Kidney Function and Urine Protein Composition in Healthy Volunteers During Space Station Fitness Tests

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BACKGROUND: There is a close physiological connection between muscular activity and kidney function. During physical exercise (PE) the qualitative and quantitative composition of urine changes. This paper explores the influence of moderate PE on urine protein composition. The study of urine protein composition will help to make corrections to the existing methods of countermeasures.

METHODS: There were 10 healthy men who exercised on a treadmill similar to the one onboard the International Space Station. We analyzed their urinary proteome composition, potassium level, sodium level, and their level of osmotically active substances before and after PE.

RESULTS: After moderate PE, a small increase in urine flow speed and a constant glomerular filtration rate were noted. The average-group index of total protein excretion within the urine was reliably increased. From the 148 proteins identified in the urine, 64 were associated with known tissue origin. We found that protein penetration into the urine had a positive correlation with their tissue expression. Selectivity of the glomerular barrier during PE decreased and high-molecular weight proteins penetrated through the glomerular barrier more easily after PE.

DISCUSSION: Performance of moderate intensity physical exercise of short duration did not lead to an increase in the glomerular filtration rate nor did diuresis increase above the limits of baseline variability. However, the protein excretion rate increased after PE. We also observed that protein composition drift indicated a change in the set of biological processes in which a given protein participated, in some cases activating, in some cases inactivating them.

KEYWORDS: International Space Station, urine proteome, physical exercises.

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Exposure to spaceflight is known to affect the cardiovascular system, muscles, water-salt balance, renal functions, and others. Effective countermeasures, such as physical exercises, are required to prevent muscle atrophy and loss of strength during spaceflight. There is a close physiological and functional connection between muscular activity and kidney function. During physical exercise (PE), blood vessels in the muscles being used expand sharply. This expansion happens mainly due to the vessel's response to the accumulation of metabolites, such as H^+, lactate, K^+, etc. As the blood flow is redistributed, more muscles contract, demanding a larger portion of cardiac output (CO), which must increase to return to a steady state. If CO increases 5-6 times during PE, reaching as much as 20-30 $L \cdot min^{-1}$, and 80–85% of this goes to the skeletal muscles being used, then during physical exercise muscles can demand 20 $L \cdot min^{-1}$ or more. The kidneys support consistency of the blood of the organism via the filtration and excretion of metabolic products. These substances enter the blood during muscular activity. During physical exercise the qualitative and quantitative composition of urine also changes. New substances appear that are usually absent in urine except in small amounts. These include products of purine exchange and underoxidized substances (lactic acid, R-hydroxy-butanoic acid, acetoacetic acid). Muscular performance activates kidney functions, which

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regulate acid-base balance via induction of the main anion exchangers AE1 and pendrine. This activation is connected with both changes of kidney blood flow and partial functions of the nephrons. However, the influence of physical exercise on kidney function depends not only on the volume of the performed physical exercise, but also on the individual's physical fitness level.

As a rule, physical exercises of moderate intensity lead to an increase in diuresis, while intense muscular exercises are accompanied by its decrease. This change depends on decreased kidney blood flow, increased secretion of antidiuretic hormone, increased tubule permeability, and motor-visceral (renal) reflexes. An increase in fitness level increases the stability of the kidney's function so that the blood flow decreases after more intensive loading and glomerular filtration is maintained at the same level even during submaximal physical exercise. The factors regulating the level of protein excretion by the kidneys during space station fitness tests have not been described. The amount of variability and the mechanisms of the processes that underlie urine formation on the level of protein excretion in various physiological conditions remain undefined. This paper explores the influence of moderate physical exercise on urine protein composition. The study of urine protein composition performed using the proteomics method will help to understand molecular mechanisms maintaining homeostasis during spaceflight and improve the existing methods of countermeasures.

METHODS

Subjects

Urine samples from 10 students (men, 21–23 yr old) from the Moscow State Pedagogical University with a high level of physical fitness (exercising at least 12 h/wk) were analyzed. The protocol of the experiment was approved by the Biomedicine Ethics Committee of the Russian Federation Scientific Research Center-Institute of Biomedical Problems (IBMP), Russian Academy of Sciences. All subjects provided written informed consent to participate in the experiment. The average bodyweight index was 22.6 ± 1.7 and ranged from 20.9 to 24.3.

Equipment

All subjects were tested with the treadmill BD-2, which is similar to the one onboard International Space Station (ISS) in passive mode. This test is periodically performed on all Russian cosmonauts on the ISS during long-duration spaceflight to evaluate their fitness level.

Procedure

The protocol of the test consisted of walking (3 min), slow running (2 min), medium running (2 min), fast running (1 min), and walking (3 min). Subjects chose a running speed according their own preference. The average total distance during 11 min of running was 1161 ± 122 m.

Two urine samples for proteomic investigation were collected: one sample was collected just before the test, and the next as a first voluntary voiding after the test. Preparation of these samples for mass spectrometric analysis followed a previously described standardized procedure.[9] In addition to protein composition levels of potassium, sodium and osmotically active substances were analyzed by conventional methods. We used ergospirometry (Oxycon Mobile, CareFusion, San Diego, CA) to analyze the gas composition of exhaled air.

Statistical Analysis

Statistical analyses were performed using software Statistica version 6.0 (StatSoft Inc., Tulsa, OK). Student's *t*-test was used for paired comparisons. The significance level was set to 0.05. Values are expressed as mean ± SD. LC-MS/MS data were searched using Mascot (Matrix Science, London, UK; version 2.0.04) against the human IPI protein sequence database from the European Bioinformatics Institute (version 3.82; released 06.04.2011; 92,104 entries). Proteomic composition of the urine was compared to the Tissue-specific Gene Expression and Regulation (TiGER) database, which provides information for tissue-specific gene expression and regulation in a variety of human tissues.[6]

RESULTS

Subject maximum heart rate (HR) ranged between 164 and 193 bpm. The exchange anaerobic threshold during the loading period was from 6 min 50 s to 9 min 10 s. Respiratory minute volume ranged from 108 to 137 L · min^{-1} and reached a maximum from 8 min to 10 min 30 s. We used the measurements of corresponding parameters in urine samples, obtained before and after the fitness test, to analyze the influence of physical exercise on kidney function. These measurements revealed a statistically significant ($P < 0.05$) increase of minute diuresis from 0.24 ± 0.1 to 0.42 ± 0.1 ml · min^{-1}. However, this parameter did not exceed the limits of variability in steady state conditions. In the other investigated characteristics of kidney function, reliable changes were not observed (**Table I**).

Table I. Average Value of the Main Parameters of Kidney Functions Before and After PE, Taking into Account Standard Deviation (± σ).

	BEFORE PE		AFTER PE	
PARAMETER	**M**	**± σ**	**M**	**± σ**
Liquid excretion, ml · min^{-1}	0.24	0.11	*0.42	0.10
Sodium excretion rate, mEq · min^{-1}	39	24	48	19
Potassium excretion rate, mEq · min^{-1}	18	12	25	10
Concentration of osmotically active substances, mOsm · L^{-1}	952	112	942	102
Osmotically active substances excretion rate, mOsm · min^{-1}	235	105	347	124
Clearance of osmotically active substances, ml · min^{-1}	0.82	0.36	1.22	0.43
Clearance of osmotically free water, ml · min^{-1}	0.57	0.26	0.85	0.31
Glomerular filtration rate, ml · min^{-1}	124	17	114	18
Urinary protein excretion rate, μg · min^{-1} · kg^{-1}	0.58	0.38	*2.13	0.93

Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula; M = arithmetic average, σ = root-mean-square deviation; *$P < 0.05$ Student's *t*-test.

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We observed that the urinary protein excretion rate, standardized on the body mass of the volunteers, increased during PE. Proteinuria can be found in some physiological conditions, such as intensive physical exercise, orthostasis, and emotional stress. The increased excretion of some proteins in urine is observed with changes in urine flow speed. Our data showed that after moderate PE, with a small increase of urine flow speed and constant glomerular filtration rate, the average-group index of urine total protein excretion was reliably increased (Table I).

Besides observing increased total protein excretion after PE, we analyzed the qualitative composition of urinary excreted proteins. In our data set, we identified 148 urinary proteins. From the total number of identified proteins, in accordance with the TiGER database, 64 proteins have known tissue localization. Tissue proteins originating from the liver (20 proteins), GI tract (9 proteins), and kidney (9 proteins) were significantly more represented in all urine samples.

The proteins expressed in the kidney are not filtered through the glomerular capillaries and enter the urine directly from the kidney and urinary tract tissues. We analyzed nine of these proteins (**Table II**). Analysis of kidney proteins in the urine before and after physical exercise showed that from the nine identified proteins four had unchanged representation. Two (alpha-methylacyl-CoA racemase and cubulin) had increased representation and three (kallikrein-1, osteopontin, vitamin K-dependent protein Z) had decreased representation after PE. We therefore analyzed the synthesis locations and functions of the proteins which were changed under the influence of PE.

Alpha-methylacyl-CoA racemase (AMACR) plays an important role in the beta-oxidation of branched-chain fatty acids and fatty acid derivatives. Specifically, it catalyzes the conversion of (2R) α-methyl branched chain fatty acyl CoAs to their (S) stereoisomers. AMACR catalyzes the chiral inversion of a diverse number of 2-methyl acids (as their CoA esters) and regulates the entry of branched-chain lipids into the peroxisomal and mitochondrial beta-oxidation pathways.[7]

Table II. Kidney Proteins in Urine Before and After Physical Exercise.

NO.	PROTEIN	MW	BEFORE PE	AFTER PE
1	epidermal growth factor	133.994	7	7 =
2	kininogen-1	71.957	9	9 =
3	megalin	521.958	1	1 =
4	uromodulin	69.761	10	10 =
5	alpha-methylacyl-CoA racemase	42.387	0	3 ↑
6	cubilin	398.736	0	1 ↑
7	kallikrein-1	28.89	4	2 ↓
8	osteopontin	35.423	3	1 ↓
9	vitamin K-dependent protein Z	44.744	1	0 ↓

MW: molecular weight, Da; PE: physical exercise; ↑: increased, ↓: decreased, or =: unchanged amount after PE.

Cubilin is one of the multiligand membrane glycoprotein receptors (together with megalin). Cubilin, which has many ligands, is involved in receptor-mediated endocytosis in the apical membrane of proximal tubular epithelial cells and plays a critical role in the reabsorption of glomerular-filtered proteins.[1]

Kallikrein-1 is a protein of the kallikrein-kinin system. This is a key proteolytic system. The kallikrein–kinin system is composed of kallikrein, kininogen, kinin receptors, and kininase and kinin. It plays an important role in the regulation of different physiological functions in humans. Kallikrein-1 is synthesized in many organs, including kidneys and arteries, where it can generate the vasodilators bradykinin and kallidin. In the kidney, kallikreins are synthesized in the proximal tubular epithelial cells. This is the source of their release into the urine.

Experimental and clinical studies have shown an inverse correlation between urinary kallikrein levels and blood pressure. Kallikrein-1 is likely involved in the maintenance of normal cardiac, renal, and neurological function.[2] It has been suggested that the kallikrein–kinin system can protect from hypoxia, prevent interstitial fibrosis, mediate vasodilatation and inflammation, and activate the innate immune system.

Osteopontin, found mainly in the kidney, is a highly phosphorylated glycoprotein present in many tissues and body fluids.[12] In urine, osteopontin is a potent inhibitor of nucleation, growth, and aggregation of calcium oxalate crystals;[5] this suggests a possible role in the prevention of renal stone formation. It has been identified among the major protein components of renal calculi, but its role in nephrolithiasis remains unclear.

Osteopontin controls the differentiation and growth of cells involved in the restoration of tissues. It accelerates the cardiovascular and myocardial remodeling process and promotes arteriosclerosis. It is also closely associated with angiogenesis. Osteopontin is expressed in the heart in response to mechanical stress and similar stimuli.[8] It is also expressed during heart failure and hypertrophy.

Vitamin K-dependent protein Z is a multidomain vitamin K-dependent plasma protein. It functions in bones and arteries, regulating the activity of matrix Gla-protein (MGP) and osteocalcin (cBGP). cMGP inhibits vascular calcifications, while cBGP has an important role in proper mineralization of bone. These proteins play pivotal roles in the physiology of mineralization and in preventing ectopic calcification. Vitamin K-dependent protein Z regulates the function of blood coagulation factor Xa on membrane surfaces,[4] suppressing thrombus formation by inhibiting activated factor Xa. Polymorphism of the protein Z gene was mentioned as a genetic risk factor for various thrombotic events.

For several biological reasons, each protein participates not in one, but in many processes taking place in the organism. Therefore, the analysis of activation or inactivation of these processes based on the presence of certain proteins in biological liquids is a difficult task. In this paper we show that protein penetration in urine has a positive correlation

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with its tissue expression. Thus, the appearance or disappearance of a protein in urine may indicate its up-regulation or down-regulation in tissues, which in turn may lead to up/down regulation of the biological processes in which it is involved.

Analysis of identified proteins showed that blood plasma, urine, bile, saliva, and liver proteins were over-represented both before and after PE. We also found over-represented biological processes for each stage (before and after PE). Among the over-represented processes were both shared (170) and specific (56) biological processes. Specific processes were divided into two groups: over-represented processes before (38) and after (18) PE.

We can assume that specific biological processes characterized before PE were negatively regulated/inactivated during PE. Their inactivation may be a compensating reaction of PE. Among these, the more significant processes are cell-substrate adhesion, bicarbonate transport, and cellular response to chemical stimulus. Some of the more significant specific biological processes characterized after PE are complement activation, the lectin pathway, the vitamin D metabolic process, and epidermis development.

It was interesting to find proteins that determine specific over-represented biological processes presented in urine before and after PE. The most interesting of all revealed proteins in our investigation were the renal proteins. Among all the renal proteins, we found only three. Two of them were identified in urine only after PE (alpha-methylacyl-CoA racemase and cubulin). One protein (vitamin K-dependent protein Z) was present in urine before PE and disappeared after PE. Vitamin K-dependent protein Z is connected with proteolysis, blood coagulation, peptidyl-glutamic acid carboxylation, posttranslational protein modification, and intracellular protein metabolic process. None of these processes were over-represented. The potential role of this protein in these specific processes is unclear.

According our data, proteins alpha-methylacyl-CoA racemase and cubulin could be involved in compensatory processes during and after PE. Thus, as revealed in urine after PE, alpha-methylacyl-CoA racemase is connected with the bile acid metabolic process, beta-oxidation of fatty acids, the cellular lipid catabolic process, and the small molecule metabolic process. Among these processes the cellular lipid catabolic process was one of the specific over-represented processes after PE. Identification of alpha-methylacyl-CoA racemase as participating in the cellular lipid catabolic process verified that PE activates fat utilization as an energy substrate.

Cubulin is involved in the tissue homeostasis process, the lipid and lipoprotein metabolic process, receptor-mediated endocytosis, the cholesterol metabolic process, the steroid metabolic process, cobalamin transport, the fat-soluble vitamin metabolic process, and the vitamin D metabolic process. Two of these biological processes (the vitamin D metabolic and fat-soluble vitamin metabolic processes) were specifically over-represented after PE.

DISCUSSION

Physical exercises are required to prevent muscle atrophy and loss of strength during spaceflight. To evaluate the effectiveness of aerobic exercise, all Russian cosmonauts on the ISS are tested with the treadmill in passive mode every 30 d. Responses of the cardiovascular and respiratory systems during long-duration spaceflights is similar to our data.[10] The level of protein excretion by the kidney during space station fitness tests has not been described previously.

Proteins synthesized in different tissues and organs of humans which enter into the blood can overcome the kidney glomerular filtration barrier and enter urine. The filtration of protein molecules at the glomerular barrier (GB) is highly size- and charge-selective. An updated view on the selective mechanisms of protein filtration at the glomerular barrier was reviewed by B. Haraldsson.[3] Studies using neutral Ficoll have demonstrated that the GB has numerous functional small pores 45–50 Å in radius and a few larger pores with radii between 80 and 100 Å. Similar size-selective properties have been found in vivo in rats and even in humans.

Protein filtration rate does not depend on protein biological activity; it is the function of the molecular physical characteristics (size, charge, form), and glomerular filtration properties [glomerular filtration rate (GFR), selective permeability]. In some physiological conditions only plasma proteins of low molecular weight (MW) are completely filtered through the basal membrane (up to 60-67 kDa, i.e., MW less than albumin). The filtration of high-MW proteins are completely restricted.[11]

The level of protein expression in tissues can influence the presence of protein in urine. In our previous investigation of cosmonaut's urine proteome composition after spaceflight, we showed a correlation between the level of protein expression and their presence in urine.[10] We chose proteins found in urine with MW higher than albumin (**Table III**). Notably, most of these proteins were represented by nonkidney proteins (i.e., they came to the urine from the blood). Moreover, we found a positive correlation between the level of protein expression and their appearance in urine.

Not taking into consideration only one unit of increase/decrease in the appearance of high-MW proteins in urine in connection with PE, an analysis of Table III showed that from 24 revealed proteins that exceed the MW of albumin, 7 were found in the urine more often after PE—6 with the same frequency as before PE and none of them less frequent after PE. This shows that the selectivity of GB during PE decreased, and high-MW proteins penetrated through the GB more easily. At the same time, the GFR (Table I) did not change with physical exercise (124 ± 17 vs. 114 ± 18 ml $\cdot$ min^{-1}).

Thus, the performance of the moderate intensity physical exercise did not lead to an increase in the GFR and diuresis higher than the limits of variability in steady state conditions. However, the protein excretion rate, according to spectrophotometric determination of total protein, increased after PE. The analysis of the protein composition and representation in the urine samples, expressed by the kidney before

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Table III. Urine Proteins with MW Higher Than Albumin.

SWISSPROT ID	PROTEIN	MW	BEFORE PE	AFTER PE
CUBN_HUMAN	Cubilin	398.736	0	1 ↑
PDS5B_HUMAN	Sister chromatid cohesion protein PDS5 homolog B	164.667	0	1 ↑
GBA2_HUMAN	Nonlysosomal glucosylceramidase	104.649	3	4 ↑
FIBA_HUMAN	Fibrinogen alpha chain	94.973	0	1 ↑
MMRN2_HUMAN	Multimerin-2	104.409	1	2 ↑
CD44_HUMAN	CD44 antigen	81.538	5	8 ↑
TRFE_HUMAN	Serotransferrin	77.064	4	8 ↑
COFA1_HUMAN	Collagen alpha-1(XV) chain	141.72	0	2 ↑
PIGR_HUMAN	Polymeric immunoglobulin receptor	83.284	3	5 ↑
GELS_HUMAN	Gelsolin	85.698	1	6 ↑
ITIH4_HUMAN	Interalpha-trypsin inhibitor heavy chain H4	103.357	4	6 ↑
LYAG_HUMAN	Lysosomal alpha-glucosidase	105.324	2	4 ↑
RGSL_HUMAN	Regulator of G-protein signaling protein-like	125.688	8	8 =
UROM_HUMAN	Uromodulin	69.761	10	10 =
CADH1_HUMAN	Cadherin-1	97.456	8	8 =
EGF_HUMAN	Proepidermal growth factor	133.994	7	7 =
KNG1_HUMAN	Kininogen-1	71.957	9	9 =
LRP2_HUMAN	Low-density lipoprotein receptor-related protein 2	521.958	1	1 =
NID1_HUMAN	Nidogen-1	136.377	1	0 ↓
HMCN1_HUMAN	Hemicentin-1	613.39	1	0 ↓
ATRN_HUMAN	Attractin	158.537	1	0 ↓
ROBO4_HUMAN	Roundabout homolog 4	107.457	1	0 ↓
CO6A1_HUMAN	Collagen alpha-1(VI) chain	108.529	1	0 ↓
UFO_HUMAN	Tyrosine-protein kinase receptor UFO	98.336	4	3 ↓

MW: molecular weight, Da; PE: physical exercise; ↑: increased, ↓: decreased, or =: unchanged amount after PE.

and after PE, showed that, from the nine identified proteins, four had unchanged representation, two (alpha-methylacyl-CoA racemase and cubulin) had increased representation, and three (kallikrein-1, osteopontin, and vitamin K-dependent protein Z) had decreased representation after PE. Protein composition drift also changed the set of biological processes in which the given proteins participated, in some cases activating them, in some cases inactivating them. Also we observed that among 24 proteins exceeding albumin on MW and found in the volunteers' urine, 7 were found in the urine more often after PE, 6 with the same frequency as before PE performance, and none of them less frequent after PE. This demonstrated a decrease in the kidney's GB selectivity during PE, causing high-MW proteins to penetrate it more easily into the urine.

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