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Research Article

Mental- and Temporal-Demand NASA-Task Load Index Scores Correlate with Decreases in Irisin Serum Levels in Healthy Individuals Subjected to 10-Day Bed Rest

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Background

Bed rest (BR) is a widely used analogue of space flight that aims to replicate microgravity conditions, such as immobilization and a lack of sensorimotor stimuli. In a previous BR study, we evaluated the changes in irisin serum levels, a myokine produced mainly by skeletal muscle that exerts pleiotropic effects on several organs, including the brain.

Objective

Here, we evaluated whether the decline in circulating irisin concentrations during 10 days of horizontal BR correlated with the National Aeronautics and Space Administration Task Load Index (NASA-TLX).

Methods

NASA-TLX was obtained from young healthy participants at the end of the BR protocol. It is a self-report measure of task load that includes six subscales: mental demand, physical demand, temporal demand, performance, effort, and frustration. Each subscale score was correlated with the decline in serum irisin levels measured while participants were supine. Irisin decline was calculated as the difference between levels on the first day of BR (BR0) and the last day (BR9).

Results

Our results show a significant positive correlation between irisin decline and both mental demand and temporal demand, whereas correlations with the remaining subscales showed a positive association with irisin decline but did not reach statistical significance.

Conclusion

These findings suggest that reduced irisin levels are associated with increased perceived mental demand and time pressure (temporal demand) during BR. Because temporal demand can exacerbate high mental activity in a state of cognitive overload, maintaining

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higher circulating irisin levels could represent an effective countermeasure to improve the cognitive performance of participants during future BR studies and may help astronauts manage mental and temporal pressure during space missions.

1. INTRODUCTION

Bed rest (BR) is a widely accepted spaceflight analogue used by the scientific community to study adaptations that occur in a simulated microgravity environment.[1] Through BR protocols, it is possible to reproduce astronaut physiology in a valid terrestrial model and, at the same time, investigate the mechanisms underlying morphological and functional changes resulting from prolonged immobilization, such as those that occur during hospitalization or in specific diseases that force bed confinement.[2,3] A considerable number of studies have investigated the effects of BR on bone and muscle mass, the immune system, hormonal regulation, and the cardiovascular system.[4-7] Interestingly, it has recently been observed that the loss of muscle function after BR is typically greater than the loss of muscle mass,[8,9] likely due to BR-induced effects on central nervous system physiological processes.[10,11] BR-induced reduction of sensory stimulation has also been shown to cause cognitive and emotional changes in the autonomic nervous system.[12] Specifically, astronauts permanently on the International Space Station are prone to negative emotions such as anxiety and depression due to weightlessness, confined space, and altered circadian rhythm.[13]

We previously performed a 10-day-BR study involving 10 young healthy participants and observed a decrease in serum irisin levels. Irisin is a myokine produced primarily by skeletal muscle. It is released into the circulation and exerts hormone-like effects on several distant target organs, including the brain.[6]

Circulating irisin crosses the blood-brain barrier[14] and stimulates the synthesis of its precursor, the fibronectin type III domain-containing protein 5, in the hippocampus and prefrontal cortex.[15] This creates a forward loop that amplifies its local concentration in the brain. Numerous studies have shown that irisin improves brain function by increasing the expression of neuroprotective genes, including the brain-derived neurotrophic factor (*BDNF*),[16] and by modulating cognitive function, learning, mood, and memory.[17]

Previous studies have also demonstrated the antidepressant properties of irisin in rats, following either systemic administration[18] or intracerebroventricularly injection.[19] Moreover, we have reported potential antidepressant effects of short- and long-term systemic irisin administration in murine models.[15,20]

The present work aimed to evaluate whether the decline in circulating irisin concentrations caused by immobility and confinement during a 10-day BR correlates with National Aeronautics and Space Administration Task Load Index (NASA-TLX) scores assessed at the end of the BR protocol. The NASA-TLX is a workload assessment tool comprising six subscales: mental demand, physical demand, temporal demand, performance, effort, and frustration.[21] NASA-TLX allows workload measurements to be collected immediately after completion of the BR protocol, when the bedridden subject's memory of the BR experience remains fresh. The six subscales are defined as follows:

(i) Mental demand: how much thinking, deciding, or calculating was required to perform the task.
(ii) Physical demand: the amount and intensity of physical effort required to complete the task.
(iii) Temporal demand: the amount of time required to complete the task.
(iv) Performance: the level of success in completing the task.
(v) Effort: how hard the participant had to work to maintain their level of performance?
(vi) Frustration: how insecure, discouraged, confident, or satisfied the participant felt during the task.

Each subscale score was correlated with the decline in serum irisin levels measured while participants were supine, therefore calculated as the difference between the first day of BR (BR0) and the last day (BR9). The BR0–BR9 delta (Δ) was selected to evaluate variations occurring exclusively during the strict bed rest phase, close in time to the NASA-TLX assessment performed at BR9. Baseline irisin values measured two days prior to BR were not considered, as they could have been influenced by pre-experimental lifestyle factors (e.g., habitual physical activity, circadian fluctuations, or pre-hospitalization conditions).

2. MATERIALS AND METHODS

2.1. PARTICIPANTS AND BED REST PROTOCOL

The study was conducted in the Izola General Hospital (Izola, Slovenia, EU). Of the 93 applications received from young males, only 16 passed the medical examination. Exclusion criteria included medication or drug intake, smokers, history of deep thrombosis with d-dimer values >500 µg/L, blood clotting defects, acute and chronic neuromuscular, cardiovascular, bone, and metabolic diseases, epilepsy or psychiatric disorders; ferromagnetic installations, and competitive sports activity.

At the end of the pre-enrollment process, 10 male individuals (mean age 23 ± 5 years; body mass index [BMI]: 23.5 ± 2.5 kg/m^2) were recruited and underwent 10 days of horizontal BR.

All study participants were housed in standard air-conditioned hospital rooms at Izola General Hospital under constant medical supervision and care. They were provided a controlled diet with three meals per day (macronutrient composition: 60% carbohydrate, 25% fat, and 15% protein). Throughout the BR protocol, participants remained supine while performing routine activities. Each subject was also monitored 2 days before and 2 days after the 10-day BR protocol.

The study was conducted in accordance with the Declaration of Helsinki and approved by the National Ethics Committee of the Slovenian Ministry of Health (reference number: 0120-304/2019/9). This study is part of the Italian Space Agency (ASI) project "MARS-PRE Bed Rest SBI 2019."

2.2. BIOCHEMICAL MEASUREMENTS

Throughout the BR protocol, blood samples were taken from each subject at 7 a.m. to avoid possible physiological fluctuations unrelated to BR status, since a previous study reported lower serum irisin levels in the morning compared

with the evening.[22] Blood was collected into serum separator tubes and left at room temperature for 30 min. After centrifugation for 15 min at 1000 × g, serum samples were aliquoted and stored at −80 °C until analysis.

Serum irisin concentrations in samples diluted 1:4 were measured using a competitive ELISA kit (Adipogen, Switzerland) with an inter-assay coefficient of variation ⩽6.9%, a measurement range of 0.001–5 µg/ml, and a sensitivity of 0.001 µg/ml. Serum myostatin was measured using a quantitative enzyme immunoassay (Cusabio, China) with a detection range of 0.625–20 ng/ml. Haptoglobin serum levels were detected using a quantitative sandwich enzyme immunoassay (R&D Systems, United States) with a minimum detectable range of 0.031–529 ng/ml. Colorimetric reaction was measured using a spectrophotometer (Eon, BioTek, United States).

2.3. WORKLOAD ASSESSMENT

To assess subjective workload during the horizontal BR period, participants completed the NASA-TLX immediately after BR period.[21] NASA-TLX is a rating scale developed by the Human Performance Group at NASA's Ames Research Center to evaluate the physical and mental load of tasks or activities in different domains, such as healthcare and aviation.[21] It is a multidimensional tool comprising six subscales categorized by domain (mental demand, physical demand, temporal demand, performance, effort, and frustration), and responses in the form of 20-point Likert scales ranging from very low (1) to very high (20). The questionnaire includes a description of the rating scales, which subjects read before completing the assessment.

2.4. STATISTICAL ANALYSIS

All data were analyzed using GraphPad Prism statistical software version 9.0 (GraphPad Software, USA). Because irisin levels decreased in 8 out of 10 participants at the end of the BR protocol, the change in serum irisin concentration was calculated as the difference between BR0 and BR9, resulting in predominantly positive Δ values. Similarly, because myostatin and haptoglobin serum levels increased to BR9 in 7 of 8 subjects, the majority of Δ myostatin and haptoglobin values were negative. The Shapiro–Wilk normality test was used to determine the normal distribution of the dataset. Analysis was performed using Pearson's or Spearman's correlation coefficient tests. Multivariate linear regression was used to investigate the determinants of each NASA-TLX domain (mental demand, physical demand, temporal demand, performance, effort, and frustration. For linear regression, r and p values are indicated in the graph. A p-value < 0.05 was considered statistically significant.

2.5. ETHICAL CONSIDERATIONS

This study was approved by the National Ethics Committee of the Slovenian Ministry of Health (reference number: 0120-304/2019/9) and conducted in accordance with the established criteria by the Declaration of Helsinki. The study is part of the Italian Space Agency (ASI), "MARS-PRE Bed Rest SBI 2019" project.

3. RESULTS

3.1. THE DECLINE IN SERUM IRISIN LEVELS CORRELATES WITH MENTAL AND TEMPORAL DEMAND SCORES OF THE NASA TASK LOAD INDEX

We firstly measured the variation in serum irisin levels (Δ), calculated as BR0–BR9 (Table 1). The mean irisin concentration was 11.34 ± 1.29 µg /ml at BR0 and 10.10 ± 1.38 µg /ml at BR9. Table 1 summarizes Δ irisin while subjects were in the supine position. Notably, Δ irisin was negative in two subjects (S2 and S10), indicating increased irisin levels, whereas 8 of 10 subjects exhibited a decline in irisin concentration (positive Δ irisin). To estimate the possible involvement of the irisin decline in BR-related cognitive effects, we correlated the decrease in circulating irisin concentrations with NASA-TLX scores obtained at the end of the BR protocol. As shown in Figure 1, a significant positive correlation was observed between irisin decline and both mental demand (r = 0.6515; p = 0.041; Figure 1A) and temporal demand (r = 0.8200; p = 0.003; Figure 1B). No significant correlations were observed between irisin decline and physical demand (r = 0.1392; p = 0.701; Figure 1C), performance (r = 0.3701; p = 0.292; Figure 1D), effort (r = 0.1898; p = 0.599; Figure 1E), or frustration (r = 0.4162; p = 0.231; Figure 1F). However, it is worth noting that all NASA-TLX domains showed a positive trend of association with irisin decline. In addition, because we previously observed increased serum levels of other skeletal muscle-derived molecules at BR9, including myostatin and haptoglobin,[6] we evaluated whether their Δ variation with BR0 correlated with any NASA-TLX domain. Nevertheless, no significant linear correlations were identified for either myostatin or haptoglobin (data not shown).

Table 1. Change in serum irisin levels from BR0 to BR9

Subjects	Irisin serum levels (ug/ml)		Delta (Δ) irisin (BR0-BR9)
	preBR (BR0)	postBR (BR9)	
S1	7.76	7.0284	0.7316
S2	15.064	15.904	−0.84
S3	9.962	8.4164	1.5456
S4	15.904	15.428	0.476
S5	13.442	7.9176	5.5244
S6	15.712	12.44	3.272
S7	8.8084	8.2796	0.5288
S8	3.31	3.2736	0.0364
S9	10.0052	6.8928	3.1124
S10	13.432	15.372	−1.94

Notably, the multivariate linear regression model revealed that Δ irisin was the only significant predictor of temporal demand (β = 1.254; p = 0.036) among the independent variables included in the model (Table 2). In contrast, physical demand was significantly predicted by Δ myostatin (β = −3.717; p = 0.012) and Δ haptoglobin (β = 5.591; p = 0.040).

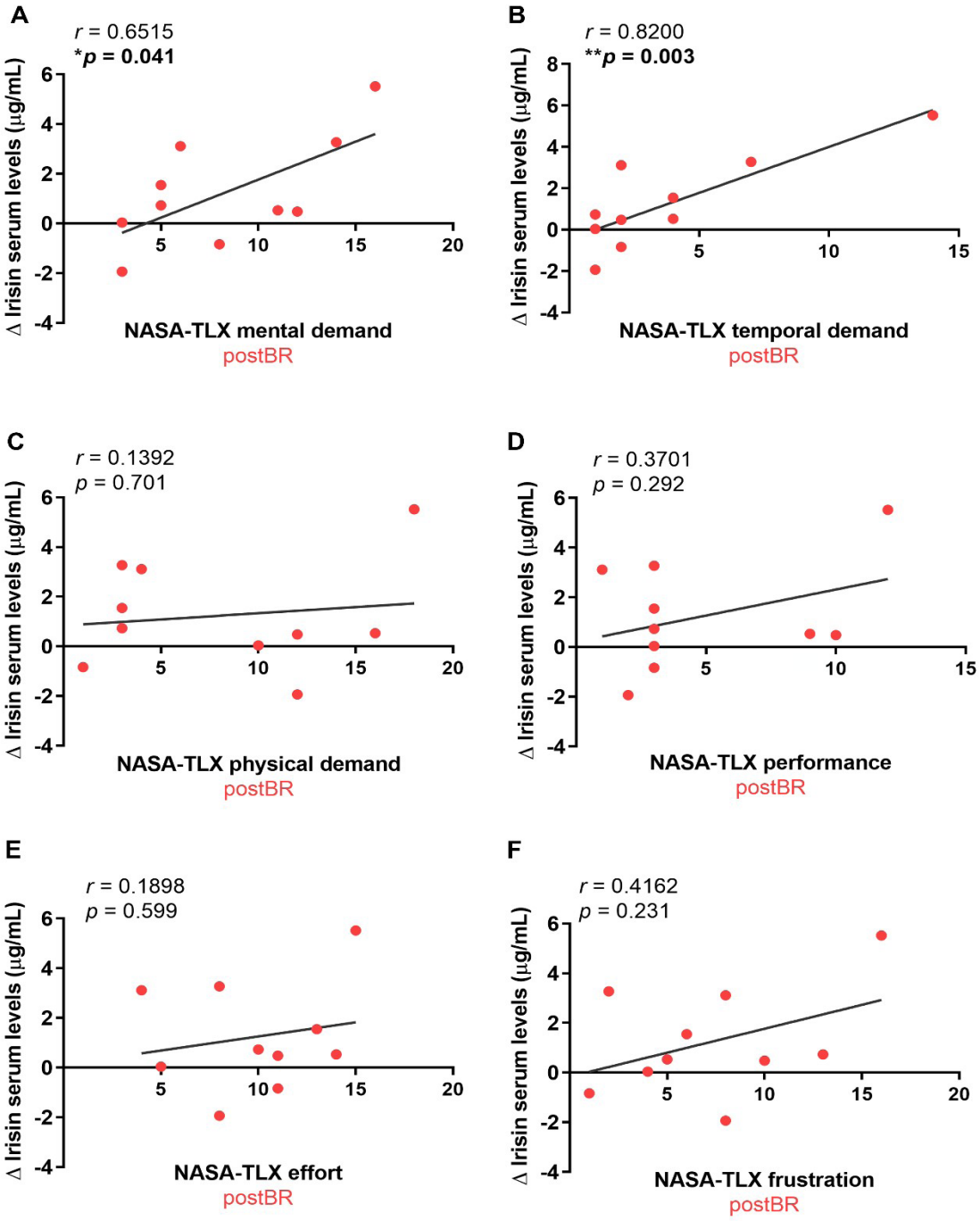

Figure 1. Correlations between changes in serum irisin levels and NASA Task Load Index (NASA-TLX) scores. Correlations between variations in serum irisin levels and (A) mental demand, (B) temporal demand, (C) physical demand, (D) performance, (E) effort, and (F) frustration subscale scores of the NASA-TLX (*N* = 10).
Note: * denotes statistical significant at $p < 0.05$.

4. DISCUSSION

The results of this unique investigation through the experimental model of 10-day BR show that perceived mental and temporal demand, assessed by the NASA-TLX test, are significantly correlated with decreases in circulating irisin. The NASA-TLX test enabled the assessment of the perceived workload immediately after completion of the BR protocol in 10 participants and allowed exploration of its possible relationships with irisin, a novel serum marker of cognitive function, learning, mood, and memory.[17] Notably, in the prefrontal cortex, irisin increases BDNF synthesis, thereby supporting decision-making, planning, and executive functions.[15] In line with our findings, a greater decline in circulating levels of irisin during the 10-day BR was associated with higher perceived mental demand (amount of mental demand required to perform the BR protocol) and greater temporal demand (the amount of time required to complete the task).

In our previous work, we reported significant increases in serum levels of myostatin, a negative regulator of muscle mass, and haptoglobin, an acute-phase inflammatory marker, demonstrating that 10-day horizontal BR negatively affects skeletal muscle physiology.[6] Accordingly, we

Table 2. Multivariable linear regression model examining associations between changes in serum biomarkers (Δ irisin, Δ myostatin, and Δ haptoglobin) and NASA-TLX domain scores (mental demand, physical demand, temporal demand, performance, effort, and frustration)

Dependent variable	Predictor	β coefficient	*p*-value
Mental demand	Δ Irisin	1.720	0.202
	Δ Myostatin	−0.509	0.718
	Δ Haptogloabin	−0.190	0.959
Physical demand	Δ Irisin	0.368	0.512
	Δ Myostatin	−3.717	0.012
	Δ Haptogloabin	5.591	0.040
Temporal demand	Δ Irisin	1.254	0.036
	Δ Myostatin	−0.333	0.534
	Δ Haptogloabin	2.640	0.099
Performance	Δ Irisin	1.088	0.276
	Δ Myostatin	−1.749	0.220
	Δ Haptogloabin	0.853	0.769
Effort	Δ Irisin	0.538	0.500
	Δ Myostatin	−0.395	0.712
	Δ Haptogloabin	−0.511	0.837
Frustration	Δ Irisin	0.322	0.841
	Δ Myostatin	−1.372	0.548
	Δ Haptogloabin	3.735	0.490

applied multiple linear regression analysis using changes in circulating irisin, myostatin, and haptoglobin as independent variables and each NASA-TLX subscale as a dependent variable. The results showed that irisin decline during bed rest was specifically associated with the perception of mental and time load, whereas muscle- or inflammation-related markers did not contribute significantly to this relationship. However, variations in myostatin and haptoglobin were more strongly associated with physical demand during the BR protocol, suggesting that these molecules are more closely related to muscle physiology rather than the mental state of the subjects.

To our knowledge, this is the first study to apply NASA-TLX workload assessment within a BR protocol. Overall, the literature describing mental and cognitive outcomes following horizontal BR remains limited. Dolenc and Petri[23] observed no major changes in cognitive function, aside from slight improvements in mental visualization, after 14 days of horizontal bed rest in young adults. In BR research, cognitive performance has more commonly been evaluated using a head-down tilt position.[3] A 16-day head-down tilt BR study reported no significant changes in executive functions,[24] and similar findings have been reported in longer-duration BR studies assessing general cognitive functions.[25,26] Several studies have evaluated cognition performance and execution during BR through neuropsychological test batteries, including the Trail Making Test, which assesses visual attention, processing speed, executive functioning, and mental flexibility. However, performance on such tests may also be influenced by participants' mental health status. Given that BR studies typically apply exclusion criteria for depressive state, participants are likely to maintain relatively good cognitive abilities while performing the psychoneurological tests.[24] In contrast, the NASA-TLX scoring system does not assess mental health, or baseline cognitive ability; rather, it captures participants' subjective perception of workload experienced during a specific task or period. The NASA-TLX has been widely used across multiple fields and offers advantages over traditional neuropsychological tests, including its use in the medical field to assess mental workload in surgery.[27] Therefore, the use of the NASA TLX test during BR studies could be a valuable tool for understanding the impact of countermeasures to be taken in simulated microgravity environments, with potential translation relevance to spaceflight or clinical settings such as patient hospitalization.

In fact, prolonged bed rest has also been identified as a risk factor for older adults and the general population. Recent studies in hospitalized elderly patients have revealed that individuals may spend up to 86% of their hospital stay inactive, despite only 5% receiving a formal medical recommendation for bed rest.[28] Such behavior is detrimental to patients' mental health and is associated with a significantly increased risk of chronic disability.[29] Importantly, prolonged immobilization is not only harmful to older adults but can also adversely affect the cardiovascular,[30] endocrine,[31] and cognitive[32] systems in younger individuals. Advances in aerospace science have enabled the development of experimental models of forced bed rest in healthy subjects, substantially improving our understanding of immobilization physiology and facilitating the development of strategies to counteract its negative physical and mental effects.

5. CONCLUSION

In conclusion, correlation analyses with the NASA-TLX subscales revealed that greater reductions in irisin levels were

associated with increased mental demand and heightened perceptions of time pressure. Noteworthy, the sensation of time demand may exacerbate high mental activity in a state of cognitive overload. Thus, maintaining higher irisin levels—such as through physical activity—may represent a promising target for the development of countermeasures to refine future BR studies or, prospectively, supporting astronauts in managing high mental workload and time-pressure conditions.

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CONFLICT OF INTEREST

All authors declare that they have no financial or non-financial competing interests.

AUTHOR CONTRIBUTIONS

Conceptualization: Patrizia Pignataro, Uros Marusic*, Maria Grano,* Silvia Colucci
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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the National Ethics Committee of the Slovenian Ministry of Health (Reference No. 0120-304/2019/9). This study is part of the Italian Space Agency (ASI) project "MARS-PRE Bed Rest SBI 2019." Written informed consent was obtained from all participants for participation in this study.

CONSENT FOR PUBLICATION

Written informed consent was obtained from all participants for the publication of anonymized data. All personal identifiers were appropriately concealed to ensure participant confidentiality.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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