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The high glycemic index diet was an independent predictor to explain changes in agouti-related protein in obese adolescents

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Abstract

The high glycemic index diet was an independent predictor to explain changes in agouti-related protein in obese adolescents.

Background & Aims: **The role of diet glycemic index (GI) in the control of orexigenic and anorexigenic factors of the energy balance is still not clear. The present study aimed to assess whether the habitual diet, according to different GI foods, exerts influence on regulation of energy balance markers and the effects of interdisciplinary intervention in obese adolescents.**

Methods: **A total of 55 obese adolescents, aged from 14 to 19 years, were submited to one year of interdisciplinary therapy and were divided in two groups, according to the predominant dietary pattern of food intake: high-GI group (H-GI; n = 29) and moderate/low-GI group (M/L-GI; n = 26).**

Results: **The concentration of orexigenic factor AgRP (p < 0.01), visceral fat (p=0.04) and visceral/subcutaneous ratio (p = 0.03) were higher in the group of H-GI when compared with M/L-GI group. Moreover, the habitual consumption of H-GI foods was an independent predictor to explain changes in AgRP concentrations. After one year of interdisciplinary therapy, the adolescents presented significant reductions in body weight, total body fat (%), visceral and subcutaneous fat and HOMA-IR, as well as a significant increase of fat free mass (%).**

Conclusions: **Our results may suggest that habitual H-GI diet could upregulate orexigenic pathways, contributing to vicious cycle between undesirable diets, deregulates energy balance and predispose to obesity. One the other hand, one year of interdisciplinary therapy can significant improves metabolic profile and central obesity in adolescents.**

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Key words: *Obesity. Energy balance. Neuropeptides. Food consumption. Glycemic index.*

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LA DIETA DE ALTO ÍNDICE GLUCÉMICO ES UN PREDICTOR INDEPENDIENTE PARA EXPLICAR LOS CAMBIOS EN LA PROTEÍNA RELACIONADA AL AGOUTI EN ADOLESCENTES OBESOS

Resumen

La Dieta de alto índice glucémico es un predictor independiente para explicar los cambios en la proteína relacionada al agouti en adolescentes obesos.

Introducción y objetivos: **El papel de la dieta de índice glucémico (GI) en el control de los factores orexigénicos y anorexígenos del balance de energía todavía no está claro. El presente estudio tuvo como objetivo evaluar si la dieta habitual, de acuerdo con diferentes alimentos con IG, ejerce influencia sobre la regulación de los marcadores del balance de energía y los efectos de la intervención interdisciplinaria en adolescentes obesos.**

Métodos: **Un total de 55 adolescentes obesos, con edades de 14 a 19 años, han sido sometidos a un año de tratamiento interdisciplinario y se dividieron en dos grupos, de acuerdo al patrón de dieta predominante de la ingesta de alimentos: el grupo IG alto (H-GI; n = 29) y GI moderada/bajo grupo (M/L-GI, n = 26).**

Resultados: **La concentración de orexigenic factor de AgRP (p < 0,01), la grasa visceral (p = 0,04) y la relación visceral/subcutánea (p = 0,03) fueron mayores en el grupo de H-GI en comparación con el grupo M/L-GI. Por otra parte, el consumo habitual de alimentos H-GI fue un predictor independiente para explicar los cambios en las concentraciones de AgRP. Después de un año de tratamiento interdisciplinario, los adolescentes presentan una reducción significativa en el peso corporal, la grasa corporal total (%), visceral y la grasa subcutánea y el HOMA-IR, así como un aumento significativo de la masa libre de grasa (%).**

Conclusiones: **Nuestros resultados pueden sugerir que la dieta H-GI habitual podría upregulate vías orexigénicos, contribuyendo al círculo vicioso entre las dietas indeseables, desregula el equilibrio energético y predisponen a la obesidad. Uno por otro lado, un año de tratamiento interdisciplinario puede perfil metabólico mejora significativa y la obesidad central en los adolescentes.**

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Palabras clave: *Obesidad. Balance energético. Neuropéptidos. Consumo de alimentos. Índice glucémico.*

Introduction

Dietary patterns in Brazil are constituted by the excessive consumption of saturate fat, sugar, food industrialized and soft drinks. There has also been insufficient consumption of healthier foods, particularly dairy products, vegetables, and fruits may be related to the increasing prevalence of obesity and its co-morbidities in children and adolescents[1-4].

Some studies in healthy children and men showed that the source and type of carbohydrate, as well as how the food is processed and consumed can affect the fat mass and body weight and seems to trigger a sequence of hormonal events that promote hunger and overeating[5,6]. The human body is involved in a complex physiological system that maintains relatively constant body weight and fat stores. This regulatory system endowed of central nervous system is crucial to multiple interactions between the gastrointestinal tract and adipose tissue. The hormone leptin has a key role in control of energy intake and expenditure, integrating multiple neural and peripheral signals, stimulating anorexigenic neurons that express pro-opiomelanocortin (POMC), precursor of melanocyte stimulating hormone (α-MSH) and cocaine- and amphetamine- regulated transcript (CART). Moreover, leptin exerts effects on the hypothalamus inhibiting orexigenic neurons that express neuropeptide Y (NPY) and Agouti-related peptide (AgRP) to decrease food intake and increase energy expenditure[7,8].

By definition, the glycemic index (GI) is measure as the incremental area under the blood glucose response curve of a 50 g carbohydrate portion of a test food expressed as a percent of the response to the same amount of carbohydrate from a standard food. GI provides a measurement of the quality, but not of the quantity of the consumed carbohydrate[9]. Previous research in animal has shown that the weight gain was greater and faster in high carbohydrates diet, specifically with high glycemic index (H-GI) carbohydrates, than in other groups. This fact suggest an initial pronounced hyperphagia and subsequent passive overconsumption, stimulating the activity of appetite-stimulatory neuron by neuropeptide Y (NPY) and agouti-related peptide (AgRP) mRNA expression in the hypothalamus[10,11]. Indeed, recent study, in healthy humans, suggest that the consumption of a low-glycemic diet may help to appetite control, decreasing orexigenic and increasing anorexigenic factors, favoring the obesity control[12]. Although these results were demonstrated only in the acute conditions in healthy adults.

Moreover, the regulation of body weight and energy balance is a homeostatic mechanism in which several coordinated systems are implicated, but in obesity it appears deregulates and impairs weight loss. As suggested by some authors the consumption of two daily low GI meals is enough to promote effects on the regulation of energy homeostasis because of its pattern of expression and physiological effects[4]. However, little is known about the role of different glycemic index foods in the control of orexigenic and anorexigenic factors of energy balance, mostly considering obese adolescents.

Therefore, the aims of the present study were a) to evaluate whether the habitual diet, according to the predominant dietary pattern of different GI foods exerts influence in the regulation of energy balance markers b) to assess the effects of interdisciplinary intervention in obese adolescents after one year.

Materials and methods

Subjects

The subjects comprised 55 obese adolescents, aged from 14 to 19 years (mean age 16.77 ± 1.96 years). Calculations of nutritional status according to BMI-for-age values were performed using WHO Anthro Plus 1.0.4 software. The nutritional diagnosis was based on the BMI-for-age (BAZ) for the children aged > 5 years and adolescents ≤ 19 years of age (Z score ≥ +2SD), according to cut-off points recognised by World Health Organization[13]. The inclusion criteria for the post-pubertal stage were based on the Tanner scale (stage five) for both boys and girls. Non-inclusion criteria were as follows: other metabolic or endocrine diseases, chronic alcohol consumption, previous use of drugs such as anabolic-androgenic steroids or psychotropics, which may affect appetite regulation and pregnancy. This study was conducted in conformed to the World Medical Association Declaration of Helsinki and approval was given by the ethics committee of the Federal University of São Paulo and registered in the Clinical trial.gov (NCT 01388773). All participants signed a term of free and informed consent.

Anthropometric measurements and body composition

The BMI was calculated as the ratio of the weight (kg) to the height squared (m^2). The weight and height were first determined using techniques recommended by WHO [13]. Body weight was determined with a Filizola® balance (Indústrias Filizola S/A, São Paulo, SP, Brazil), with a maximum capacity of 200 kg and a calibration of 0.01 kg. Height was measured to the nearest 0.5 cm with a wall-mounted stadiometer (Sanny, model ES 2030). Fat mass (% and kg) and fat free mass (% and kg) were measured by air displacement plethysmography in a BODPOD body composition system (version 1.69; Life Measurement Instruments, Concord, CA).

Visceral and subcutaneous adiposity measurements

All abdominal ultrasonographic (US) procedures and measurements of visceral and subcutaneous fat

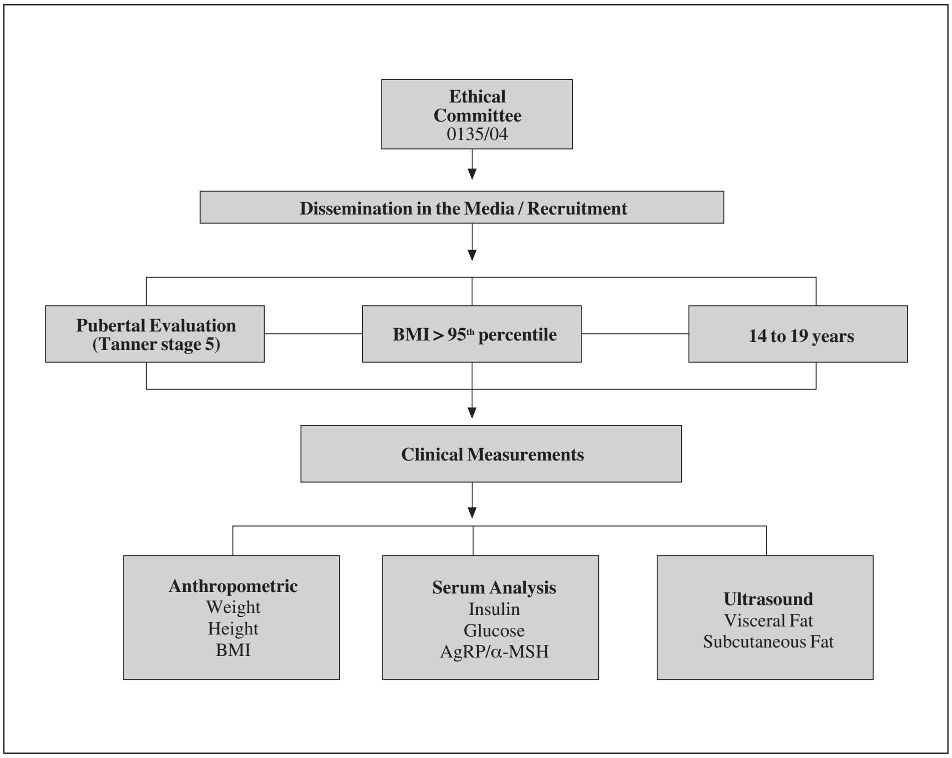

Fig. 1.—Description of the methodology adopted to develop the study.

tissue were performed by physician. US measurements of intra-abdominal (visceral) and subcutaneous fat were obtained. US-determined subcutaneous fat was defined as the distance between the skin and external face of the rectus abdominis muscle, and visceral fat was defined as the distance between the internal face of the same muscle and the anterior wall of the aorta. Cut-off points to define visceral obesity by ultrasonographic parameters were based on previous methodological descriptions by Ribeiro-Filho[14].

Assessment of food consumption

The dietary consumption data were acquired by the administration of a validated semi quantitative food-frequency questionnaire[15]. An interview was performed by trained dietitians. For each food item, a unit or portion size was specified (e.g., a slice of bread or a glass of soft drink), and each participant was asked how frequently, during the last six months, was consumed that food item and in what quantity.

Food intake was categorized by the frequency of consumption fixed as frequently in this study-minimum consumption of food item ≥ 4 days per week. The classification of the groups was based according to the predominant dietary pattern of food intake as shown in table I.

Glycemic index (GI) of each food item was assigned using a previously published method. Foods with a H-GI are those with values ≥ 70 (refined sugar, soft drinks and white bread), while those with a M/L-GI present values of 56 to 69 (beans), and those of a low-GI values ≤ 55 (fruits, leafy vegetables, beef, chicken and fish, milk)[16]. Area under the curve (AUC) is calculated and GI is determined by the following equation:

Table I
Food items and quantity considered to classification of dietary pattern of adolescents obese

Dietary pattern	*Food items*	*Quantity*
High Glycemic Index group (H-GI)	Sugar Soft drink White bread	≥ 3 of H-GI food items
	Fruits Vegetables Beef, chicken and fish Milk	≤ 1 of M/L- GI food item
Moderate/low Glycemic Index group (M/L-GI)	Fruits Vegetables Beef, chicken and fish Milk	≥ 3 of M/L- GI food items
	Sugar Soft drink White bread	≤ 1 of H-GI food item

*Sugar includes sugar added in the processing or preparation of foods and beverages.

$$GI = \frac{\text{Increase in the area under the curve of the tested food} \times 100}{\text{Increase in the area under the curve if the reference food item}}$$

After categorizing by the frequency of consumption according glycemic index, the subjects were divided into two groups: H-GI (n = 29) and M/L-GI (n=26). The participants were matched by BMI.

Biochemical analysis

After an 8-hour fast, blood was collected from the intermediate vein of the forearm by trained individuals. The glucose, α-MSH, AgRP concentrations were measured using a commercially available enzymelinked immunosorbent assay (ELISA) kit from Phoenix Pharmaceuticals, Inc. (Belmont, CA, USA) according to the manufacturer's instructions. Insulin resistance was assessed by the homeostasis model assessment-insulin resistance index (HOMA-IR) and calculated as the product of blood glucose (fasting blood glucose) and immunoreactive insulin (I): (fasting blood glucose (mg/dl) × I (mU/l)/405).

Dietary intervention

Energy intake was set at the levels recommended by the dietary reference intake for subjects with low levels of physical activity of the same age and gender following a balanced diet[17]. No drugs or antioxidants were recommended. Once a week, adolescents had dietetics lessons (providing information on the food pyramid, diet record assessment, weight-loss diets, food labels, dietetics, fat-free and low-calorie foods, fats (kinds, sources and substitutes), fast-food calories and nutritional composition, good nutritional choices on special occasions, healthy sandwiches, shakes and products to promote weight loss, functional foods and decisions on food choices). All patients received individual consultation during the intervention program.

Physical program

The aerobic training plus resistance training (AT+RT) regimen was performed three times per week for one year. This training included 30 minutes of AT plus 30 minutes of RT per session. The volunteers were oriented to invert the order of the exercises at each training session: in one session, the adolescent started the training session with aerobic exercises, and in the subsequent session, the same adolescent started with the RT. The AT mode consisted of running on a motor-driven treadmill at the cardiac frequency intensity of the ventilatory threshold I, which was determined by the results of an initial oxygen uptake test for aerobic exercises (cycle-ergometer and treadmill). The detection threshold ventilatory threshold -1 corresponds to the identification indirectly, the exercise intensity at which blood lactate suffers rise in the value of rest, during progressive exercise test through evaluation by spirometry test. This index has been used to detect the maximum intensity of work safe for some individuals with comorbid cardiac or is sedentary. That intensity safe stress is predicted by the identification of heart rate corresponding to ventilatory threshold-1. The test for the identification of the ventilatory threshold-1 is done through a progressive exercise protocolwhich can be done either on a treadmill and a stationary bicycle. The evaluation is conducted by an expert evaluator for testing.

The physiologists controlled the cardiac frequency, which was measured with a cardiometer at intervals of 5 minutes during all training sessions. The physical program was based on the American College of Sports Medicine (ACSM) recommendations[18]. We used physical exercises for the main muscle groups (bench press, leg press, sit-ups, lat pull-down, hamstring curls, lower back, military press, calf raises, arm curls, and triceps pushdown), and the order of the exercises was strictly followed by the group[19].

Statistical Analysis

Parametric data are presented as mean ± standard deviation (SD) and non-parametric data as median ± standard error of mean (SEM). The association between the variables studied was determined by Chi-squared test, followed to Fischer exact test when appropriated. To evaluate the homogeneity of variables was performed Shapiro Wilk test. Comparisons between the measures at baseline and after therapy were made using Mann-Whitney test (non-parametric variables). We used multiple stepwise linear regression model to identify the variables that made an important contribution to influence AgRP concentrations. In the model, the homocedasticity was checked using *Durbin-Watson* test, considering appropriate values between 0.8-1.6 (D -W = 1.52). The statistical program Statistical Package for the Social Sciences *SPSS* for Windows, version 16.0 (SPSS Inc., 2006, Chicago, IL, USA) was used to analyze the data. Minimal significance value was $p \leq 0.05$.

Results

Comparison between the groups according to different glycemic indexes at baseline

Energy intake, anthropometric measurements and body composition

The mean of energy intake was significantly major in the H-GI group compared to values found for M/L-GI group (2034.43 ± 562.77 kcal *vs* 1626.56 ± 419.68 kcal; $p = 0.04$). Participants of H-GI group presented higher visceral (5.22 ± 1.87 cm *vs* 4.19 ± 1.17 cm; $p = 0.04$) and visceral/subcutaneous ratio (1.29 ± 0.54 *vs* 1.00 ±

0.41; $p = 0.03$) compared with M/L-GI group. Body weight (107.41 ± 12.91 kg *vs* 107.76 ± 13.39 kg; $p = 0.48$), body mass index (BMI) (37.22 ± 4.62 kg/m² *vs* 38.12 ± 5.13 kg/m²; $p = 0.63$), BAZ-score (2.83 ± 0.93 *vs* 3.39 ± 0.70; $p = 0.07$), fat body mass (47.61 ± 6.53% *vs* 46.45 ± 4.70%; $p = 0.28$), subcutaneous fat (4.20 ± 0.81 cm *vs* 4.46 ± 1.11 cm; $p = 0.55$) and lean body mass (52.38 ± 6.53% *vs* 53.54 ± 4.70%; $p = 0.28$) were not significantly different between the groups (Table II).

Biochemical analysis

It was showed higher serum concentration of orexigenic factor AgRP in patients of H-GI group compared with subjects of M/L-GI group (0.49 ± 0.09 ng/mL *vs* 0.21 ± 0.05 ng/mL; $p < 0.01$), while the anorexigenic factor (α-MSH) did not present significant difference between the groups (0.76 ± 0.11 ng/mL *vs* 0.91 ± 0.13 ng/mL; $p = 0.93$) (Table II).

Moreover, multiple stepwise linear regression analyses were performed with the changes in AgRP as dependent variable. This analyse revealed that intake of higher glycemic index was an independent predictor to explain changes in AgRP concentrations (β coefficient = 0.388; $P < 0.01$) (Table III).

Analyzing the food intake data, it was observed improvements in dietary pattern considering that 86.2% of adolescents moved from the H-GI group at the baseline to M/L-GI group at the end of therapy. Therefore, due to a reduced number of adolescents that remained in the H-GI group at the end of therapy was not possible to compare statistically the variables.

Table III
Multiple linear regression analysis for the determinants of changes on AgRP concentrations

Variables	*β coefficient*	*P*
Age (years)	-0.120	0.43
Body mass (kg)	0.034	0.79
Groups in conformity to glycemic index	0.388	**<0.01**
Age (years) -0.073	0.58	
Visceral fat (cm)	0.130	0.35
Groups in conformity to glycemic index	0.317	**0.02**
Age (years)	-0.123	0.34
BMI (kg/m²)	0.147	0.25
Groups in conformity to glycemic index	0.402	**<0.01**
Age (years)	-0.105	0.48
BAZ (Z score)	0.265	0.10
Groups in conformity to glycemic index	0.373	**0.03**
Age (years)	-0.074	0.57
Visceral / Subcutaneous fat (cm)	0.134	0.33
Groups in conformity to glycemic index	0.318	**0.02**

Effects of therapy for the entire study population

Energy intake, anthropometric measurements and body composition

The energy intake in baseline time was around 1806.02 ± 514.21 kcal decreased significantly to 1286.24 ± 359.66 kcal ($p < 0.01$), at the end of therapy.

Table II
Energy intake, body composition, biochemical and anthropometric parameters of obese adolescents, according to dietary pattern of consumption of foods in conformity to the glycemic index

	Dietary pattern High Glycemic Index group	*Dietary pattern Moderate and Low Glycemic Index group*	
Variables	*Baseline (n = 29)*	*Baseline (n = 26)*	*p*
Energy intake (kcal)	2034.43 ± 562.77	1626.56 ± 419.68	**0.04**
Body weight (kg)	107.41 ± 12.91	107.76 ± 13.39	0.48
BMI (kg/m²)	37.22 ± 4.62	38.12 ± 5.13	0.63
BAZ (Z score)	2.83 ± 0.93	3.39 ± 0.70	0.07
Body fat (%)	47.61 ± 6.53	46.45 ± 4.70	0.28
Fat free mass (%)	52.38 ± 6.53	53.54 ± 4.70	0.28
Subcutaneos fat (cm)	4.20 ± 0.81	4.46 ± 1.11	0.55
Visceral fat (cm)	5.22 ± 1.87	4.19 ± 1.17	**0.04**
Visc/Subc ratio	1.29 ± 0.54	1.00 ± 0.41	**0.03**
Glucose (mg/dL)	91.45 ± 7.77	92.07 ± 8.06	0.52
HOMA-IR	4.01 ± 0.48	3.74 ± 0.50	0.86
Alpha-MSH (ng/mL)	0.76 ± 0.11	0.91 ± 0.13	0.93
AgRP (ng/mL)	0.49 ± 0.09	0.21 ± 0.05	**< 0.01**

BMI = body mass index; BAZ=BMI-for-age; HOMA-IR= homeostasis model assessment insulin resistance index; Visc/Subc ratio = Visceral fat/Subcutaneos fat ratio; AgRP (ng/mL) = agouti related-peptide (ng/mL). Reference value: glucose 60-110 mg/dL, HOMA-IR (<2.0). Mann-Whitney test. Comparison between high glycemic index group *vs* moderate and low glycemic group in baseline, $p \leq 0.05$

After one year of interdisciplinary intervention were observed significant reduction of total body weight from 108.26 ± 19.02 kg to 100.62 ± 19.80 kg ($p = 0.03$), body mass index (BMI) from 37.81 ± 5.25 kg/m^2 to 34.43 ± 6.07 kg/m^2 ($p < 0.01$), BAZ-score from 3.32 ± 0.78 to 2.64 ± 0.83 ($p = 0.01$), fat body mass decreased from 46.65 ± 5.43% to 40.35 ± 5.58% ($p < 0.01$), a decrease in visceral (5.18 ± 1.67 cm *vs* 3.31 ± 1.57 cm; $p < 0.01$) and subcutaneous fat (4.41 ± 0.97 cm *vs* 3.23 ± 1.11 cm; $p < 0.01$) and increase of lean body mass from 53.34 ± 5.93% to 59.65 ± 5.58% ($p < 0.01$) (Table IV).

Biochemical analysis

After weight loss intervention, the serum concentration of AgRP (0.53 ± 0.21 ng/mL *vs* 0.38 ± 0.06 ng/mL; p=0.25) and -MSH (0.66 ± 0.06 ng/mL *vs* 0.58 ± 0.12 ng/mL; p=0.63) were not significantly different when compared with baseline values. After one year, we observed significant improvement in HOMA-IR, reducing from 3.88 ± 0.34 to 2.01 ± 0.31 (p<0.01) (Table IV).

Frequency of food consumption according to glycemic index

At baseline conditions, the assessment of food intake with a H-GI revealed that 52.7% of the adolescents consumed soft drink and 78.2% consumed white bread frequently. After the therapy, the frequency of these foods consumption decreased significantly to 7.3% and 56.4%, respectively. Considering the intake of foods with M/L-GI, it was also observed a significantly association between the frequency analysed before and after 1 year of interdisciplinary intervention. The consumption of fruits and vegetables increased from 43.6% to 85.5% and from 38.1% to 83.6% respectively, at the end of therapy (Figs. 2 and 3).

Discussion

We investigated the impact of habitual diet with different glycemic indexes on neuropeptides in the neuroendocrine regulation of energy balance, including total and visceral body fat. Therefore, one of the most important findings in the present investigation was that H-GI diet could upregulate of orexigenic pathways in obese adolescents, leading a positive energy balance promoting obesity.

In fact, recent studies, in animal experiments and adolescents, have consistently shown that the obesity is caused by a deregulation of orexigenic and anorexigenic factors that can influence energy homeostasis[3,5,19]. AgRP is one of the strongest peptides that were reported to induce sustained hyperphagia and possibly make weight loss difficult in obesity[20-22]. Alterations in AGRP expression have been observed in chronic conditions of positive energy balance sustained hyperphagia and leads to obesity[23]. In our study, the frequently consumption of refined sugar, soft drink and white bread were included in the habitual H-GI diet as it contains a H-GI carbohydrates. Thus, we observed a higher serum concentration of orexigenic factor AgRP in patients that reported in long-term frequently intake of H-GI foods, but not in the M/L-GI group.

Studies have reported that H-GI carbohydrates diet can significantly activate the peripheral sympathetic

Table IV
Energy intake, body composition, biochemical and anthropometric parameters before and after interdisciplinary therapy for obese adolescents

Time	*Baseline (n = 55)*	*After therapy (n = 55)*	
Variables	*Mean ± SD*	*Mean ± SD*	*P*
Energy intake (kcal)	1806.02 ± 514.21	1286.24 ± 359.66	**<0.01**
Body weight (Kg)	108.26 ± 19.02	100.62 ± 19.80	**0.03**
BMI (Kg/m^2)	37.81±5.25	34.43±6.07	**<0.01**
BAZ (Z score)	3.32 ± 0.78	2.64 ± 0.83	**0.01**
Body fat (%)	46.65 ± 5.43	40.35 ± 5.58	**<0.01**
Fat free mass (%)	53.34 ± 5.93	59.65 ± 5.58	**<0.01**
Subcutaneos fat (cm)	4.41 ± 0.97	3.23 ± 1.11	**<0.01**
Visceral fat (cm)	5.18 ± 1.67	3.31 ± 1.57	**<0.01**
Visc/Subc ratio	1.22 ± 0.45	1.04 ± 0.46	0.06
Glucose (mg/dL)	90.87 ± 7.43	91.80 ± 5.99	0.31
HOMA-IR	3.88 ± 0.34	2.01 ± 0.31	**<0.01**
Alpha-MSH (ng/mL)	0.66 ± 0.06	0.58 ± 0.12	0.63
AgRP (ng/mL)	0.53 ± 0.21	0.38 ± 0.06	0.25

BMI = body mass index; BAZ = BMI-for-age; HOMA-IR= homeostasis model assessment insulin resistance index; Visc/Subc ratio = Visceral fat/Subcutaneos fat ratio; AgRP (ng/mL) = agouti related-peptide (ng/mL). Reference value: glucose 60-110 mg/dL, HOMA-IR (<2.0). Mann-Whitney test. p = difference between baseline and after therapy, $p \leq 0.05$.

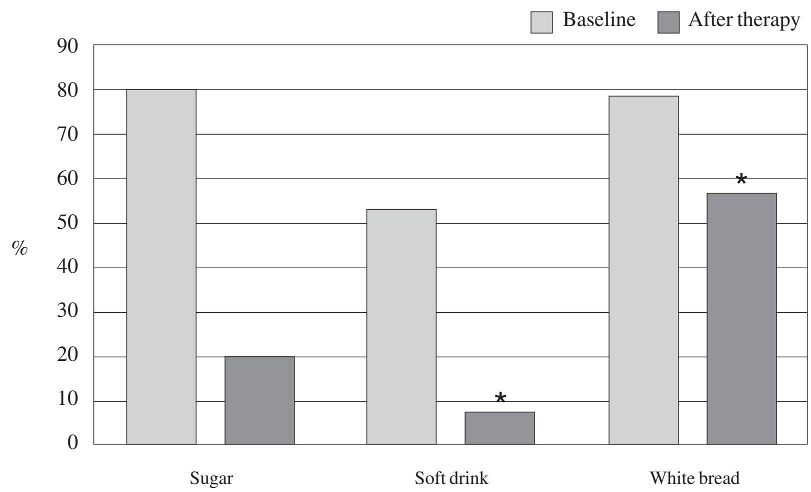

Fig. 2.—Foods of high glycemic index frequently consumed (≥ 4 days/week) by obese adolescents submitted to long-term interdisciplinary therapy. Difference between baseline and after therapy, $p \leq 0.05$.

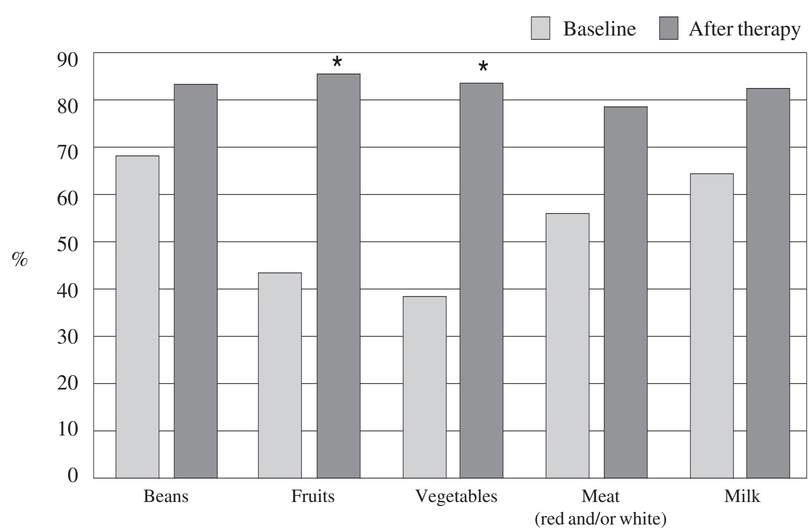

Fig. 3.—Foods of moderate and low glycemic index frequently consumed (≥ 4 days/week) by obese adolescents submitted to long-term interdisciplinary therapy. Difference between baseline and after therapy, $p \leq 0.05$.

nervous system (SNS), however, diets with a M/L-GI, may not be associated with a significant sympathoexcitory effect[24]. Another study, showed acute activation of the SNS after a H-GI diet accompanied to a significant release of the serum NPY in healthy individuals[12]. In nonalcoholic fatty liver disease obese adolescents it was demonstrated positive correlation between carbohydrate intake and NPY[25]. Although in this study the authors did not analyze the orexigenic effects of H-GI diet on obese adolescents.

Recent studies in experimental model have shown the diets effects on hypothalamic inflammation in the regulation of energy homeostasis[26]. This is supported by the fact that when mice fed linolenic (C18:3, ω3) and oleic (C18:1, ω9) unsaturated fatty acids diet there was significantly reduced hypothalamic expression of a number of inflammatory markers, enhanced the anorexigenic act of leptin and these effects were accompanied by reductions in the mRNA expressions of orexigenic neuropeptide NPY and increase of POMC and CART[27]. The major contribution these findings were improvement of leptin signal transduction while decreased expression of NPY in the hypothalamus, these pathways seems to constitute the molecular basis for obesity, in both animal and human. Moreover, the data of this study showed that, besides pharmacological and genetic approaches, nutrients can also be attractive candidates for controlling hypothalamic inflammation in obese subject.

A similar associations have also been reported between H-GI diet and raised inflammatory status[28,29].

This mechanism could be hypothesized to explain that the predominant dietary pattern of H-GI observed in the present investigation can be modulated inflammation of the hypothalamus, leading higher AgRP concentrations.

Therefore, the present investigation provided for the first time evidence that a habitual H-GI diet affects hunger, accompanied the significant releasing of the serum AgRP when compared with a M/L-GI dietary pattern. It is likely that H-GI diet plays a modulatory role in feeding; suggesting affects the neuroendocrine energetic balance, stimulating the orexigenic factors and favoring adiposity and its metabolic consequences of the obese adolescents.

In fact, this finding might partially explain why visceral fat and visceral/subcutaneous ratio were significantly higher in the H-GI group compared to M/L-GI dietary group. Corroborating, previously it was showed that the expansion of visceral fat was an independent predictor of NAFLD in obese adolescents and it was associated with chronic diseases, such as diabetes, metabolic syndrome and atherosclerosis[25,30,31]. In the other long-term study (20 wk), authors investigated effects of high- vs low-GI diets on molecular markers of fat metabolism. The data support the hypothesis that the liver might be particularly prone to early metabolic changes on nutritional challenges of a high-GI diet. Apart from the long- term high-GI diet induced hyperinsulinemia, increased de novo lipogenesis in animals might be a contributing factor to accumulation of body and liver fat, given that metabolites such as malonyl-CoA are known to decrease mitochondrial fatty acid oxidation[32].

In contrast, we found that the type of carbohydrate was not related to body weight, glucose and HOMA-IR. In the crossover study, 17 subjects with BMI >25 kg/m^2 consumed 2 daily low GI meals for 30 consecutive days led to a significant reduction in waist circumference and hip-waist relation, however, was not affected body weight[33]. Other studies demonstrated that the H-GI diet might influence weight control, metabolic and hormonal profile[34,35].

Taking into account the main results after one year of interdisciplinary therapy, it was verified significant reductions in body weight, total body fat, visceral and subcutaneous fat; and HOMA-IR, as well as a significant increase of fat free mass. The magnitude of weight loss in long-term interdisciplinary treatments, showed improvements in insulin resistance, body composition, metabolic syndrome risks factors in obese adolescents[19,30]. Additionally to these findings, a previous study from our group demonstrated that long-term therapy was effective to promote weight loss and improve the food intake profile of obese adolescents by decreasing the energy intake, carbohydrate, lipids, and mainly saturated fatty acids[25]. On the other hand, another study suggested that only carbohydrate restriction of H-GI sources without reduced energy intake does not induce weight loss or reduce serum markers associated with obesity-related diseases[36].

Interestingly, we did not observe an effect on α-MSH levels after moderate weight loss (8 kg). In fact, previous study reported that only a significant increase of α-MSH was observed after massive weight loss (≥ 14 kg) in obese adolescents[37] and when they normalize the state of hyperleptinemia[3]. Important evidences reinforces the concept that states of hyperleptinemia in obesity, resulting in disruption between leptin and its main mediators NPY and α-MSH, playing a pivotal role in energy balance. AGRP also plays a role in paracrine-signaling molecule that inhibits the effect of α-MSH hormone, on MC-1 receptor[23]. Thus, this could modulate feeding behavior predispose individuals to weight regain[3]. This hypothesis needs to be confirmed in future clinical trials.

Nevertheless, some limitations of the study warrant discussion. Due to a reduced number of subjects that participated of this investigation and the improvement of dietary habits in relation to H-GI foods, it was not possible to identify the effects of different dietary patterns by food glycemic indexes on biochemical parameters studied before and after one year of interdisciplinary therapy. Therefore, further investigation should be performed with a large sample to examine others parameters of neuroendocrine regulation of energy balance, in order to obtain deepen understanding of how orexigenic and anorexigenic systems are regulated by consumption of different glycemic indexes.

Despite this, we were able to show that habitual H-GI diet could affect the secretion of AgRP, increasing the risk of metabolic diseases, such as obesity, mainly because it was associated to a metabolic response to sympathetic nervous system stimulation, which may up regulate food intake in the hypothalamus and reduce peripheral energy expenditure[12].

It is apparent that more effort is required to completely elucidate and understand the exact mechanism evolved different glycemic index in the control of orexigenic factors and its consequences in the complex milieu of energy balance, aiming to be considered in nutritional clinical practices for obese individuals. Indeed, we showed that one year of interdisciplinary therapy promoted a significant improvement of metabolic profile in this analyzed population.

Conclusions

In conclusion, our study revealed that food intake in long-term of higher glycemic index foods was an independent predictor of body weight and visceral fat to explain changes in AgRP concentrations in obese adolescents. Therefore, these results may suggest that habitual H-GI diet could upregulate orexigenic pathways, contributing to vicious cycle between undesirable diet, deregulates energy balance and promote obesity.

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Conflict of interest

There is no conflict interest.

Authors contributions

Netto and Masquio had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Netto, Masquio and Dâmaso. Acquisition of data: Campos, Sanches, Corgosinho, Tock, Oyama, Tufik and de Mello. Analysis and interpretation of data: Netto, Masquio, Dâmaso and Campos. Drafting of the manuscript: Netto, Dâmaso, and Masquio. Critical revision of the manuscript for important intellectual content: Dâmaso, Netto and Corgosinho. Statistical analysis: Netto, Masquio and Campos. Final approval of the version to be submitted: Netto and Dâmaso.

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