RNA was extracted from the subcutaneous adipose tissue samples by the phenol-chloroform extraction method [6] from 1.0 ml of Trizol (Invitrogen, Carlsbad, CA, USA). The complementary DNA (cDNA) was synthesized using the High-Capacity cDNA Reverse Transcription (Life Technologies) kit following the manufacturer's instructions. The analysis was performed in triplicate by qPCR using the 7500 Fast Real PCR System (Applied Biosystems).

Relative quantification of *UCP3*, *PLIN1* and *PPARG2* gene expression was calculated using the logarithmic base 2 $\Delta\Delta$ Ct. *GAPDH* and β -actin were used as reference genes and the MIQE guideline was followed [5].

2.4. Statistical analysis

A descriptive statistic consisted of mean and standard deviation (SD) was performed. *t*-test for paired samples was performed to compare the moments before and after dietary intervention. To verify associations between the quantitative variables of the study, the Spearman correlation was used. Multiple linear regression was performed to verify the contribution of gene expression in the substrates oxidation, adjusting for the caloric, carbohydrate and lipid content of the diet. Statistical significance (*p*-value) was set at values lower than 5% (*p* < 0.05). All analyzes being performed in Statistical Package software for Social Science (SPSS version 17.0 [Inc. Chicago, IL]).

3. Results

Table 2 shows the anthropometric variables and substrates oxidation of the participants before and after 6 weeks of dietary intervention and of the eutrophic women. There was a significant reduction in weight (8.4 ± 4.3 kg, equivalent to $5.2 \pm 1.8\%$ of initial weight). Regarding the substrates oxidation, VO₂ reduction was

Table 1
Equations by Frayn [14] for estimation of glucose and lipid oxidation.

Glucose oxidation (g/min):	$4.55V_{CO_2} - 3.21V_{O_2} - 2.6N_2$
Lipid oxidation (g/min):	$1.67V_{O_2} - 1.67V_{CO_2} - 1.92N_2$

VO₂ = volume of oxygen; VCO₂ = volume of carbon dioxide; N₂ = nitrogen in the urine.

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