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Plasma and salivary irisin response to moderate load/high volume resistance exercise in young, resistance-trained men

Luigi Marano,[1,2] Sara Missaglia,[1,2] Eleonora Martegani,[1,2] Andrea Bonanomi,[3] Chiara Tremolada,[4] Daniela Tavian,[1,2] Ferdinando Cereda[5]

[1]Laboratory of Cellular Biochemistry and Molecular Biology, CRIBENS, Catholic University of Sacred Heart, Milan, Italy; [2]Department of Psychology, Catholic University of Sacred Heart, Milan, Italy; [3]Department of Statistical Science, Catholic University of Sacred Heart, Milan, Italy; [4]Bachelor's degree in Exercise and Sport Sciences, Catholic University of Sacred Heart, Milan, Italy; [5]Department of Education, Catholic University of Sacred Heart, Milan, Italy.

Abstract

Irisin's response to Resistance Exercise (RE) remains unclear. We investigated plasma and salivary irisin levels following acute moderate load/high volume (ML/HV) RE and explored correlations with muscle damage markers. Eight healthy, resistance-trained young males (23.3±2.5 yrs) completed one ML/HV RE session (full-body, 30 sets to failure, 70% 1RM). Plasma/saliva irisin, plasma Creatine Kinase (CK), and Visual Analogue Scale (VAS) for muscle soreness were assessed at baseline, 15 min, 24h, and 48h post-exercise. Plasma irisin increased significantly by ~9% ($p=0.01$) and salivary irisin by ~4% ($p=0.02$) at 15 min post-exercise, returning towards baseline by 24h. A strong correlation ($rho=0.8$, $p=0.03$) existed between percentage changes in plasma and salivary irisin at 15 min. CK and VAS peaked at 24h ($p<0.001$; $p=0.02$ vs 48h, respectively), but showed no significant correlation with irisin changes. Acute ML/HV RE elicits a transient increase in plasma and salivary irisin. Saliva may be a useful non-invasive proxy for irisin changes post-RE. This acute irisin response appears independent of EIMD markers in this population. Findings require confirmation in larger studies.

Key Words: irisin; resistance exercise; saliva; acute exercise; creatine kinase; exercise-induced muscle damage; myokine.

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Physical Exercise (PE) induces a range of physiological adaptations that enhance both endurance and strength, contributing not only to improved physical performance but also to long-term health benefits.[1] Endurance training optimises cardiovascular efficiency, increases maximal oxygen uptake, and drives mitochondrial biogenesis,[2] thereby enhancing endurance performance and capacity.[3] Strength training, on the other hand, promotes muscle hypertrophy, neural adaptations, and increases in maximal force production, collectively augmenting physical power and functional capacity.[4] Together, these adaptations improve quality of life and reduce the risk of age-related diseases.[5-7] More and more articles about the effectiveness of exercise on performance and health are focusing on the study of molecular responses to exercise, with significant efforts directed at better studying and characterising the activity of exercise-induced signalling molecules termed "exerkines".[8] Exerkines encompass molecules of various biological origins and are released in response to both acute and chronic exercise, mediating their effects through endocrine, paracrine, and autocrine pathways to facilitate inter-organ communication. Exerkines are produced by multiple systems -including musculoskeletal, cardiovascular, nervous, and immune systems- and contribute to the complex, systemic effects of exercise.[9] This emerging field offers promising avenues for understanding the complex molecular landscape shaped by exercise. Among exerkines, irisin, discovered by Boström in 2012,[10] is released in response to PE, both in mice and humans. Indeed, physical activity activates the Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α) pathway, leading to increased expression of Fibronectin type III domain-containing protein 5 (FNDC5). The FNDC5 protein undergoes proteolytic cleavage in its extra cytoplasmatic part, resulting in the formation of irisin, which is subsequently released into the bloodstream. The first identified function of irisin was promoting the «browning» of White Adipose Tissue (WAT) into Brown

Adipose Tissue (BAT).[10] However, with the growing body of evidence regarding its effects, additional functions of irisin have been identified. In addition to its role in adipose tissue, recent research has shown that irisin also affects various physiological processes across multiple organs, including enhancing muscle metabolism, supporting bone health, protecting cardiovascular function, improving liver metabolism, and offering neuroprotective effects.[11] A significant number of articles have already been published on the acute irisin response to exercise. However, the existing body of evidence is highly heterogeneous, particularly in terms of sampling timing (ranging from immediately after exercise to 24 hours post-exercise,[12-14] biological sample employed for analysis (saliva,[15] plasma,[16] serum,[14] muscle biopsy[17]), participant health and fitness status[18] and last training type and training variables used.[19] While the evidence regarding Aerobic Exercise (AE) and irisin production is relatively clear, the results from Resistance Exercise (RE) are less consistent. This research gap is due to both a smaller number of studies on the acute irisin response to RE compared to AE, and the fact that conclusions from the available studies are not unidirectional. In fact, while three studies report a clear increase in circulating irisin levels,[20,21,22] others suggests no changes.[17,23] Therefore, further investigation is needed to explore the irisin response to RE with different variables in healthy population. To address this gap, we aimed to evaluate whether moderate load/high volume RE could lead to increased plasma and salivary levels of irisin, by also considering exercise-induced muscle damages (EIMD).

Materials and Methods

Participants

Eight young healthy male participants (age, 23.3±2.5 years; BMI, 24.5±2.4 kg/m^2; RT (resistance training) experience 4.9±2.5 years) were recruited. To take part in this study, subjects must have to meet the following inclusion criteria: aged less than 39 years, more than 18, have a body mass index (BMI): ≤ 25 kg/m^2, be at least moderately active, have an experience with RT of at least six months of regular practice (minimum 2 sessions per week). Only male participants were recruited to minimise potential variability associated with hormonal fluctuations inherent in the female menstrual cycle, which could influence metabolic and irisin responses. Experienced individuals were chosen to ensure proficiency in resistance exercise techniques, thereby reducing the risk of injury and variability in physiological responses due to learning effects. Exclusion criteria for the study, included history of neurological disorders, musculoskeletal impairments, motor restrictions, pharmacotherapy, recent myocardial infarction, severe cardiac arrhythmia, unstable angina, hypertension, and metabolic disease. None of them were current smokers.

Procedures

The experimental protocol used in this study is presented in Figure 1.

For each participant a period composed of 2 weeks was used to ensure them enough balance between training and recovery within sessions. First week experimental proce-

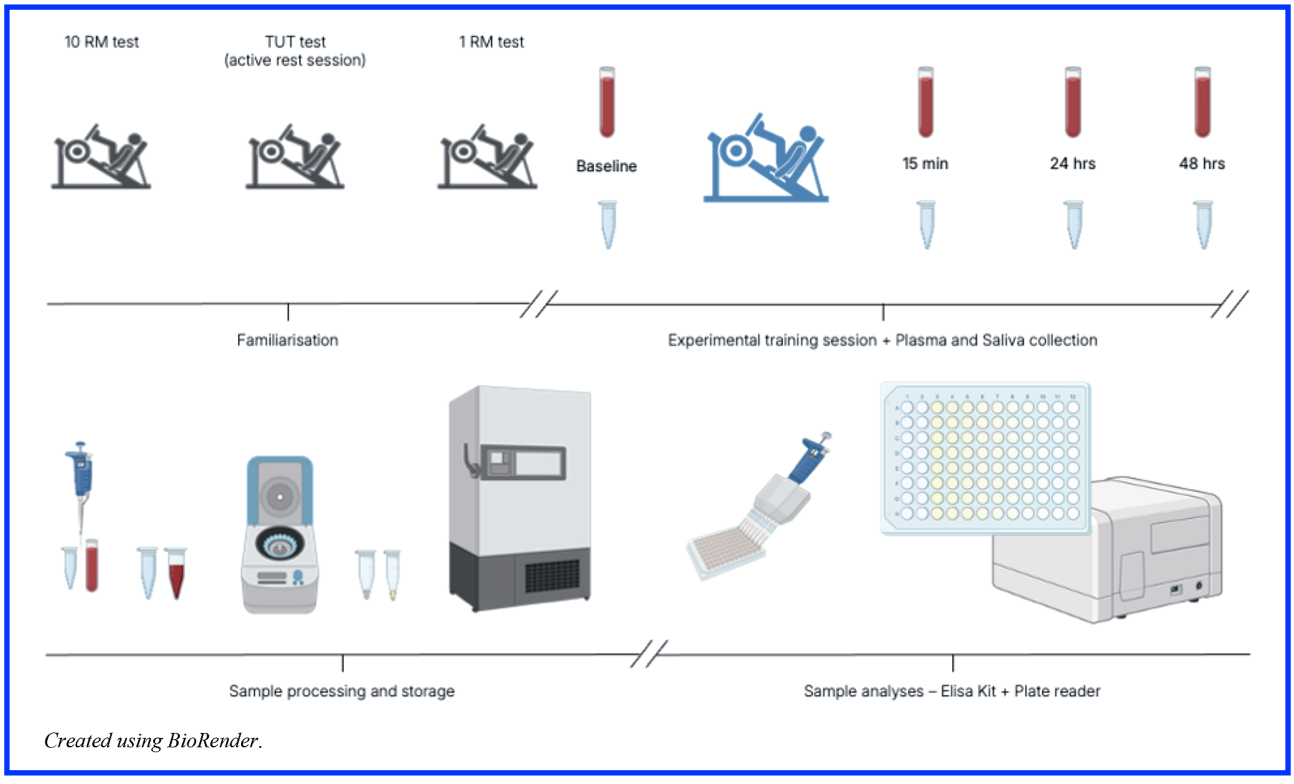


Figure 1. *Graphical representation of the procedures.*

dures consisted of three sessions used with the twofold purpose of familiarisation and load determination. These three sessions were organised as follows: ten repetition maximum test session (10-RM), a Time Under Tension familiarization session (TUT) and one repetition maximum test session (1-RM). Between each testing session participants stayed at rest for at least 24h. Thereafter in week 2 the Moderate Load/High Volume (ML/HV) Experimental Testing Session (ETS) was performed. Each session was conducted in a private gym with a controlled environment with a humidity level below 60% and a temperature range of 18°C to 22°C. During this period, participants were instructed to abstain from any form of exercise, that range from moderate to vigorous activity, from at least 48 hours before the experimental session. Before each session, both test and experimental, we advise the participants to have a consistent sleep routine, not consume alcoholic beverages and caffeinated product or other stimulants. All assessments were conducted between 09:00 a.m. and 1:00 p.m. to minimize potential bias from circadian rhythms. During familiarisation sessions anthropometric parameters were analysed, including Body Mass (BM) and height measurements, and BMI calculation. BM and height were measured using a mechanical scale (Seca 762, Hamburg, Germany) and a stadiometer (Seca 217, Hamburg, Germany), respectively, following procedures previously described.[24] The analysis of body composition and hydration status was assessed using Bioelectrical Impedance Analysis (BIA) (BIA 101 BIVA® PRO IPS, ItaAkern s.r.l, Pisa - Italy). For study the molecular response to exercise, this study underwent the sampling of venous blood and saliva at 4 time points, for experimental testing session: pre-exercise (baseline), 15-minute (15 min), 24 hours (24 hrs.) and 48 hours (48 hrs.) post exercise. At 24 hrs. and 48 hrs., VAS scale (0-10 arbitrary units, A/U, derived from a 100mm line) was administered to assess the individual perception of muscle soreness after exercise.

Exercise test and exercise program

Test session (10-RM and 1-RM) were conducted following the procedures suggested by the American College of Sports Medicine (ACSM).[24] Between these two load-determination sessions (10-RM and 1-RM), we conducted a separate, lower-intensity, lower-volume session specifically to familiarize participants with the prescribed 5-1-2-1 time under tension (TUT) cadence to be used during the experimental testing session, ensuring proper execution speed and minimizing potential effects from coordination factors during the ETS. We opted for isotonic gym machines to minimize potential effects from coordination factors. The protocol provided one exercise for each larger muscle groups and were administered with this sequence for all sessions, both test and experimental:

90° Leg Press (LP), Prone Lat Machine Pulldown, Prone Lying Leg Curl, Seated Chest Press, Leg Extension, Seated Shoulder Press, Standing Cable Triceps Extension, Standing Biceps Dumbbells Curl. These exercises were selected to recreate a total body split routine largely used between gym members.

The total number of sets during ETS was 30, with 4 sets for lower and upper body exercises (*i.e.* the larger muscles) and 3 sets for arms exercises (biceps and triceps).

For ETS the load used correspond to the 70% of the individual 1-RM, tested during familiarization session. This load was used for the purpose to induce either a good MechT (mechanical tension, the force experienced by muscle fibres), and as it is in the continuum spectrum of recommended load for inducing adaptation to resistance exercise such as muscle strength, hypertrophy and local endurance.[25] To have also a high MetS (metabolic stress, the accumulation of metabolites) the 30 sets, were carried out to muscular failure as well with a TUT of 5-1-2-1, emphasising the eccentric phase of the movements.

Rest intervals between sets were standardized at 90 seconds for all exercises to maintain consistent exercise density (*i.e.*, work-to-rest ratio) and metabolic stress.

The exercise session consisted of a total of 220 repetitions, with a standard deviation of 31.49. The corresponding volume load, calculated as weight × repetitions × sets, was 121704.8±29592.33.

A trained researcher supervised each workout session carefully so that exercise prescriptions were correctly administered during resistance exercise session (RES, e.g., number of repetitions, rest and movement' speed). Compliance with the study was 100% of the programmed sessions.

Biological sample treatment and biochemical analyses

Blood samples were collected using a vacutainer system and immediately centrifuged at 11,000 rpm for 10 minutes. The plasma was then separated and stored at -80°C until analysis. For saliva samples, participants rinsed their mouths thoroughly five times without swallowing before filling a 1.5 ml Eppendorf tube with saliva. Saliva samples were centrifuged for 4 minutes and stored at -80°C until analysis. The levels of plasmatic and salivary irisin were detected by an Enzyme-Linked Immunosorbent Assay kit (ELISA) (Irisin kit: Cat. EK-067-29 Phoenix Pharmaceuticals) using the Victor Nivo multimode plate reader (PerkinElmer), following the manufacturer's instructions. All samples were analysed in duplicate. The intra- and inter-assay Coefficients of Variation (CVs) for plasma and salivary irisin, as determined in our laboratory following manufacturer's instructions, were <10% and <15%, respectively. All samples conformed to the parameters of the standard curve provided by manufacturer instruction. Creatine Kinase (CK) levels were measured using a Chemiluminescent Immunoassay method (CLIA, Siemens Healthcare Diagnostics, USA).

Statistical analyses

JASP (Version 0.19.1, JASP Team 2024, Netherlands) was used to analyse the data. Results were considered significant when $p<0.05$. Data distribution was assessed using Shapiro-Wilk test. Given the very limited sample size (N=8), even if data were normally distributed, we opted to use nonparametric tests to enhance analytical robustness. Differences in irisin and CK across all the time points, were assessed using Friedman test. Spearman correlation analysis was conducted to test the correlations between percentage

changes in plasma and salivary irisin across time points, considering correlation strength as follows: 0.00–0.10 negligible; 0.10–0.39 weak; 0.40–0.69 moderate; 0.70–0.89 strong; and 0.90–1.00 very strong correlation.

Results

Participants descriptive characteristics

In Table 1, the descriptive characteristics of participants are reported.
According to ACSM's 2021 ratio between BM in kg and the 1RM of LP percentile (BM/1RM LP) participants could be defined as well trained, as their percentile classifies them as "above average" for individuals of their age. Indeed, as also shown in the table, participants had a great experience in RT practice.

Plasma and salivary irisin values

This study primarily aimed to evaluate whether ML/HV RES induce an increase in plasma and salivary irisin levels. A significant rise in plasma irisin concentration was observed between baseline and 15 min (Figure 2a). Specifically, plasma irisin levels increased from 10.3±1.04 to 11.1±1.5 ng/ml, (mean increase + 9%; p = 0.01). Following this acute elevation, irisin levels decreased to 10.6±1.06 ng/ml (p = 0.05) (24 h) and then to 10.5±1.03 ng/ml (48 h). A significant increase in salivary irisin levels has been found too. Interestingly salivary irisin increased from 0.053±0.007 ng/ml to 0.055±0.008 ng/ml (mean increase: + 4%; p = 0.02) from baseline to 15 min post-exercise (Figure 2b).

Correlation between plasma and salivary percentage irisin changes

The secondary aim of this study was to determine whether salivary and plasma irisin exhibit similar responses to the same exercise stimulus. To address this, a correlation analysis was conducted on the percentage changes in salivary and plasma irisin from baseline to 15 minutes after exercise. A significant correlation was observed between baseline and 15 min, where plasma and salivary irisin demonstrated a similar trend. Spearman's rank correlation coefficient confirmed a significant correlation (ρ = 0.8; p = 0.03). These findings are reported in Figure 2c.

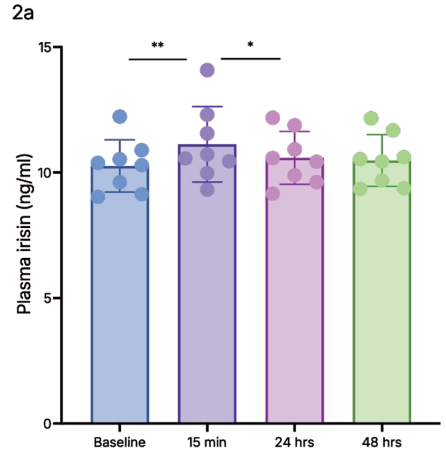
Plasma creatine kinase levels and visual analogue scale value

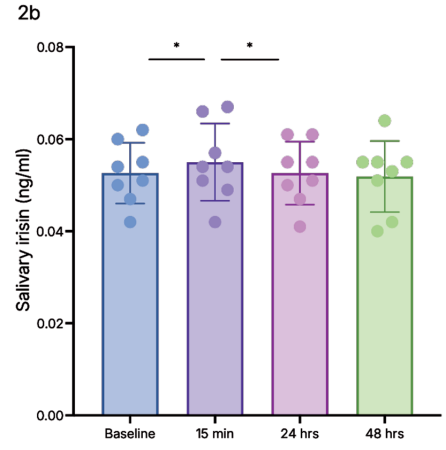
Finally, this study aimed to assess the amount of EIMD and delayed onset muscle soreness (DOMS), as evaluated through plasma CK levels (Figure 3a) and Visual Analogue Scale (VAS) scores (Figure 3b), respectively. As expected CK levels exhibited significant changes. CK concentrations increased from 128.5±26.31 U/L to 279.8±112.71 U/L, reaching a peak 24 hour post-exercise,

Table 1. *Participants descriptive characteristics.*

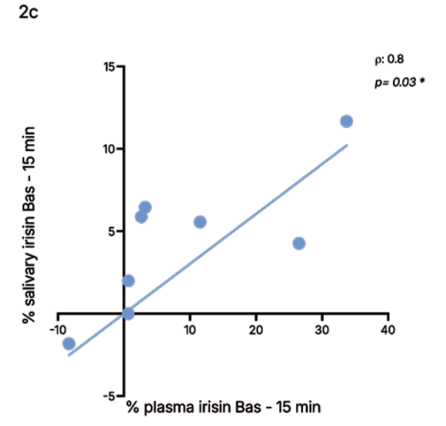
Variables	Mean	Standard deviation
n	8	/
Age (yrs)	23.3	2.5
Height (cm)	176.2	8.5
Body mass (kg)	76.1	8.6
BMI kg/m^2	24.5	2.4
Muscle mass (kg)	45.4	4.6
% Muscle mass	59.8	3.5
% FM	17.1	4.3
% FFM	83.0	4.3
Fat mass (kg)	13.1	4.3
Resistance training experience (yrs)	4.9	2.5
Ratio BM/1RM LP	2.8	0.33
ACSM's ratio BM/1RM LP percentile	90.0	0.0

Descriptive values are reported as mean and standard deviation. BM, body mass; BMI, body mass index; FFM, fat free mass; FM, fat mass; 1RM, one repetition maximum; LP, leg press.





a-b, Friedman test for differences across time points; levels of significance: *p<0.05; **p<0.01.



c, Spearman's ρ rank correlation coefficient; levels of significance: *p<0.05. (*Created using GraphPad*).

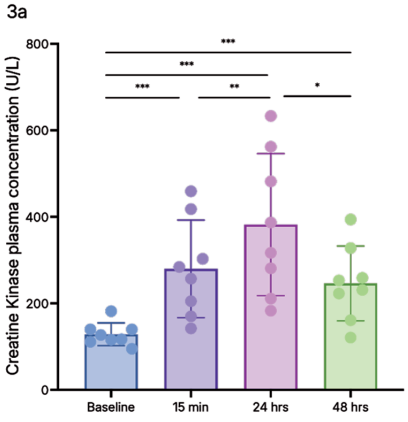
Figure 2. *Differences in plasma (a) and salivary (b) irisin levels in response to ETS and Correlation between percentage changes in plasma and salivary irisin levels between baseline and 15 min (c).*

382.0±164.18 U/L, before declining to 246.3±86.56 U/L at 48 hours. The Friedman test revealed significant differences across the following time points: baseline to 15 min - 24 hours and 48 hours post-exercise ($p < 0.001$); 15 min to 24 hours ($p = 0.01$); and 24 hours to 48 hours post-exercise ($p = 0.03$).

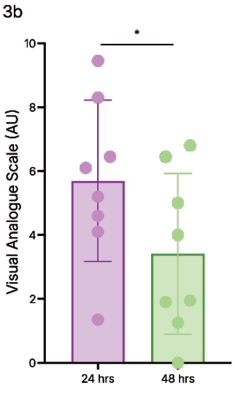
Consistent with the CK data, VAS scores showed significant differences in response to exercise, highlighting the impact of EIMD on post-exercise pain perception.

Wilcoxon signed-rank test indicated a significant reduction in VAS scores from 24 hours (5.7±2.52 A/U) to 48 hours post-exercise (3.4±2.52 A/U, $p = 0.02$).

Furthermore, no significant correlation was found between the percentage change in plasma or salivary irisin at 15 minutes post-exercise and the peak changes in CK or VAS scores (data not shown, $p > 0.05$ for all correlations).



a, Friedman test for differences across time points; levels of significance: *p<0.05; **p<0.01; ***p<0.001.



b, Wilcoxon signed rank test for differences across time points; levels of significance: *p<0.05. (*Created using GraphPad*).

Figure 3. *Differences in plasma Creatine Kinase concentration (3a) and Visual Analogue Scale values (3b) in response to ETS.*

Discussion

This investigation sought to elucidate the acute plasma and salivary irisin response to a demanding Moderate Load/High Volume (ML/HV) resistance exercise (RE) protocol in resistance-trained young men, and to explore potential associations with markers of Exercise-Induced Muscle Damage (EIMD). Our principal finding is a significant, albeit transient, increase in both plasma (~9%) and salivary (~4%) irisin concentrations 15 minutes post-exercise. This acute elevation suggests that this specific type of RE, characterised by substantial Mechanical Tension (MechT) and Metabolic Stress (MetS) induced by exercise to failure across multiple sets with controlled tempo, serves as an effective stimulus for irisin release. While direct comparisons with endurance exercise are complex due to varying protocols and irisin responses reported in the literature, this acute response is noteworthy within the context of RT-induced irisin changes.

The observed immediate post-exercise rise in irisin aligns with some previous RE studies reporting increases shortly after exercise cessation,[20,21,22] yet contrasts with others, notably He *et al*. (2018)[23] and Pekkala *et al*. (2013),[17] who found no significant change at 15 minutes post-exercise following a lower-volume, isolated knee extension protocol. This discrepancy likely underscores the importance of the exercise stimulus characteristics. Our ML/HV protocol involved a substantially greater total work volume, engaged significantly more muscle mass via a full-body routine, and purposefully induced high metabolic stress through sets to failure with controlled eccentric emphasis (5-1-2-1 tempo). These factors may have contributed to the observed irisin surge, possibly by triggering cleavage of pre-existing FNDC5 protein located on the muscle cell membrane. This rapid, post-translational mechanism could explain the quick appearance of irisin in circulation shortly after exercise. The return towards baseline levels by 24 hours suggests this irisin surge is a feature of the immediate post-exercise recovery phase, rather than a sustained response.

A key secondary finding is the strong positive correlation (rho=0.8) between the percentage changes in plasma and salivary irisin at the 15-minute post-exercise time point. This indicates that, at least for assessing acute, exercise-induced fluctuations, saliva may serve as a valuable, non-invasive proxy for plasma irisin. While baseline and absolute concentrations differ between the fluids, the concordance in their relative response to the RE stimulus is noteworthy. This finding warrants further investigation, as salivary sampling offers considerable logistical advantages for future studies examining acute exercise responses, although caution is needed as saliva may reflect punctual changes rather than an integrated systemic level over time.[15]

We also investigated the response of EIMD markers, namely plasma Creatine Kinase (CK) and perceived muscle soreness (VAS). As anticipated, both CK and VAS demonstrated significant increases, peaking 24 hours post-exercise, confirming the efficacy of the ML/HV protocol in inducing muscle damage and delayed onset muscle soreness[26].

While direct molecular mechanisms were not assessed in this study, the findings prompt consideration of the cellular events triggered by ML/HV RE. In particular it is reasonable to speculate that the acute irisin release is primarily driven by rapid post-translational modifications, specifically the cleavage of membrane-bound FNDC5, rather than new protein synthesis. Furthermore, the systemic hormonal milieu (e.g., acute changes in catecholamines, growth hormone, or testosterone) induced by such demanding exercise could potentially modulate FNDC5 expression or irisin processing, representing an area for future research integrating hormonal and myokine measurements.

Several limitations must be acknowledged. The small sample size restricts statistical power and the generalisability of our findings. The study population consisted solely of young, healthy, resistance-trained men, precluding extrapolation to females, older adults, untrained individuals, or clinical populations. Additionally, the trained status of our participants might have attenuated the EIMD response and potentially influenced the magnitude of irisin release compared to untrained individuals, a factor that warrants consideration in future studies. The focus on a single, specific ML/HV RE protocol means results may not apply to other RE modalities differing in intensity, volume, or contraction type.

Conclusions

In conclusion, this study provides preliminary evidence that an acute bout of high-volume, moderate-load resistance exercise performed to failure elicits a significant, transient increase in both plasma and salivary irisin concentrations 15 minutes post-exercise in trained young men. Saliva shows promise as a non-invasive proxy for assessing these acute changes. Importantly, this early irisin response appears temporally and mechanistically distinct from the subsequent development of EIMD markers like CK and VAS. These findings highlight the sensitivity of irisin to specific RE stimuli characterised by high metabolic stress and volume, but suggest its acute release is not directly coupled to the magnitude of delayed muscle damage in this context. Further research employing larger sample sizes, diverse populations, and potentially muscle biopsies is required to confirm these observations and fully elucidate the molecular mechanisms governing irisin regulation in response to different resistance exercise paradigms.

List of abbreviations

1-RM, One Repetition Maximum
10-RM, Ten Repetition Maximum
A/U, Arbitrary Units
ACSM, American College of Sports Medicine
AE, Aerobic exercise
BAT, Brown Adipose Tissue
BIA, Bioelectrical Impedance Analysis
BM, Body Mass
BMI, Body Mass Index
CERPS, Ethics Commission of the Department of Psychology

CK, Creatine Kinase
CLIA, Chemiluminescent Immunoassay
DOMS, Delayed Onset Muscle Soreness
EIMD, Exercise-Induced Muscle Damage
ELISA, Enzyme-Linked Immunosorbent Assay
ETS, Experimental testing session
FFM, Fat-Free Mass
FM, Fat Mass
FNDC5, Fibronectin Type III Domain-Containing Protein 5
LP, Leg Press
MechT, Mechanical tension
MetS, Metabolic stress
ML/HV, moderate load/high volume
PE, Physical exercise
PGC1-α, Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha
REP, Repetition
RIR, Repetitions in Reserve
RT, Resistance training
RE, Resistance exercise
RES, Resistance exercise session
TUT, Time Under Tension
VAS, Visual Analogue Scale
VL, Volume Load
WAT, White adipose tissue

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the department of Psychology at the Catholic University of the Sacred Heart of Milan (CERPS) (protocol code n: 36/24).

Author contributions

Conceptualization, DT and FC; methodology, LM and FC; writing—original draft preparation, LM; writing—review and editing, LM, DT, SM and FC; designed and supervised the research, FC and DT; administered exercise, LM, CT and FC; molecular investigation, SM, EM and DT; statistical analysis, AB and LM; exercise protocol results interpretation, LM and FC. All authors have read and agreed to the published version of the manuscript.

Informed consent statement

All participants in this study signed a written informed consent form for participation and anonymized information publication.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Corresponding author

Ferdinando Cereda, Catholic University of Sacred Heart, Department of Education, Largo Gemelli 1, 20123 Milan, Italy.
Tel.: +390272342209.
ORCID ID: 0000-0002-3120-0684
E-mail: ferdinando.cereda@unicatt.it.

Co-authors

Luigi Marano
ORCID ID: 0000-0002-9833-8055
E-mail: luigi.marano@unicatt.it

Sara Missaglia
ORCID ID: 0000-0001-6551-6698
E-mail: sara.missaglia@unicatt.it

Eleonora Martegani
ORCID ID: 0000-0002-8103-686X
E-mail: eleonora.martegani@unicatt.it

Andrea Bonanomi
ORCID ID: 0000-0003-2857-1430
E-mail: andrea.bonanomi@unicatt.it

Chiara Tremolada
ORCID ID: 0009-0004-9662-7541
E-mail: chiara.tremolada03@icatt.it

Daniela Tavian
ORCID ID: 0000-0003-3333-0068
E-mail: daniela.tavian@unicatt.it

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