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# Fetuin-A as a potential biomarker of metabolic variability following 60 days of head-down-tilt bed rest.

**Kiera Ward[1*], Edwin Mulder[2], Petra Frings-Meuthen[2], Donal J. O'Gorman[3,4], Diane Cooper[1]**

[1]Faculty of Science and Health, Athlone Institute of Technology, Athlone, Ireland;
[2]Department of Muscle and Bone Metabolism, Institute of Aerospace Medicine, German Aerospace Center (DLR), Cologne, Germany;
[3]3U Diabetes Partnership, School of Health and Human Performance, Dublin City University, Dublin, Ireland;
[4]National Institute for Cellular and Biotechnology, Dublin City University, Dublin, Ireland.
*Corresponding author's email: k.ward@research.ait.ie.

## Introduction

Physical inactivity and exposure to microgravity can cause a pronounced reduction in whole-body insulin sensitivity, which is influenced by the secretion of proteins from tissues of metabolic importance [1,2]. Fetuin-A, a novel liver-derived protein or hepatokine, induces insulin resistance by attenuating insulin signalling [3]. However, it is unknown whether head-down-tilt (HDT) bed rest, the ground based analogue of microgravity, alters the circulating concentration of fetuin-A and if changes to this biomarker impacts whole-body insulin sensitivity under these conditions.

## Purpose of the Study

The aim of this study was to determine if 60 days of strict HDT bed rest altered the circulating concentration of fetuin-A and if this change impacted whole-body insulin sensitivity. In addition, we examined whether reactive jump training (RJT), a countermeasure used to maintain skeletal muscle mass, was able to attenuate the metabolic disturbance that occurs with prolonged inactivity.

**Figure 1**. A participant lying in the 6° HDT bed rest position ©DLR.

**Figure 2**. A participant exercising in the horizontal sledge-jump system ©DLR.

## Methods

This parallel-design randomized controlled training study was conducted at the :envihab facility at the German Aerospace Centre (DLR). In brief, the study was split into 3 phases: a baseline data collection phase (BDC-15 to BDC-1), 60 days of strict 6° HDT bed rest (HDT1 to HDT60), and a post-intervention testing phase (R+0 to R+14). On HDT1, participants were randomly assigned to either the control group (CTRL, n = 11, age 28 ± 6 years, BMI 23.3 ± 2kg/m$^2$) or the countermeasure group (JUMP, n = 12, age 30 ± 7 years, BMI 23.8 ± 2kg/m$^2$) which performed RJT 5 – 6 days per week in a horizontal sledge jump system (Figure 2).

A total of 48 training sessions were completed during HDT bed rest. Each training session involved a varying amount of repetitive hops and countermovement jumps with an average load equal to or exceeding 80% of the individual's body weight. The maximal workload in one session, excluding breaks, did not exceed 4 minutes. During the entire study, the subjects received a strictly controlled and individualised diet which was tailored to maintain energy balance.

Before and after HDT bed rest, body composition and $\dot{V}O_{2peak}$ were measured and an oral glucose tolerance test was performed to estimate insulin sensitivity. Serum fetuin-A was measured using the ELISA technique. Area under the curve for glucose (AUCG) and insulin (AUCI) were calculated according to the trapezoidal rule. Indexes of insulin resistance and insulin sensitivity including the Matsuda index, liver insulin sensitivity (liver IS), muscle insulin sensitivity (muscle IS) and adipose tissue insulin resistance (adipose IR) were also calculated.

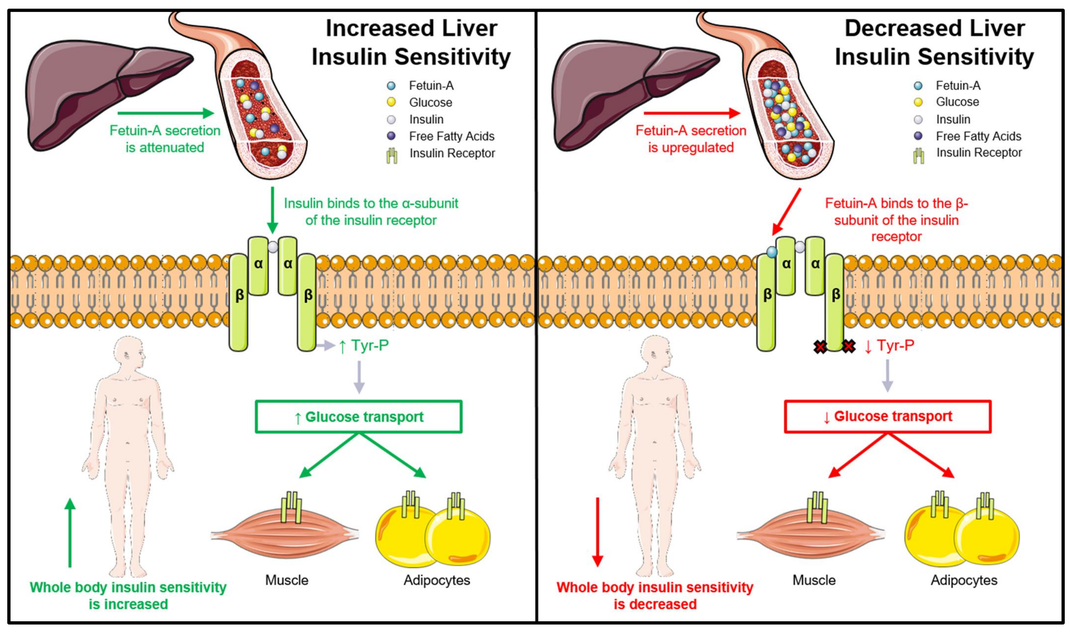


**Figure 5.** The impact of liver insulin sensitivity and fetuin-A secretion on whole body insulin sensitivity.

**References**

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## Results

**Table 1**. Effects of 60 days HDT bed rest on measures of anthropometry and cardiorespiratory capacity.

| Measurement | CTRL | | JUMP | | Statistical Analysis | | |
|---|---|---|---|---|---|---|---|
| | BDC | HDT | BDC | HDT | Time | Int | Time*Int |
| **Physical Characteristics** | | | | | | | |
| **Body Weight (kg)** | 76.10 ± 8.06 | 72.47± 6.76* | 77.85 ± 6.55 | 75.63 ± 6.39* | **<0.001** | 0.405 | **0.027** |
| **Lean Mass (kg)** | 56.94 ± 6.57 | 53.03 ± 5.11* | 56.41 ± 5.18 | 55.08 ± 4.29* | **<0.001** | 0.731 | **0.002** |
| **Fat Mass (kg)** | 16.91 ± 3.95 | 17.00 ± 3.41 | 19.21 ± 6.42 | 18.34 ± 6.18* | 0.055 | 0.412 | **0.018** |
| **$VO_{2peak}$ (L/min)** | 3.80 ± 0.66 | 2.57 ± 0.47* | 3.33 ± 0.74 | 2.90 ± 0.63* | **<0.001** | 0.796 | **0.006** |

Data are presented as mean ± standard deviation (SD). Anthropometric measurements were taken on BDC-3 and HDT60 (CTRL n = 11, JUMP n = 12). $\dot{V}O_{2peak}$ was measured on BDC-8 and R+1 (CTRL n = 10, JUMP n = 11). When a significant interaction effect was found, an asterisk (*) denotes a significant difference from pre in each intervention group. Abbreviations: CTRL, control group; JUMP, jumping countermeasure group; Time, main effect of time; Int, main effect of intervention; T*Int, time*intervention interaction effect.

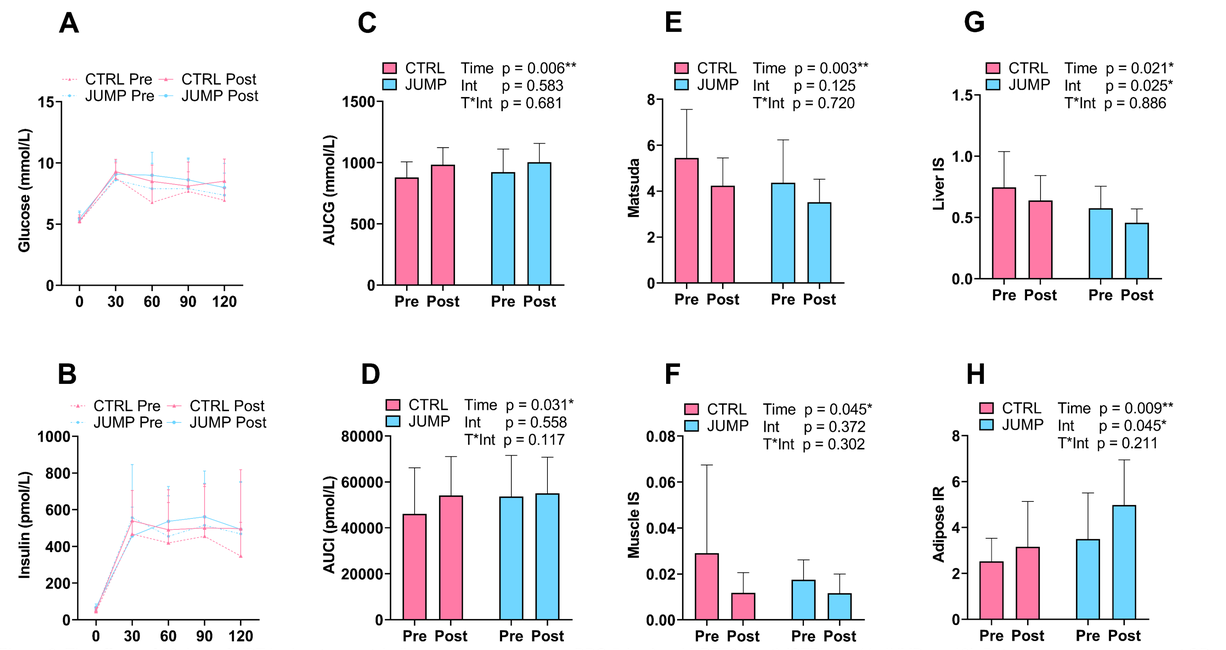


**Figure 3.** The effects of 60 days of HDT bed rest on metabolic variables measured on BDC-5 (pre) and HDT59 (post) (CTRL n = 11, JUMP n = 12). Data are presented as mean±SD. The glucose and insulin response curve to the OGTT are displayed in A and B, respectively. The area under the curve (AUC) totals for glucose are shown in C and for insulin in D. The pre to post changes in OGTT derived indexes of Matsuda, liver IS, muscle IS and adipose IR are presented in E-H. Abbreviations: CTRL, control group; JUMP, jumping countermeasure group; IS, insulin sensitivity; IR, insulin resistance; Time, main effect of time; Int, main effect of intervention; T*Int, time*intervention interaction effect.*p ≤ 0.05, **p ≤ 0.010, ***p ≤ 0.001.

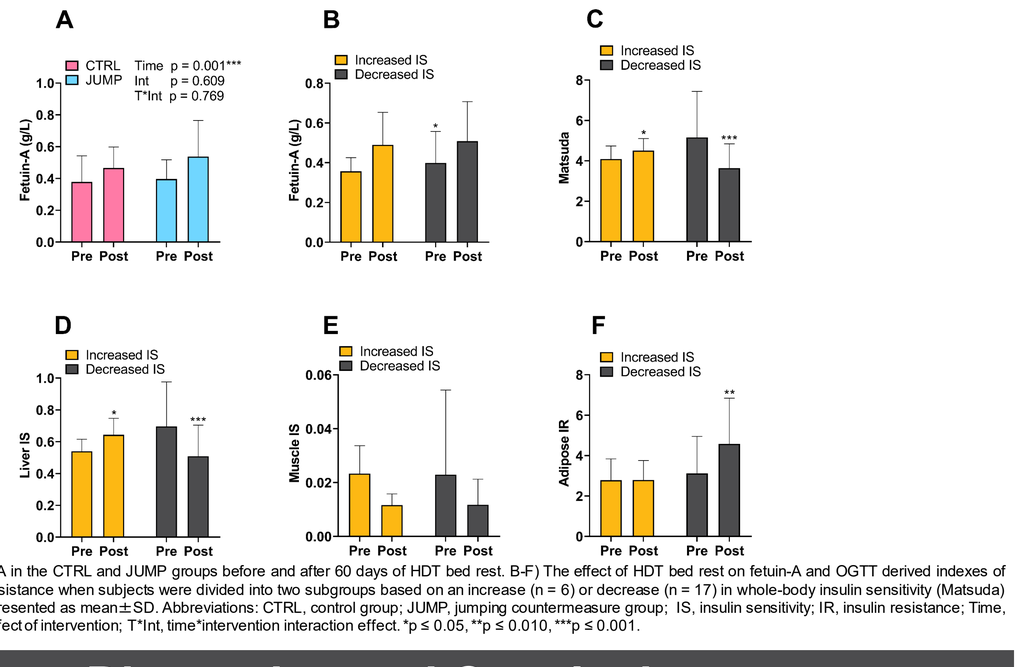


**Figure 4.** A) Circulating fetuin-A in the CTRL and JUMP groups before and after 60 days of HDT bed rest. B-F) The effect of HDT bed rest on fetuin-A and OGTT derived indexes of insulin sensitivity and insulin resistance when subjects were divided into two subgroups based on an increase (n = 6) or decrease (n = 17) in whole-body insulin sensitivity (Matsuda) post- HDT bed rest. Data are presented as mean±SD. Abbreviations: CTRL, control group; JUMP, jumping countermeasure group; IS, insulin sensitivity; IR, insulin resistance; Time, main effect of time; Int, main effect of intervention; T*Int, time*intervention interaction effect. *p ≤ 0.05, **p ≤ 0.010, ***p ≤ 0.001.

## Discussion and Conclusion

The main findings of the current study demonstrate that 60 days of HDT bed rest elicited a significant increase in fetuin-A concomitant with reduced insulin sensitivity, which could not be mitigated by RJT.

Exploring individual responses to lifestyle interventions is a growing area of interest in personalised medicine. While HDT bed rest reduced insulin sensitivity at the group level, there was considerable individual responses, including a subgroup for which whole-body and liver insulin sensitivity improved with no change in fetuin-A.

We propose that the amount of fetuin-A released by the liver is an important determinant of changes in whole-body insulin sensitivity (Figure 5). In this regard, circulating fetuin-A may also be a useful biomarker to track individual metabolic variability in response to physical inactivity, bed rest and lifestyle interventions.

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