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IRISIN LEVELS ARE NOT ASSOCIATED TO RESISTANCE TRAINING-INDUCED ALTERATIONS IN BODY MASS COMPOSITION IN OLDER UNTRAINED WOMEN WITH AND WITHOUT OBESITY

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Abstract: *Objective:* The present study aimed to determine whether Irisin levels are correlated with body composition changes following 16 weeks of resistance training (RT) in older women with and without obesity. *Design, Setting, Participants, Intervention:* We recruited 49 inactive women (n = 23, non-obese: < 41.0% and n = 26, obese: ≥ 41.0% of body fat) aged 61–68 years to perform 16-week of RT consisting of 10 exercises (three sets of 10 exercises, 6-12 repetitions maximum and 1-min and 30-s rest intervals between sets and exercises, respectively) with two sessions per week. *Measurements:* Before and after the intervention period, blood samples were collected to determine Irisin levels and body composition (percentage body fat and fat-free mass) was measured by dual energy x-ray absorptiometry. *Results:* Circulating Irisin displayed a decrease for the non-obese group as compared with pre-intervention and obese group ($p = 0.01$ and $p = 0.04$, respectively), with no change for the obese group ($p = 0.79$). In addition, fat mass displayed a significant reduction ($p < 0.05$) following the training period only for the obese group. Furthermore, there was no association between changes in circulating Irisin with body mass index, body fat, fat-free mass and muscle strength. There was an increase in muscle strength ($p < 0.05$), regardless of obesity status. *Conclusion:* The modulation of body composition and muscle strength induced by 16-week of resistance training in older women with and without obesity is not associated with changes in circulating Irisin levels.

Key words: Aging, myokines, obesity, resistance training.

Introduction

Aging of the population is a worldwide phenomenon that is accompanied by modifications in several physiological parameters, such as progressive increase in fat mass and decrease in fat-free mass resulting in the prevalence of overweight and obesity, combined (6, 28, 33) with a decline in the capacity to develop force and power (32), and consequently functional capacity, mainly after the decade of life between 60 and 70 years of age (11, 18).

To counteract the negative effects of aging, resistance training (RT) can improve the strength, power, functional capacity, and decreases fat mass and systemic markers of inflammation in older obese subjects (1, 5, 16, 26). These positive effects of RT can be partially attributed to release of cytokines from skeletal muscle, termed myokines, which mediate the effects of exercise at the systemic level (2, 13). Irisin is a newly discovered exercise-induced myokine suggested to induce browning in adipose tissue and thus increase energy expenditure (4, 17). Recent exercise studies have shown a significant transient increase in circulating Irisin following an acute bout of aerobic or RT (15, 19, 21). However, the link between exercise training status, Irisin levels, and body composition in humans is inconsistent and needs more elucidation (7, 12, 27).

Regarding to the chronic effects of exercise, the results are also inconsistent. Norheim et al. (20014) found that circulating Irisin was reduced in response to 12-week of combined endurance and RT with four sessions of training per week in subjects aged 40–65 years (21). However, Hecksteden et al. (2013) observed no alterations on Irisin concentrations following 26 weeks both aerobic training (45 minutes of walking/running at 60% of heart rate reserve, 3 times per week) and local muscle endurance training (2 sets of 15 repetitions with 20 repetitions maximum load, 3 times per week) in male and female adults with 30 to 60 years (12). In addition, the circulating Irisin is lower in old versus young and active versus sedentary subjects (14). Interestingly, although Irisin was unchanged following an exercise program in obese and pre-diabetic patients, almost 40% of the patients with type 2 diabetes had their Irisin levels reduced (14, 20). Therefore, several aspects of Irisin physiology in response to chronic RT in different populations, especially in old and obese subjects, need more elucidation.

Thus, the aim of the present study was to investigate whether chronic RT induces reduction in circulating Irisin concentration in untrained non-obese and obese older women. Furthermore, we examined the associations between RT induced Irisin-changes with body fat, fat-free mass and muscle strength. The initial hypothesis is that 16-week of RT modifies circulating

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Irisin levels in association with modification on body composition and muscle strength.

Methods

Subjects

Older women (≥ 60 years) were recruited on a voluntary basis from local community following informative posters and lectures about the study. Each subject underwent a thorough physical examination, which included a medical history, resting and exercise electrocardiogram, blood pressure, and orthopedic evaluation prior to initiation of the RT program. Following the clinical examinations for inclusion, forty-nine sedentary older women were selected. The International Physical Activity Questionnaire was used to determine inactive status in the past 6 months (3, 10). Women undergoing hormonal replacement therapy and with manifestation of diabetes, cardiovascular/pulmonary/neuromuscular or immune disease that could affect the results and training were excluded. The older women were divided into non-obese (n = 23) and obese (n = 26) groups according to the percentage of body fat values, assuming the Gallagher cut-off points for older women: non-obese: < 41.0% and obese: ≥ 41.0% of body fat (9). The study design and employed procedures are in accordance with ethical standards and the Declaration of Helsinki. Each subject was fully informed about the risk associated with study design participation and gave their written informed consent. The study was approved by the Catholic University of Brasilia Research Ethics Committee for Human.

Experimental Design

The study investigated the effects of 16 weeks of RT on circulating Irisin, body fat, fat-free mass and muscle strength in untrained non-obese and obese older women. Subjects completed 2 weeks of familiarization prior to RT program. During the familiarization weeks, subjects were advised regarding the execution of proper technique, and completed 3 sessions per week, with 1 exercise for each main muscle group (same exercises of the RT) performing 2 sets of 12–15 submaximal repetitions at 60% of estimated 10 repetitions maximum (10RM). After the familiarization period, subjects completed a 1-repetition maximum test (1RM) to determine the maximal strength in each exercise. The RT program was performed on two non-consecutive days of the week and was comprised of three sets of 10 exercises, with 6-12 repetitions maximum (RM) and 1-min and 30 s rest intervals between sets and exercises performed, respectively. Before training (Pre) and five days after (Post) the end of the RT all subjects reported to the laboratory between 08:00–10:00 a.m. for the body composition analysis and blood samples were collected for Irisin analysis. In addition, the subjects were encouraged to avoid smoking, alcohol, caffeine, unusual physical activity and to maintain their usual diet consumption.

Resistance training

After a general warm-up, the subjects performed a whole-body RT program including 10 different exercises as follows: barbell bench press, 45° leg press, seated row, knee extension, lateral raise, knee flexion, arm extension, hip adduction and abduction, arm curl and standing calf raise followed by 3 sets of 20-30 repetitions of abdominal crunches. The RT lasted four months, with two weekly sessions, consisting of 3 sets to concentric failure (inability to perform a repetition with the correct movement pattern). The number of repetitions was 6-12 repetitions maximum (RM) in each set and rest between sets and exercises was 1 min and 30 s. Subjects were instructed to perform each repetition at a moderate speed (i. e., 2 s concentric and 2 s eccentric) to avoid Valsalva maneuver and the mean duration of each session was 50 min. During the sessions, the loads (kg) in each set were adjusted to maintain the number of maximal repetitions, according to individual increases in the muscle capacity. All sessions were supervised by experienced strength training professional. This progression of a RT was 'individualized' and designed specifically to achieve training goals for untrained older subjects (1, 24).

Determination of circulating Irisin

Subjects reported to the laboratory between 08:00–10:00 a.m., after an overnight fast (12h), and blood samples (5 mL) were drawn from the antecubital vein into Vacutainer tubes (Becton Dickinson, Brazil). Samples were then centrifuged at room temperature at 2.500 rpm for 15 min. Serum was stored and frozen at -80°C for subsequent analysis. Serum Irisin concentrations were determined using a commercial ELISA (Enzyme Linked Immuno-Sorbent Assay) kit (MyBioSource Inc., San Diego, CA, USA), according to the manufacture´s recommendations. All samples were determined in duplicate to guarantee reliability. The minimum detectable level was 27.85 ng/mL. The intra-assay coefficient of variation was 2.9–9.5 %, the inter-assay coefficient of variation was 5.9–7.0 %, and the sensitivity was 0.0093 pg/mL.

Body composition analysis

Body composition analysis (percentage body fat and fat-free mass) was conducted before (Pre) and after the RT period (Post) for each subject, using dual energy x-ray absorptiometry (General Electric-GE model 8548 BX1L, year 2005, Lunar DPX type, software Encore 2005; Rommelsdorf, Germany) with an in vivo variation coefficient of 0.9%–1.1%. Briefly, the tests included a complete body scan of the volunteers in a supine position with the apparatus always regulated and operated by a technically trained professional. Legs were secured by nonelastic straps at the knee and ankles, and the arms were aligned along the trunk with the palms facing the thighs. The following variables were evaluated: body mass, fat free mass, fat body mass and percent of fat body mass.

One-repetition maximum muscle strength test (1-RM)

All subjects completed a familiarization protocol on the resistance exercise equipments before the testing procedures took place (30). During this period, standard instructions and explanations regarding the procedures of the test protocols and the proper execution of exercise technique were provided to the subjects. To enhance reliability, testing procedures were administered by the same investigator. Two tests on two different days with a minimum of 72 h of rest were conducted (test-retest). The 1RM test was used to determine the dynamic muscle strength of upper and lower limbs using conventional isoinertial weight training machines (Righetto, São Paulo, Brazil).

The 1RM protocol was conducted according to the method of Tibana et al. (2014) including load standardization, exercise range of motion, and lifting technique during the performance of each exercise (31). Prior to the 1RM tests, two light warm-up sets were interspersed with 2-minute rest periods. Then, the participants had up to five attempts to achieve the 1RM load (ie, maximum weight that could be lifted once with proper technique), with a 5-minute interval between attempts and 10-minute interval between exercises. The tests were randomly conducted for leg press, bench press, and biceps-curl exercises. Both testing sessions took place between 2 p.m. to 3 p.m. after lunch and under a controlled standardized temperature.

Statistical analysis

The results are expressed as means ± standard deviation (SD). Shapiro-Wilk tests were applied to check for normality distribution of study variables. In case of nonparametric distribution, logarithmic transformation (log10) was performed and the normality distribution was achieved. Differences between non-obese and obese groups were tested for significance using independent samples t-test. Differences between pre- and post-exercise were tested for significance using paired samples t-test. Based on linear correlation ratios between Irisin concentration and other study variables, multiple regression analysis was used to analyze influencing factors on baseline Irisin concentration and training-induced changes. Non-obese and obese groups were pooled for regression analysis of training-induced changes. The power of the sample size (1 – ß) related to Irisin concentration was determined using G*Power version 3.1.3 and it is presented in the results section for each analysis as 1 – ß (8). The level of significance was $p \leq 0.05$ and SPSS version 20.0 (Somers, NY, USA) software was used.

Results

Pre-intervention subjects' characteristics and changes over the intervention period

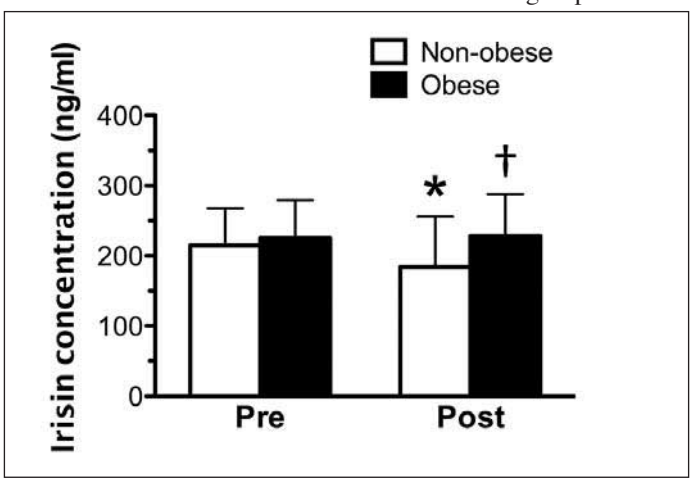
Baseline subjects' characteristics and changes over the RT intervention period are summarized in table 1. As expected, there were significant differences ($p < 0.05$) in anthropometric variables between non-obese and obese groups before and after the training intervention. Fat mass (% and kg) displayed a significant reduction ($p < 0.05$) after the training period only for the obese group. There were no other significant differences ($p > 0.05$) in anthropometric variables after the intervention period for the obese or non-obese groups.

Table 1
Baseline and after training intervention characteristics of non-obese and obese groups (mean ± SD)

	Non-obese (n = 23)		Obese (n = 26)	
	Pre	**Post**	**Pre**	**Post**
Age, yr	68.0 ± 6.2	-	66.5 ± 5.0	-
Weight, kg	56.4 ± 8.4	56.7 ± 9.0	71.8 ± 8.0†	71.4 ± 7.9†
BMI, kg/m^2	24.3 ± 3.6	24.4 ± 3.7	30.9 ± 3.1†	30.8 ± 3.1†
Waist circumference, cm	78.6 ± 9.2	77.7 ± 9.5	91.4 ± 9.4†	90.0 ± 8.5†
Neck circumference, cm	32.6 ± 2.5	32.7 ± 2.9	35.5 ± 2.7†	34.7 ± 2.1†
Hip to waist ratio	0.85 ± 0.08	0.83 ± 0.06	0.86 ± 0.07†	0.86 ± 0.07†
Body fat, %	36.1 ± 5.3	36.5 ± 5.0	46.5 ± 3.0†	45.6 ± 3.7*†
Body fat, kg	19.9 ± 5.0	20.1 ± 5.4	32.3 ± 4.6†	31.5 ± 5.2*†
Fat free mass, kg	34.1 ± 4.0	33.8 ± 4.1	36.8 ± 3.7†	37.1 ± 4.1†

† $p < 0.05$ between non-obese and obese groups; * $p < 0.05$ between pre and post intervention.

Figure 1
Baseline (Pre) and after training period (Post) Irisin concentrations for non-obese and obese groups



*$p < 0.05$ vs Pre; † $p < 0.05$ vs non-obese. Values are presented as mean and SD.

Muscle strength

Table 2 shows the 1-RM performance before and after the training period. There were no significant differences ($p > 0.05$) between groups for leg press and bench press exercises. Before the training period, the obese group had higher strength ($p < 0.05$) as compared with the non-obese group in the biceps curl exercise. After the training period, both the obese and non-

obese group had a significant increase ($p < 0.05$) in leg press, bench press and biceps curl strength. There were no significant differences ($p > 0.05$) between groups in 1-RM performance after the training intervention.

Table 2
Baseline and after training intervention strength performance of non-obese and obese groups (mean ± SD)

	Non-obese (n = 23)		Obese (n = 26)	
	Pre	Post	Pre	Post
Leg press, kg	102.4 ± 38.8	140.3 ± 51.7*	122.7 ± 41.5	160.3 ± 37.1*
Bench press, kg	23.2 ± 6.0	26.2 ± 5.8*	25.2 ± 4.3	27.1 ± 4.7*
Biceps curl, kg	15.2 ± 2.9	17.0 ± 3.2*	17.2 ± 2.3†	18.3 ± 2.7*

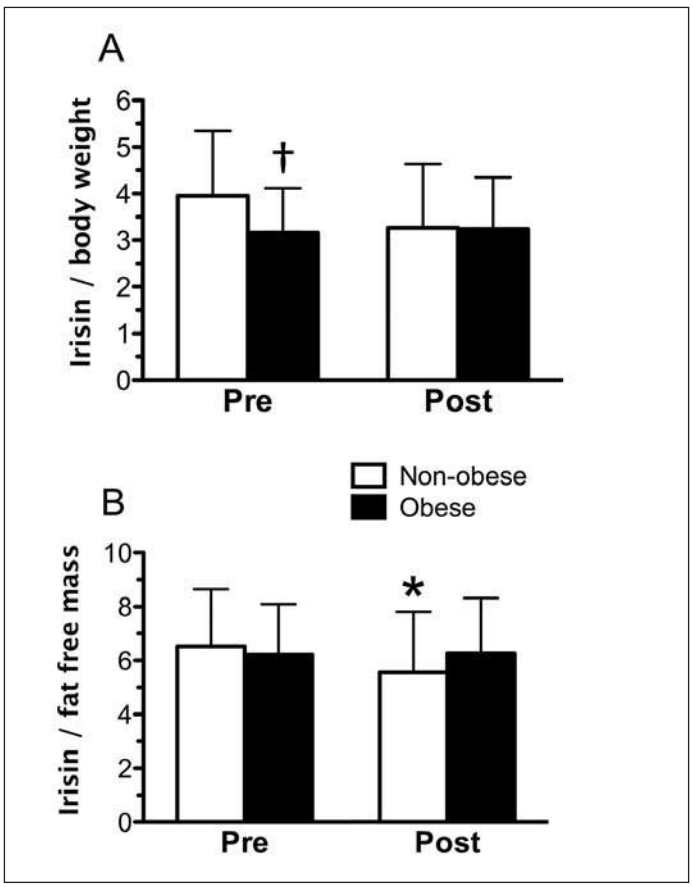
† $p < 0.05$ between non-obese and obese groups; * $p < 0.05$ between pre and post intervention.

Baseline changes in circulating Irisin over the intervention period

Mean baseline Irisin concentration was 214.7 ± 53.2 ng/mL for the non-obese and 225.0 ± 54.6 ng/mL for the obese group (figure 1), with no differences between groups ($p = 0.56$). Multiple linear regression analysis revealed that age ($p = 0.19$, ß = 0.23), BMI ($p = 0.82$, ß = 0.09), body fat ($p = 0.55$, ß = 0.20) and fat free mass ($p = 0.10$, ß = -0.42) were not predictors of the baseline Irisin concentration.

After the training period, circulating Irisin concentration presented a significant decrease for the non-obese group (184.1 ± 72.5 ng/mL; $p = 0.011$, 1 – ß = 0.95) with no change for the obese group (228.2 ± 59.5 ng/mL; $p = 0.79$), with significant differences between groups at the end of the training intervention ($p = 0.04$; 1 – ß = 0.74). There were no correlations between changes in circulating Irisin over the intervention period and the baseline Irisin concentration, BMI, body fat and fat free mass as verified by the multiple regression analysis (age: $p = 0.72$, ß = -0.06; baseline Irisin: $p = 0.63$, ß = -0.10; BMI: $p = 0.22$, ß = -0.52; fat mass: $p = 0.14$, ß = 0.55; fat free mass: $p = 0.12$, ß = 0.42). When corrected for body weight (ng/mL/kg of body weight), the non-obese group had higher baseline Irisin concentration than the obese group ($p = 0.046$). Irisin concentration corrected for body weight presented a tendency toward a significance decrease ($p = 0.07$) and for fat free mass presented a significant decrease for the non-obese group after the training period ($p = 0.012$) (figure 2). Considering that, muscle is considered the primary organ expressing Irisin and might interfere on the final analysis of Irisin. Its values might fluctuate according to the body weight and fat-free mass of the subjects. Because of this Irisin concentration was corrected for body weight and fat-free mass. In a supplementary analysis, there were no differences in pre- and post-exercise circulating Irisin concentration when the groups were classified by BMI following the classification of the World Health Organization (BMI ≥ 30 kg/m2 for obese and BMI ≤ 30 kg/m2 for non-obese).

Figure 2
Baseline (Pre) and after training period (Post) irisin concentrations corrected for body weight (A) and fat-free mass (B) for non-obese and obese groups



*p < 0.05 vs Pre; † p < 0.05 vs non-obese. Values are presented as mean and SD.

Discussion

The present study demonstrates that 16 weeks of RT program improves muscle strength, decrease fat mass and an increase in fat-free mass with no change in circulating Irisin levels in obese older women. Furthermore, serum Irisin decreased in non-obese older women with no significant improvements in body composition. Our initial hypothesis was not confirmed, and the results did no confirm an association between changes in circulating Irisin over the intervention period and baseline Irisin concentration with BMI, body fat, fat-free mass and muscle strength.

Studies have shed light on the role of nontraditional endocrine tissues, including skeletal muscle tissue, in the regulation of energy metabolism, body composition, and insulin sensitivity (22, 23). A number of cytokines and other peptides, also known as myokines, are expressed and released by muscle fibers in response to contraction. Irisin has also been shown to be related to various physiological and pathophysiological conditions in mice and humans (2, 17). Therefore, Irisin is

an attractive target for investigation of obesity and related metabolic disorders.

Overall, the findings of the present study suggest no association between circulating-Irisin over the intervention period and baseline Irisin concentration with body mass index, body fat, fat-free mass and muscle strength. On the other hand, Boström et al. (2012) reported an increase in fibronectin type III domain containing protein 5 (FNDC5) mRNA in the skeletal muscle of mice and humans after exercise (4). Based on these results, it was suggested that Irisin, which is cleaved from FNDC5 by an unknown protease, is an exercise protein that is secreted into the bloodstream, which acts on white adipose tissue, and interacts with an unknown receptor, causing the conversion of white fat tissue to brown fat tissue.

However, it should be noted that this link between exercise training, Irisin and body composition modification in humans is inconsistent (7, 12, 27). For example, Scharhag-Rosenberger et al. (2014) found that six months of RT (2 sets of 16-20 RM in eight exercises for the whole body, 3 times per week) increased muscle strength and resting metabolic rate without changes in body composition and circulating-Irisin in sedentary healthy males and females (27). Similarly, Ellefsen et al. (2014) found that 12 weeks of whole-body heavy RT (3 sets of 7-12 RM, 3 times per week, eight exercises for the whole body), did not modulate steady-state expression of FNDC5 in skeletal muscle or levels of serum-Irisin of untrained female subjects (7). Moreover, there was no association between serum-Irisin and changes in body mass composition.

A previous study from Bostrom et al. (2012) indicated that the proposed beneficial role of Irisin may be relevant only in a select population of subjects (4). In this regard, it is possible that some subjects may be high responders, moderate responders, or low responders to RT induced Irisin changes based on genetic make-up. In addition, the time point of assessment or age-related alterations of regulatory processes accounting for the observed differences and controversial findings should be further investigated. In addition, the circulating Irisin was corrected for body weight and fat-free mass and interestingly for the fat-free mass, the non-obese group displayed lower circulating Irisin levels post-intervention when compared to the obese group. Although, skeletal muscle is the primary organ of FNDC5 expression (14), it is possible that lower muscle mass in the older non-obese group has resulted in a lower level of Irisin when compared to the older obese group, or the training stimulus was insufficient to alter body composition after 16 weeks of RT. These hypotheses are speculative and more studies are needed to understand this complex outcome.

The present study has some limitations that should be considered, such the lack of a control group, although it has been speculated that a control group is not always necessary, particularly considering that the health of the older could be compromised as a result of not participating in RT. Additionally, results from a control group would likely reveal no positive effect on anthropometric, and biochemical factors, as has been previously reported in the literature (25). Finally, we assessed only the concentration of circulating Irisin, while the expression of FNDC5 in skeletal muscle was not studied. Although subjects were advised to maintain their diet during the entire study, nutritional intake was not precisely controlled. The relationship between dietary quality, body composition, fall risk, classification of frailty and physical function appear to be gender specific (29). Moreover, the biochemical kit, antibody type and sample storage period are widely variable and may impact comparisons between studies.

In conclusion, the changes in Irisin over 16 weeks of resistance training in older women with obesity are inconsistent. This limits the putative role of Irisin for training-induced improvements of body composition and metabolic health. The association between changes in circulating Irisin over the intervention period and baseline Irisin concentration with body mass index, body fat, fat-free mass and muscle strength could not be substantiated as initially proposed in the hypothesis of the present study. Finally, resistance training was efficient in improving body composition in elderly obese women, which is important to present several metabolic and functional disorders associated with obesity and aging.

Conflict of interest: The authors declare no conflict of interest.

Ethical Standards: The authors declared that the study design and employed procedures are in accordance with ethical standards and the Declaration of Helsinki. Each subject was fully informed about the risk associated with study design participation and gave their written informed consent. The study was approved by the Catholic University of Brasilia Research Ethics Committee for Human use (N: 235/2010).

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