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Acute effects of moderate-intensity constant training on circulatory fibroblast growth factor 21, resistin, and adiponectin of physically inactive young adults

Efectos agudos del ejercicio de intensidad moderada y constante sobre los niveles circulantes de factor de crecimiento de fibroblastos 21, resistina y adiponectina de adultos jóvenes inactivos físicamente

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Abstract. Introduction: physical inactivity affects metabolic health, and it has been described that physical exercise is able to counter these disturbances. Fibroblast growth factor (FGF) 21, resistin, and adiponectin are known cytokines that are sensitive to physical inactivity and exercise, however, their acute behaviour after one session of exercise in physically inactive young adults is unclear. Therefore, this study aimed to investigate the effects of a session of moderate-intensity continuous training (MICT) on the circulatory levels of FGF21, resistin, and adiponectin of physically inactive young adults. Material and methods: quasi-experimental study, where 20 physically inactive young adults, with body mass indexes between 18 and 30 kg/m^2 were included. All performed one MICT session, with an intensity of 60% of their heart rate reserve on a treadmill for 30 minutes. Anthropometric measurements were evaluated (weight, height, waist and hip circumferences, lean and fat mass) prior to exercise, and venous blood samples were taken before and after exercise, where glycemia, insulin, lipid profiles, transaminases, FGF21, resistin, and adiponectin were assessed. Results: one MICT session decreased the circulatory levels of insulin (median 23.5 vs 10.9 µUI/ml; $p<0.05$) and FGF21 (median 527 vs 409 pg/ml; $p<0.05$). On the other hand, resistin and adiponectin levels did not change after exercise (both $p>0.05$).
Conclusion: one MICT session decreased FGF21 plasma levels, whereas it did not modify resistin and adiponectin circulatory levels. The specific mechanisms behind this different behavior are needed to be elucidated in future studies.
Keywords: exercise, sedentary behavior, metabolic syndrome, endurance training, cytokines

Resumen. Introducción: la inactividad física afecta a la salud metabólica mientras que se ha observado que el ejercicio revierte estas alteraciones. El factor de crecimiento de fibroblastos (FGF) 21, la resistina y la adiponectina son citoquinas que se ven afectadas por la inactividad física y el ejercicio, sin embargo, su respuesta aguda al ejercicio en adultos jóvenes físicamente inactivos es desconocida. Por tanto, este estudio tuvo por objetivo investigar los efectos de una sesión de ejercicio de intensidad moderada y continua (MICT) sobre el FGF21, resistina y adiponectina circulante en ellos. Material y métodos: estudio cuasi-experimental donde 20 adultos jóvenes físicamente inactivos con índices de masa corporal entre 18 y 30 kg/m^2 fueron reclutados. Se realizó una sesión de MICT a una intensidad del 60% de su frecuencia cardiaca de reserva por 30 minutos. Se midieron el peso, talla, circunferencias de cintura y cadera, y porcentajes de masa adiposa y muscular antes del ejercicio, y se tomaron muestras de sangre venosa antes y después del ejercicio, donde se valoró la glicemia, insulinemia, perfiles lipídicos, transaminasas, FGF21, resistina y adiponectina. Resultados: después del ejercicio disminuyeron los niveles circulantes de insulina (mediana 23.5 vs 10.9 µUI/ml; $p<0.05$) y FGF21 (mediana 527 vs 409 pg/ml; $p<0.05$). Mientras que no se observaron cambios en los niveles de resistina y adiponectina (ambos $p>0.05$).
Conclusión: Una sesión de MICT disminuye los niveles sanguíneos de FGF21, sin modificar las concentraciones de resistina y adiponectina. Los mecanismos detrás de estos cambios necesitan ser investigados en futuros estudios.
Palabras claves: ejercicio, comportamiento sedentario, síndrome metabólico, entrenamiento de resistencia, citoquinas.

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Introduction

Physical inactivity is one of the most prevalent cardiovascular risk factors in modern era, where recent studies have point out that more than one in four adults have this condition (Nikitara et al., 2021; WHO, 2022). The mechanisms behind this increased risk are several and still undergoing arduous research, however, physical inactivity promotes the excessive accumulation of visceral adipose tissue, which in turn is infiltrated by immune cells favoring its inflammation, by which cytokines with pro-inflammatory and insulin-resistant functions, such as tumor necrosis factor (TNF) and resistin are released to the circulation (Pedersen, 2019). Physical inactivity is particularly prevalent during the first years of adulthood (18 to 25 years old), because of the college years and lifestyle changes that are usually undertaken during this period, such as smoking, long sitting hours, and fast-food consumption (Downes, 2015; González-Zapata, Carreño-Aguirre, Estrada, Monsalve, & Álvarez, 2017), therefore, its study is particularly relevant during this age.

Physical inactivity can also promote metabolic dysfunction in the absence of an increased adiposity or obesity. More than a decade ago this was reported by Hamer et al. where after following for 10 years to more than 4000 participants, they observed that persons that complied with the physical activity standards (150 weekly minutes of moderate/vigorous physical activity) showed lower levels of pro-inflammatory markers such as C-reactive protein and interleukin 6 (Hamer et al., 2012). A possible mechanism behind these results, it has been described that adipose tissue from sedentary normal-weight mice were more prone to develop inflammation after injections of lipopolysaccharide compared to the adipose tissue from physically active animals (Peppler, Anderson, MacRae, MacPherson, & Wright, 2017).

To sustain the metabolic function, even in conditions of stress, such as physical inactivity, there are several cytokines

that have opposite function to maintain homeostasis. Fibroblast growth factor (FGF) 21 is a small protein firstly described in the year 2000 (Kharitonenkov & Adams, 2014), which has insulin-sensitization actions, promotes beta-oxidation of lipids, glucose uptake, and is anti-inflammatory (Porflitt-Rodriguez et al., 2022). Interestingly, in conditions of metabolic dysfunction, such as insulin resistance, its levels are increased where possible development of resistance to the action of this protein has been proposed (Fisher et al., 2010). Resistin was first reported in 2001 by Steppan et al. (Steppan et al., 2001), primarily secreted from macrophages and adipocytes in humans, which has opposite functions to FGF21, given that promotes insulin resistance, liver glycogenolysis, and inflammation (Rachwalik, Hurkacz, Sienkiewicz-Oleszkiewicz, & Jasinski, 2021), where evidence has shown that higher resistin levels are seen in patients with type 2 diabetes (Siddiqui, Scaria Joy, & George, 2020). Adiponectin is a 30 kDa protein that forms multimers (high and low molecular weight isoforms), where its circulatory levels are mainly produced by adipocytes, however skeletal muscles and liver also produces it in an autocrine/paracrine manner (Martinez-Huenchullan et al., 2020). Its main functions are described as insulin-sensitizer and anti-inflammatory (Kadowaki et al., 2006), similar to FGF21.

Exercise is one of the main lifestyle-based strategies to counter the metabolic alterations behind physical inactivity, where one of its main mechanisms is the regulation of circulatory mediators to improve metabolic health (Chow et al., 2022). For instance, previous studies have reported that 2 weeks of exercise training promotes increases in FGF21 in young healthy women (Cuevas-Ramos et al., 2012). Complementarily, in a systematic review and meta-analysis, Becic et al. described that, exercise training promotes increases in circulatory adiponectin in patients with pre-diabetes and type 2 diabetes (Becic, Studenik, & Hoffmann, 2018), whereas reductions of circulatory resistin were described after 16 weeks of exercise training in a similar population (Kadoglou et al., 2007). However, the exercise prescription heterogeneity between the described studies is high, the acute effects of each type of training were unexplored, and the participants recruited in those studies had preexisting comorbidities, which hinder the possibility to address the effects of specific exercise programs on the circulatory concentration of these proteins in a context of physical inactivity. Therefore, the aim of this study was to investigate the effects of one session of moderate-intensity continuous (MICT) training on the circulatory levels of FGF-21, resistin and adiponectin in physically inactive young adults. We selected MICT as exercise program given its previously described benefits in different contexts of health and disease (Collados-Gutiérrez & Gutiérrez Vilahú, 2023; Farhani et al., 2022; Sari et al., 2023).

Material and methods

Study design

This was a quasi-experimental study where the acute effects of a single session of moderate-intensity constant exercise were assessed. This study was reviewed and approved by the Scientific Ethics Committee of Los Rios (code 484/2022). The sample size required was calculated by the following: considering an effect size of 0.6 considering a previous study regarding acute effects of exercise on FGF21 (Slusher et al., 2015), an alpha coefficient of 0.05, a power β of 0.95, and a correlation between measurements of 0.5, we required 20 subjects to conduct the study.

Participants

Subjects of both genders were recruited through social media and posters located throughout the University. Participants were included if they were aged between 18 to 28 years old, had a body mass index (BMI) between 18 and 30 kg/^{2}, be physically inactive according with the short form of the international physical activity questionnaire (IPAQ) (Balboa-Castillo et al., 2023), and perform less than 150 of 75 weekly minutes of moderate/vigorous physical activity. Subjects that had known metabolic comorbidities (e.g. insulin resistance, hypertension), restriction to perform exercise by the physical activity readiness questionnaire (PARQ&YOU) (Warburton et al., 2011), and/or anti-inflammatory treatment during the last 2 weeks were excluded from the study (Figure 1). All participants signed an informed consent prior to their participation on this study.

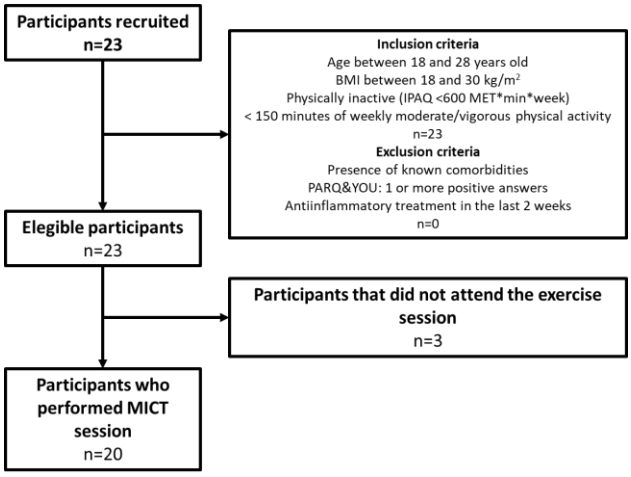

Figure 1. Participants flow diagram. IPAQ: International physical activity questionnaire; PARQ&YOU: Physical Activity Readiness Questionnaire; MICT: moderate-intensity constant training.

Clinical and metabolic outcomes

The participants were instructed to attend the laboratory two times (Figure 2). During the first session, anthropometric measurements such as weight, height, waist circumference (lower perimeter between last rib and the iliac crest), hip circumference (most prominent at the gluteus level) were obtained. From there, the waist-to-hip and waist-to-height ratio were obtained. A body composition analysis was performed with a InBody® 270 where the total fat and muscle mass was obtained.

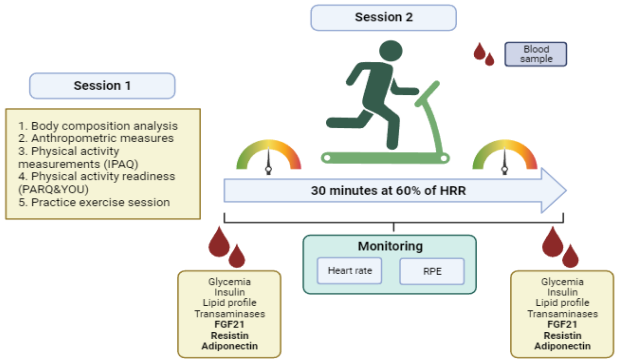

Figure 2. Study design. IPAQ: international physical activity questionnaire; PARQ: physical activity readiness questionnaire; HRR: heart rate reserve; RPE: rating of perceived exertion; FGF21: fibroblast growth factor 21. Created with BioRender.com

During the second session, the exercise session was performed. Before and immediately after the exercise, venous blood samples were obtained from the antecubital vein. Samples were stored in tubes with (lipid profile, transaminases, glycemia, and insulin) and without EDTA (FGF21, resistin, adiponectin). Lipid profiles (Colestat and TG color, Wiener lab®), transaminases, glycemia (based on glucose oxidase/peroxidase activity), and insulinemia (specific fluorometric enzymatic assay ST AIA-PACK IRI, Tosoh®) were measured in the Clinical Laboratory of the Universidad Austral de Chile.

For the measurement of FGF21 and resistin, ELISA kits were purchased and performed following the manufacturer's instructions (ELH-FGF21, dilution 1:2, RayBiorech®, USA; ELH-resistin, dilution 1:50, RayBiorech®, USA). For adiponectin, western immunoblotting was performed using the following protocol: 0.5 µL of plasma was mixed with 2.5 µl of 6x loading buffer and 12 µL of RIPA buffer and loaded directly onto pre-cast gels (Bio-Rad®, catalog number 4568086). Afterwards, those proteins were transferred to a nitrocellulose membrane (Bio-Rad®, catalog number 1704158) using the Trans-Blot® Turbo™ Transfer System (Bio-Rad®, Hercules, CA, USA). Membranes were blocked for 1 h using 5% bovine serum albumin (BSA) in buffer (TBST) containing 0.6% Tris HCl w/v, 0.1% Tris-base w/v, 0.6% NaCl w/v, and 0.05% Tween-20 v/v. After washing the membranes in TBST (3x10 min), they were incubated in adiponectin primary antibody (1:1000, rabbit monoclonal Cell Signaling®, catalog number 2789S) overnight at 4°C. Membranes were washed again in TBST (3x10 min), and then incubated with a secondary antibody labelled with peroxidase (1:2000, Anti-rabbit IgG, Cell Signaling®, catalog number 7074S) for 1 h at room temperature. Membranes were then washed with TBST and developed with a chemiluminescent substrate (ClarityTM Western ECL substrate, Bio-Rad®, catalog number 170-5061) and visualized on a G:Box system (Syngene®, USA). Densitometric measurements of the bands was performed using the ImageJ software. Protein loading was confirmed and normalized using Ponceau S staining of the whole membrane in each respective experiment.

Exercise prescription

A moderate-intensity constant session was prescribed to be performed on a treadmill with a duration of 30 minutes and an intensity of 60% of the heart rate reserve (HRR). This target was obtained by the following: first, the theoretical maximum heart rate (HRmax) was estimated through this equation 220-age (years); then the resting HR was obtained after keeping the participants in a seated position for 5 minutes. Afterwards, with the following equation we estimated the target HR that each participant had to reach: (HR max – resting HR) * 0.6 + resting HR. HR during the exercise session was monitored in real-time through a cardiac band (Polar® H10). Complementarily, the ratings of perceived exertion (RPE) were asked throughout the session using the original Borg's scale (from 6 to 20, where higher values indicated higher perceived efforts). A 5-minute warm-up period was considered before starting the MICT session and a 5-minutes cool-down period as well.

Statistical analysis

Continuous outcomes were described in terms of mean ± standard deviation, whereas qualitative outcomes were summarized by absolute frequencies. The normality distribution of the different outcomes was tested by the Kolmogorov-Smirnov's. Given that all outcomes of interest had a no-parametric distribution, the comparison between the pre- and post-exercise levels was done with the Wilcoxon's test. For all analysis, a p value below 0.05 was considered statistically significant, and SPSS version 20 and GraphPad version 8 software were used.

Results

20 volunteers completed both study sessions, where the gender-parity was kept and in terms of mean they were classified as normal-weight (BMI) and with anthropometric measures in normal values (waist-to-hip and waist-to-height ratios; table 1). A moderate-intensity exercise was achieved in all participants given that all achieved the utilization of their 60% of their HRR along with RPEs in the moderate-effort range. Lipid profile outcome did not change with exercise ($p>0.05$), however, GOT transaminase showed a significant increase ($p<0.05$, table 2) suggesting an expected muscle microdamage derived from exercise, and insulin exhibited a significant decrease after exercise (figure 3A; $p<0.05$).

Table 1.
Phenotypic characteristics of the participants

Parameter	Values
Gender (M/F)	10/10
Age (years)	23.2 ± 1.8
Weight (kg)	63.9 ± 7.7
Height (cm)	166 ± 8
BMI (kg/m^2)	23.2 ± 2.8
Waist circumference (cm)	77.1 ± 7.0
Hip circumference (cm)	97.3 ± 6.7
Waist-to-hip ratio	0.79 ± 0.06
Waist-to-height ratio	0.47 ± 0.04
Fat mass (% body weight)	22.0 ± 8.3
Skeletal muscle mass (% body weight)	41.7 ± 6.3

Values expressed in mean ± SD
Abbreviation list: BMI: body mass index.

Table 2.
Effects of MICT on cardiovascular and metabolic outcomes.

Parameter	Pre	Post
HR (beats/min)	82 ± 12	150 ± 6
RPE (points)	6 ± 0	12 ± 2
Glycemia (mg/dl)	88 ± 15	86 ± 10
HDL (mg/dl)	48 ± 21	36 ± 23
LDL (mg/dl)	89 ± 22	87 ± 24
VLDL (mg/dl)	21 ± 11	21 ± 10
Triglycerides (mg/dl)	114 ± 61	116 ± 63
GOT (UI/L)	31 ± 21	35 ± 22*
GPT (UI/L)	27 ± 24	28 ± 23

Values expressed in mean ± SD
Abbreviation list: HR: heart rate; RPE: rating of perceived exertion; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase.
*: significant difference between pre vs. post ($p<0.05$).

The circulatory levels of FGF21 decreased after exercise (figure 3B; $p<0.05$), whereas one MICT session did not promote any changes in resistin and adiponectin (figure 3C-D, both $p>0.05$).

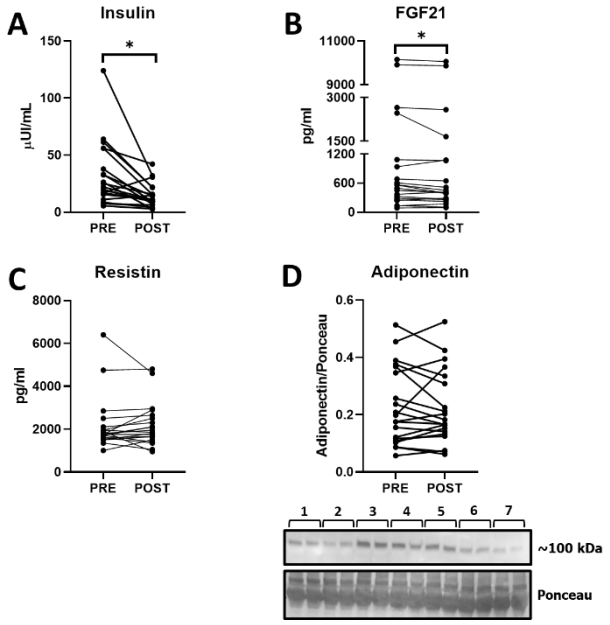

Figure 3. Acute effects of MICT on circulatory metabolic outcomes. Comparison between the pre- and post-exercise levels of A) Insulin, B) FGF21, C) resistin, and D) adiponectin, where a representative blot with seven samples (pre-left and post-right) are shown with its respective Ponceau S staining for normalization. *: $p<0.05$ with Wilcoxon's test.

Discussion

This study aimed to investigate the acute effects of one session of MICT on three circulatory metabolic markers, such as FGF21, resistin, and adiponectin of physically inactive young adults. Our main results indicate that this type of exercise decreased the plasmatic levels of FGF21 whereas it did not influence resistin and adiponectin. Complementarily, insulin was also decreased after one session of this type of training.

FGF21 is an attractive protein regarding its multiplicity of metabolic functions towards the improvement of metabolic health in a context of obesity and insulin resistance (Porflitt-Rodriguez et al., 2022). Therefore, recent studies have been focused on elucidate possible effects of exercise on this protein. In terms, of chronic effects, most of the literature agrees that exercise decreases the circulatory levels of FGF21 (Martinez-Huenchullan et al., 2019) which may be due to an increased sensitivity to the action of this polypeptide because of increases in tissue receptors (FGFR1 and FGFR2) and co-receptor (β-klotho) (Geng et al., 2019; Xiong, Chen, Liu, & Zhang, 2020). In terms of acute effects, the literature is less clear given that the few clinical studies known have described increases (Sabaratnam et al., 2018; Slusher et al., 2015) or absence of changes (Garneau et al., 2020; Sargeant et al., 2018) in the circulatory FGF21 levels. These differences compared to our study might reside, partially, in the perceived exercise intensity differences between studies. For instance, Slusher et al. prescribed one exercise session at 75% of VO_2 max in 24 healthy and sedentary participants and they reported a ~20% increase in circulatory FGF21. However, the insulinemia of those participants significantly increased after exercise (Slusher et al., 2015), which is a sign that, even when the theoretical intensity was in the moderate range, the physiological responses to exercise were closer to a high-intensity exercise, given that this type of effort evokes the release of catecholamines which transiently increases insulin levels (Vranic et al., 1984). Sabaratnam et al. also described similar increases of FGF21 in healthy and of persons with type 2 diabetes, however, insulin levels were nor reported (Sabaratnam et al., 2018). We believe that the decrease of FGF21 could reflect possible increases in peripheral sensitivity to FGF21, considering the effects that others have reported in animal studies, however, because of the nature of this study, we cannot corroborate this hypothesis.

Resistin has gained scientific interest in the last years given that it has been described as marker for cardiovascular death. For instance, after assessing more than 6600 adults and following them for 15 years, it was reported that participants with the higher quintile of circulatory resistin had higher risk of all-cause mortality, and an even higher risk of cardiovascular deaths (Del Cristo Rodriguez Perez et al., 2022). This is associated with the pro-inflammatory and insulin-resistant function of this protein (Rachwalik et al., 2021), therefore, strategies such as exercise has been assessed to see if they are able to modify this outcome. In terms of chronic effects of exercise, decreases of this protein have been described after 16 weeks of physical training in subjects with type 2 diabetes (Kadoglou et al., 2007), however, in our study one MICT session did not replicate those results. Our findings are in agreement with the study of Jamurtas et al. given that after one session of exercise at 65% of the VO_2 max of overweight males, circulatory levels of resistin were unchanged (Jamurtas et al., 2006), which make us hypothesize that possible the exercise volume was not enough to promote changes on this outcome. However, other reason might reside in the type of exercise used, given

that a group of men with overweight or obesity after one session of strength training decreased their plasmatic levels of resistin one hour after the session (Fortes et al., 2023). These findings raise two hypotheses, first, the type of exercise is relevant when investigating possible effects on resistin, and secondly, the time after the exercise session could also be relevant. Therefore, future studies should focus on these two factors when investigating the effects of exercise on circulatory resistin.

Adiponectin is one of the most abundant adipokines in the circulation, therefore and considering its metabolic functions as an anti-inflammatory cytokine, stimulant of glucose uptake and lipid oxidation (Martinez-Huenchullan et al., 2020), has been heavily investigated in conditions of health and disease. Previous studies have reported that in condition of obesity and physical inactivity, circulatory adiponectin levels are lower compared to healthy controls (Lim & Kim, 2020; Yang et al., 2002), whereas exercise training has the ability to increase them, at least partially (Kondo, Kobayashi, & Murakami, 2006). In our study, we observed that one MICT session did not change plasmatic adiponectin levels in physically inactive young adults, results that agree with others. For instance, one session at 65% of the VO_2 max in overweight males did not promote changes in circulatory levels of this protein (Jamurtas et al., 2006). However, others have seen increases of adiponectin but in slightly different conditions. That is how in physically inactive men with abdominal obesity after three sessions (performed during 1-week) at 50% and 75% of their VO_2max they reported significant increases of total adiponectin. Similar results were reported after one session of strength training in 12 young untrained males (Barroso et al., 2023), which suggests that the metabolic condition of the subject, along with the exercise type used are relevant for modifications in the circulatory levels of adiponectin. This is particularly relevant knowing that people with higher levels of obesity exhibited lower levels of adiponectin (Yang et al., 2002), which may suggest that in our sample, since the participants were young and with a fairly normal weight and body composition, their baseline levels were close to normal values, therefore no major effect was seen by exercise. This study has limitations, for instance, the absence of a control untrained group does not allow us to take out possible time effects between the before and after measurements. The indirect determination of target intensities through HRR ranges are not as precise as gas-exchange based prediction of exercise intensities, however, the utilization of these methods makes it closer to what is usually seen in a clinical setting. Since we were not able to study possible changes in metabolic active tissues, such as skeletal muscle, all hypotheses regarding acute metabolic adaptations (i.e. increases in sensitivity to the action of certain proteins) is merely speculative.

Conclusion

According to our results, one MICT session decreased the circulatory levels of FGF21, whereas it did not have major effects on the plasmatic levels of resistin and adiponectin. The specific mechanisms behind this different behavior are needed to be elucidated in future studies, along with the exploration of this exercise protocol in other populations with deeper metabolic dysfunctions and with other types of exercise, such as strength training.

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