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ORIGINAL ARTICLE

Body composition and metabolic changes during a 520-day mission simulation to Mars

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Abstract

Purpose The "Mars-500 project" allowed to evaluate the changes in psychological/physiological adaptation over a prolonged confinement, in order to gather information for future missions. Here, we evaluated the impact of confinement and isolation on body composition, glucose metabolism/insulin resistance and adipokine levels.

Methods The "Mars-500 project" consisted of 520 consecutive days of confinement from June 3, 2010 to Nov 4, 2011. The crew was composed of six male subjects (three Russians, two Europeans, and one Chinese) with a median age of 31 years (range 27–38 years).

Results During the 520-day confinement, total body mass and BMI progressively decreased, reaching a significant difference at the end (417 days) of the observation period (− 9.2 and − 5.5%, respectively). Fat mass remained unchanged. A progressive and significant increase of fasting plasma glucose was observed between 249 and 417 days (+ 10/+ 17% vs baseline), with a further increase at the end of confinement (up to + 30%). Median plasma insulin showed a non-significant early increment (60 days; + 86%). Total adiponectin halved (− 47%) 60 days after hatch closure, remaining at this nadir (− 51%) level for a further 60 days. High molecular weight adiponectin remained significantly lower from 60 to 168 days.

Conclusions Based on these data, countermeasures may be envisioned to balance the potentially harmful effects of prolonged confinement, including a better exercise program, with accurate monitoring of (1) the individual activity and (2) the relationship between body composition and metabolic derangement.

Keywords Gender · Male · Chronic stress · Insulin resistance · Mars mission · "Mars-500 project" · Adiponectin

Introduction

Prolonged spaceflight for planetary exploration requires the ability of spacefarers to remain confined and isolated for a very long time. Within this context, the "Mars-500 project" was organized by the European Space Agency (ESA) in close collaboration with the Institute for Biomedical Problems (IBMP; Moscow, Russia) as a simulation of an interplanetary voyage from the Earth to Mars and back. This unique experiment provided an outstanding opportunity to evaluate the changes in psychological and physiological adaptation over 520 days of confinement [1], by simulating the crew's confinement, cohabitation and communication to Earth, along with the specific activities and workload taking place in these conditions [2].

Previous reports on the "Mars-500 project" described mood and sleep–wake changes [3, 4], as well as modifications of muscle strength [5] and autonomic nervous system

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function [6] and of some circulating biomarker levels associated with chronic environmental stress [3]. The potential body composition and metabolic changes associated with these psychological and physiological features have, however, not yet been reported.

This study opportunity appears novel, since only a few data on the impact of similarly extreme conditions in humans are available. Interestingly, people living in polar regions and exposed to both isolation–confinement and suboptimal light conditions, which make them comparable to subjects volunteering for the "Mars-500 project", were found to show insulin resistance [7]. Moreover, some information was collected in the previous 105-day isolation experiment, conducted within the frame of the "Mars-500 project", in the same setting, but with a different male cosmonaut team, which displayed some degree of insulin resistance and cortisol increase [8]. This experimental paradigm did not include exposure to microgravity and cosmic radiation, two important features of spaceflight [9–12], therefore making it closer (than true spaceflight) to on-Earth chronic stressful conditions that any individual may encounter.

Based on these premises, the present study was aimed at exploring whether the specific environmental conditions of the "Mars-500 project" may lead to a series of physiological adaptations related to body composition, glucose metabolism/insulin resistance and circulating adipokine levels.

Methods

Study design–"Mars-500 project"

The "Mars-500 project" consisted of 520 consecutive days of confinement from June 3, 2010 to Nov 4, 2011. The crew was composed of six male subjects (three Russians, two Europeans, and one Chinese) with a median age of 31 years (range 27–38 years). During the mission simulation, all of the crewmembers received the same diet, whose composition was almost identical to that one used in the International Space Station (ISS). The isolation facility, located at IBMP in Moscow, consisted of four hermetically sealed interconnected 550 m^3 habitat modules kept under artificial lighting conditions (50–300 lx) at a constant 24 °C temperature with a relative humidity of 35–45% and with normoxic, normobaric hypercapnia (0.15–0.65% CO_2), which is close to the parameters of the atmosphere of manned space objects, such as the ISS.

Water and food, which reflected the diet used in the ISS, were limited as in a real space flight. During the study, subjects had free access to water, while caloric drinks, e.g., juices, were limited.

The energy intake was dependent on the subjects' body weight and age and was calculated as follows [2]:

$$\text{Age } 18\text{–}30\text{years}: \text{ kilocalories (kcal/day)} = 1.7 \times (15.3 \times \text{body weight} + 679),$$

$$\text{Age} > 30\text{years}: \text{ kilocalories (kcal/day)} = 1.7 \times (11.6 \times \text{body weight} + 879).$$

The meal plans included different types of food products, ready or semi-ready for consumption, by Russian, European, Korean, and Chinese firms, with up to four menu variants, providing an average 15.1% protein, 33.4% fat, and 51.2% carbohydrate [13].

Further information about all crewmembers and the whole project is available on the ESA website (http://www.esa.int/Our_Activities/Human_Spaceflight/Mars-500/Scientific_protocols).

Clinical and anthropometric sampling

Height, body weight and body mass index of the six crewmembers were periodically recorded. After an overnight fast, subjects, wearing light clothes, were evaluated by dual-energy X-ray absorptiometry (DXA) for body composition parameters, including total body mass, fat mass and lean mass.

Biochemical and hormonal sampling

After an overnight fast, 7 mL of blood samples was drawn into blood tubes containing EDTA as anticoagulant between 7 and 8 am in the morning. Plasma samples were transferred into new tubes as 500 mL aliquots and kept at − 20 °C. Baseline data samples were collected 7 days before the beginning of the isolation. The sampling time points were day 60, 120, 168, 249, 300, 360, 418, 510 and 7 days after the confinement. Two crewmembers with medical training were in charge of blood sampling. Total cholesterol, HDL cholesterol, triglycerides and fasting plasma glucose (FPG) were measured by standard enzymatic techniques (Cobas 600 analyzer, Roche, USA). Frozen samples were assayed immediately after thawing by means of commercially available enzyme-immuno-assays (ELISA), which have been previously validated in our laboratory and used in published studies [14, 15]. Plasma leptin ELISA (R&D Systems, MN, USA) showed a minimum detectable dose of 7.8 pg/mL and inter-assay and intra-assay coefficient of variations (CV) was 5.4 and 3.3%, respectively.

Plasma total adiponectin ELISA (R&D Systems, MN, USA) showed a minimum detectable concentration of 0.891 ng/mL and inter-assay and intra-assay CV was 3.4 and 4.7%, respectively. Plasma high molecular weight (HMW) adiponectin ELISA (R&D Systems) showed a minimum detectable concentration of 0.98 ng/mL and inter-assay and intra-assay CV were 8.6 and 3.6%, respectively.

Plasma insulin ELISA (Millipore Corporation, MA, USA) had a minimum detectable concentration of 2 mU/mL and inter-assay and intra-assay CV was 9.1–11.4 and 4.6–7.0%, respectively. The homeostasis model assessment of insulin resistance (HOMA-IR) score was calculated as follows: fasting insulin, μU/mL × fasting glucose, mmol/L]/22.5 [16].

Statistical analysis

For descriptive statistics, results are presented as median, interquartile ranges ($Q1$ and $Q3$) for all parameters. Normality was assessed by the Kolmogorov–Smirnov test; since no variables reached this assumption Friedman test was applied as a non-parametric alternative to the one-way ANOVA with repeated measures. Sums of ranks and the sample sizes were taken into consideration. When repeated measures were significant, Dunn's multiple comparison test was applied to compare the mean rank of each time point with the mean rank of baseline. We set the criterion for statistical significance at 5%. Data were analyzed using the SAS System Software for Windows, release 8.0 (SAS Institute, NC, USA).

Results

Clinical and biochemical features of the study subjects

All six male crewmembers successfully completed the entire 520-day isolation experiment, showing no major clinically appreciable pathological changes. The anthropometric and biochemical features of the six participants are summarized in Table 1. The total body mass range was 72.0–98.0 kg (median 81.5 kg) corresponding to a BMI range of 23.0–31.3 kg/m^2 (median 25.5 kg/m^2) and a fat mass range of 2.4–17.8 kg (median 11.1 kg). All subjects showed normal baseline metabolic biomarkers.

Anthropometric and metabolic parameters over the 520-day confinement

To further investigate the effect of long-term confinement over the entire course of the simulation, the parameters reported in Table 1 were evaluated, performing a non-parametric Friedman test (Tables 2, 3, 4). As shown in Table 2, total body mass and BMI progressively decreased over time, reaching a significant difference only at the end (417 days) of the observation period (− 9.2 and − 5.5%, respectively; all $p<0.01$). Such total body mass reduction can be attributed to a decrease of lean mass (− 12% at 417- vs. − 7-day; $p<0.01$), without significant changes of fat mass (Table 2). Comparison of the body mass changes of the crewmembers during the Mars-500 experiment and at the end of the mission simulation indicated that one subject (#5002) displayed a significant reduction in body mass (− 21 kg). For the other subjects, the reduction was lower (subjects #5003, #5004, #5005, #5006, from − 4 to − 11 kg) or negligible (subject #5001, − 1 kg).

Table 1 Clinical and biochemical features of the study subjects ($n=6$) at baseline (7 days before the isolation)

	7 days before the isolation			
	Median	$Q1$	$Q3$	Range
Total body mass (kg)	81.5	74.2	90.5	72.0–98.0
Lean mass (kg)	71.3	65.5	78.3	62.7–80.2
Fat mass (kg)	11.1	7.6	15.3	2.4–17.8
BMI (kg/m^2)	26.0	23.7	28.9	23.0–31.3
FPG (mg/dL)	83.7	75.3	85.9	70.1–87.3
Insulin (mU/L)	2.79	1.61	7.31	1.10–8.80
HOMA-IR	0.58	0.30	1.59	0.23–1.75
Adiponectin (μg/mL)	6.79	6.30	8.39	6.10–8.50
HMW adiponectin (μg/mL)	4.06	3.61	4.56	3.47–4.58
Leptin (ng/mL)	6.36	4.74	15.3	4.01–17.7

BMI body mass index, *FPG* fasting plasma glucose, *HOMA-IR* the homeostasis model assessment insulin resistance, *HMW* high molecular weight, *Q1* 25% percentile, *Q2* 75% percentile

A moderate, but progressive, increase of FPG was observed between 249 and 417 days, with a further increase in the last part of the confinement period. Specifically, median FPG was significantly elevated and ranged from 99.8 to 108.5 mg/dL (Table 3). The median values of plasma insulin showed a non-significant early increment (60-day; + 86%), which was steadily maintained up to the end of confinement. A similar profile was observed also for the HOMA-IR (60 days; + 67%).

No changes were found in lipid profile parameters (data not shown). Changes of plasma leptin and total and HMW adiponectin, the two main adipokines, were evaluated (Table 4). Over the entire observation period, no significant changes in leptin levels were observed. Total adiponectin approximately halved 60 days after the hatch closure (− 47%, $p<0.05$), remaining at this nadir level for a further 60 days. It then progressively returned to baseline levels around the end of the isolation period. A similar profile was observed for HMW adiponectin, which remained significantly lower from 60 to 168 days. The leptin/adiponectin ratio tripled at 60 days and progressively decreased down to the baseline values at 520 days.

Table 2 Anthropometric parameters evaluated at different time points of the "Mars-500 project"

Independent variable	Time (day)	Median	*Q*1	*Q*3	*p*
BMI (kg/m^2) Friedman's test: $p < 0.001$	− 7	26.0	23.7	28.9	–
	60	26.5	25.1	28.3	ns
	119	26.3	24.9	27.3	ns
	168	25.5	24.5	26.6	ns
	249	25.9	24.0	27.4	ns
	280	25.5	24.1	26.9	ns
	301	25.4	23.6	26.2	ns
	361	25.5	24.5	25.9	ns
	417	24.6	22.6	25.1	**
Total body mass (kg) Friedman's test: $p < 0.001$	− 7	81.5	74.2	90.5	–
	60	83.1	78.5	88.7	ns
	119	82.5	78.8	85.7	ns
	168	80.0	76.7	83.4	ns
	249	81.3	75.2	84.3	ns
	280	79.7	75.5	82.1	ns
	301	79.5	74.0	81.2	ns
	361	80.0	74.5	81.4	ns
	417	74.0	56.1	78.5	**
Lean mass (kg) Friedman's test: $p < 0.001$	− 7	71.3	65.6	78.3	–
	60	71.3	66.8	75.3	ns
	119	68.8	64.9	75.8	ns
	168	70.4	62.3	73.2	ns
	249	68.3	62.9	73.7	ns
	280	71.5	63.7	75.4	ns
	301	69.4	60.1	74.7	ns
	361	70.1	63.9	73.3	ns
	417	62.9	51.8	69.9	**
Fat mass (kg) Friedman's test: ns	− 7	11.1	7.6	15.3	–
	60	10.4	7.8	18.5	ns
	119	12.3	8.7	16.9	ns
	168	9.60	7.6	17.2	ns
	249	9.50	7.2	17.3	ns
	280	5.60	3.5	15.3	ns
	301	7.90	4.7	16.5	ns
	361	6.45	5.4	13.9	ns
	417	10.1	4.9	17.4	ns

BMI body mass index, *Q1* 25% percentile, *Q2* 75% percentile

**$p < 0.01$ (Dunn's multiple comparison for time)

Table 3 Glucose parameters evaluated at different time points of the "Mars-500 project"

Independent variable	Time (day)	Median	*Q*1	*Q*3	*p*
FPG (mg/dL) Friedman's test: $p < 0.0001$	− 7	83.7	78.0	85.1	–
	60	82.4	69.1	88.8	ns
	119	78.8	76.8	88.1	ns
	168	80.3	75.0	83.2	ns
	249	91.7	88.3	98.6	ns
	301	97.9	97.1	103.2	ns
	361	95.9	89.8	98.6	ns
	417	95.6	91.6	98.3	ns
	511	108.5	103.6	110.5	***
	518	99.8	91.4	105.2	*
Insulin (mU/L) Friedman's test: ns	− 7	2.8	1.9	7.3	–
	60	5.2	3.1	9.4	ns
	119	4.3	2.4	7.3	ns
	168	7.2	3.6	9.3	ns
	249	6.7	3.4	8.8	ns
	301	9.2	2.4	10.2	ns
	361	6.4	4.9	11.9	ns
	417	6.8	1.3	11.8	ns
	511	6.5	3.1	10.0	ns
	518	4.0	1.7	7.9	ns
HOMA-IR Friedman's test: $p < 0.05$	− 7	0.6	0.3	1.5	–
	60	1.0	0.6	2.1	ns
	119	0.9	0.5	1.5	ns
	168	1.4	0.7	1.9	ns
	249	1.6	0.8	2.0	ns
	301	2.2	0.6	2.6	ns
	361	1.5	1.1	2.8	ns
	417	1.7	0.3	2.6	ns
	511	1.8	0.8	2.6	ns
	518	1.0	0.4	1.9	ns

FPG fasting plasma glucose, *HOMA-IR* the homeostasis model assessment insulin resistance, *Q1* 25% percentile, *Q2* 75% percentile

*$p < 0.05$ and ***$p < 0.001$ (Dunn's multiple comparison for time)

Discussion

Focusing on body composition changes and metabolic derangements, the present study aimed at extending to this important field the available information on simulated flight to Mars within the "Mars-500 project". Moreover, the findings of such an extreme experiment, based on prolonged chronic stress, appear to have a relevant clinical value, since they identified changes of biomarkers associated with glucose and energy metabolism, which are in turn related to risk of cardiovascular and endocrine–metabolic diseases [1]. The main findings show that 520 days of confinement and cohabitation led to progressive body mass and lean mass reduction and to moderate insulin resistance and earlier adiponectin reduction. Interestingly, we observed a significant reduction of body mass and BMI, which mainly derive from a reduction of lean mass rather than fat mass. The pathophysiology of such a complex process may be multifactorial.

During the 520-day isolation, some sleep–wake alterations were reported and a relevant and prolonged chronic stress has been described [4, 17, 18], which may have produced potential effects on the circadian dynamics of some

Table 4 Hormonal parameters evaluated at different time points of the "Mars-500 project"

Independent variable	Time (day)	Median	*Q1*	*Q3*	*p*
Adiponectin (µg/mL) Friedman's test: $p < 0.001$	− 7	6.8	6.4	8.3	–
	60	3.6	2.9	4.7	*
	119	3.3	2.4	3.9	*
	168	4.0	3.1	4.7	ns
	249	4.5	3.5	6.6	ns
	301	5.2	4.3	6.5	ns
	361	5.0	3.8	7.8	ns
	417	7.0	5.1	9.0	ns
	511	7.6	5.2	9.0	ns
	518	8.3	6.2	8.8	ns
HMW adiponectin (µg/mL) Friedman's test: $p < 0.0001$	− 7	4.1	3.7	4.6	–
	60	1.6	1.2	2.7	**
	119	1.6	1.0	2.0	**
	168	1.9	1.5	3.0	*
	249	2.2	1.9	3.2	ns
	301	2.5	2.1	3.4	ns
	361	2.9	2.4	3.2	ns
	417	3.5	2.2	4.7	ns
	511	3.8	3.2	4.2	ns
	518	4.4	3.6	5.6	ns
Leptin (ng/mL) Friedman's test: ns	− 7	6.4	5.1	14.2	–
	60	12.7	5.9	15.3	ns
	119	6.2	5.1	12.9	ns
	168	8.6	4.8	16.9	ns
	249	5.7	3.5	16.4	ns
	301	6.8	3.5	15.3	ns
	361	6.1	4.0	14.2	ns
	417	5.6	3.4	13.2	ns
	511	5.4	2.7	11.1	ns
	518	6.8	3.9	10.0	ns
Leptin/adiponectin Friedman's test: $p < 0.001$	− 7	1.0	0.8	1.7	–
	60	3.1	1.9	4.2	ns
	119	2.4	1.4	3.7	ns
	168	2.4	2.0	3.5	ns
	249	1.3	1.0	2.5	ns
	301	1.6	0.6	2.7	ns
	361	1.4	0.8	2.0	ns
	417	1.0	0.5	2.1	ns
	511	1.0	0.3	1.4	ns
	518	0.9	0.6	1.4	ns

HMW high molecular weight, *Q1* 25% percentile, *Q2* 75% percentile

*$p < 0.05$ and **$p < 0.01$ (Dunn's multiple comparison for time)

hormonal secretions (i.e., growth hormone, cortisol) known to impact on body composition. Indeed, a high salivary cortisol has been reported in the same crewmembers during the whole isolation period [18, 19]. Moreover, in these subjects, qualitative and quantitative changes of food ingestion could also have occurred, due to these and other alterations reported, i.e., diminished amplitude of the circadian rhythm of the parasympathetic autonomic nervous system [6] and a rise in serotonin and norepinephrine [3]. In addition, the sedentariness of the crewmembers increased across this simulated mission; a relevant hypokinesis occurred due to the increased sleep and rest times [4].

Adipokines, including leptin and adiponectin, are involved in the regulation of a wide variety of physiological processes including insulin responsiveness, glucose and lipid metabolism [20–23]. Leptin has also been shown to reciprocally interact with insulin in physiological and pathological conditions, is positively correlated with insulin resistance [24, 25] and shows a marked gender dimorphism [26, 27].

Adiponectin is an abundant adipokine secreted by the adipose tissue, with anti-inflammatory, antiatherogenic and cardioprotective properties. Adiponectin and especially its HMW form is a potent insulin sensitizer in muscle and liver, regulating energy homeostasis and glucose tolerance [28]. Adiponectin levels are inversely related to insulin resistance, and reduced adiponectin levels are linked with insulin resistance-associated conditions and greater vascular damage [29]. In our six male volunteers, plasma leptin levels did not change during the entire confinement period. Interestingly, in the early phase of the long-term isolation, a significant decrement of total and HMW adiponectin was observed. Various studies have shown that the ratio of plasma leptin to adiponectin (L:A ratio) is a better surrogate marker for insulin resistance compared to these values assessed individually [30–33]. Although in a non-significant way, our data show that L:A ratio showed a threefold increase at 60 days and progressively decreased to baseline values at the end of the confinement period. Of note, at 60 days, the L:A ratio positively correlate with insulin ($r^2 = 0.917$, $p = 0.010$) and HOMA-IR ($r^2 = 0.953$, $p = 0.003$). In this context, a study reported how the L:A ratio may be more powerful than HOMA-IR for evaluating insulin resistance in subjects with or without hyperglycemia [25].

The evaluation of insulin resistance allowed us to observe that, after the half of the experiment duration, FPG started to increase as a consequence of the development of insulin resistance, with insulin and HOMA-IR peaking at 301 days. In any case, increased insulin secretion in these healthy subjects appears sufficient to keep FPG within the normal range, although close to the upper limit of 100 mg/dL and in some instances even slightly above this value, which is nowadays diagnostic of impaired fasting glucose, i.e., a reversible pre-diabetic condition. A modest derangement of FPG was observed also in the 105-day simulated Mars mission [8], but in this situation confinement produced an FPG increase during the first 5 weeks without indications of development of insulin resistance, probably because the observation time was too short to elicit such phenomenon in young healthy subjects. Interestingly, some contribution to insulin resistance may also derive from skeletal muscle changes, which have recently been described in the participants to the Mars-500 experiment [5]. Moreover, some degree of insulin resistance seems a common feature of conditions comparable to the 520-day isolation/confinement, such as, for example, people living in polar regions [7].

Additional factors may have also contributed to the development of subtle cardiovascular [1] and metabolic alterations in the 520-day experiment subjects, who were otherwise healthy. Interestingly, they have been found to have some degree of intestinal inflammation [34], although a contribution by changes in gut microbiome has been excluded in the participants of the "Mars-500 project" [13].

A limitation of this study is that, since only male subjects were included in the "Mars-500 project", we could not evaluate the impact of such prolonged chronic stressful conditions on female metabolism and body composition. Since women show peculiar endocrine and metabolic features, as well as a very different body composition than men, it will be very important to conduct similar studies also in the female gender. As mentioned before, microgravity and cosmic radiation, two crucial aspects of spaceflight with major health impact [9–11], were not included in the design of the "Mars-500 project". Apparently a limitation, this condition conversely allowed to dissect out the specific contribution of confinement, cohabitation and (delayed) communication to Earth to psychological and physiological features, including the data presented in this paper. Future studies bearing a greater level of complexity should combine all the components of a challenging space flight as that from Earth to Mars, before a manned mission will reach the Red Planet.

On the basis of the data obtained, it is possible to envision a series of countermeasures to balance the potentially harmful effects observed, to be applied both to the very restricted field of prolonged spaceflight, as well as to people subjected to chronic stress. Specifically, a well-focused exercise program, with accurate monitoring of the actual individual activity and of the relationship between body composition and metabolic derangement, may be useful [35]. Moreover, it might be important to promote improvements of nutrition monitoring and sleep–wake cycle, as well as an accurate evaluation of the individual cardiovascular and metabolic risk in cosmonauts directed to Mars (i.e., accurate selection of crewmembers, in-flight monitoring of related biomarkers and arterial wall thickness), but also, with a much broader view, in selected subjects exposed (or to be exposed) to relevant and prolonged chronic stress conditions.

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Compliance with ethical standards

Conflict of interest All the authors have nothing to declare.

Ethical approval This research was conducted in accordance with the principles expressed in the Declaration of Helsinki. All of the investigations performed in the frame of the "Mars-500 project" were reviewed and approved by the Institute of Biomedical Problems (IBMP) Committee on Bioethics, and all volunteers signed the written informed consent for participation in the experiment.

Informed consent Informed consent was obtained from all individual participants included in the study.

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