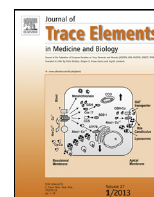
Journal of Trace Elements in Medicine and Biology 37 (2016) 31–36

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb



Investigating the intra-individual variability in the human metabolic profile of urinary selenium

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ARTICLE INFO

Article history:
Received 22 April 2016
Accepted 15 June 2016

Keywords:
Selenosugar
Trimethylselenonium (TMSe)
Urine
Selenium metabolism
HPLC/ICPMS
Selenoneine

ABSTRACT

Selenium is an essential micronutrient widely present in our diet. It plays its role through the selenoproteins. Previous reports have shown marked variation between individuals in the excretion of this trace element, but the intra-individual variability in selenium excretion has not been specifically investigated. The present study investigates the intra-individual variation in the urinary excretion of selenium in a group of healthy volunteers. We also discuss inter-individual variability trends. Urine samples were collected from healthy volunteers without selenium supplementation twice a day for 7 days and then once a week for an additional 7 weeks. A total of 168 urine samples were collected and analyzed for total selenium and individual selenium species using elemental mass spectrometry and HPLC/mass spectrometry, respectively. We found only modest day-to-day and week-to-week intra-individual variation of selenium excretion. Two commonly reported urine metabolites, selenosugar **1** and selenosugar **3**, were detected in all urine samples, and our data suggest that selenosugar **3** is a deacetylated product of selenosugar **1** produced in a manner dependent on selenium intake. Trimethylselenonium displayed no intra-individual variability but considerable inter-individual variability in agreement with the involvement of genetic polymorphisms, as recently reported. Se-methylselenoneine was consistently detected in the urine of all volunteers and was a significant metabolite in one volunteer contributing up to 24% of total urinary selenium. Our data indicate that selenium urinary excretion is consistent within an individual, and that intra-individual variation in selenium excretion is unlikely to complicate future inter-individual variation studies.

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1. Introduction

Although selenium was long regarded as being merely a toxic element, its biological importance was recognised following the discovery that it had protective effects against liver necrosis induced by certain dietary conditions in rats [1]. Later, selenium deficiency was found to be associated with Keshan disease in humans which highlighted its important health effects [2]. Today, selenium is known as an essential micronutrient that plays its roles in the form of selenocysteine which is co-translationally inserted during the synthesis of selenoproteins and is encoded by an in-frame UGA stop codon [3]. Currently, at least twenty five selenoproteins that contribute to a variety of biological processes have been discovered in humans [4].

Selenium is present in our diet in an organic form, as selenomethionine and selenocysteine, and as the inorganic forms selenite and selenate. Selenomethionine can be either non-specifically incorporated into proteins in place of methionine, or converted into selenocysteine via the transsulfuration pathway, whereas inorganic selenium and selenocysteine are metabolized in the liver to hydrogen selenide which is used to synthesize selenophosphate, the active selenium donor for selenoprotein synthesis [5]. Excess selenium is excreted primarily via urine in the form of selenosugars and the trimethylselenonium ion [6].

Despite the importance of selenium as an essential trace element, little has been discovered about the human metabolic pathways of selenium [7]. In particular, the precise pathways and enzymes involved in the biosynthesis of selenium urinary metabolites and their excretion remain unknown. It has been consistently reported that selenium excretion via urine shows inter-individual variability; specifically, that the selenium metabolite trimethylselenonium is excreted by some individuals at much higher levels relative to other individuals [8–11], independently of the selenium intake level [9]. To investigate the etiology of inter-individual variation, it is necessary to first understand the intra-individual

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http://dx.doi.org/10.1016/j.jtemb.2016.06.008
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variability of background selenium excretion on a short- and long-term basis.

The aim of the present study was to investigate the intra-individual variation in the excretion of selenium in urine.

2. Materials and methods

2.1. Study population and sample collection

The study population consisted of 8 healthy volunteers (18–60, 37 (13) years old (age range, mean (SD)); 5 males and 3 females). All volunteers were non-smokers except for volunteers G and H. The volunteers did not take any form of selenium supplementation during the sample collection period. Volunteers gave informed consent to participate in the study, and all procedures were in accordance with the Declaration of Helsinki.

Each volunteer was asked to collect 1 morning urine sample and 1 evening urine sample for 7 consecutive days, and then to collect 1 morning urine sample on a weekly basis for an additional 7 weeks, giving an overall sample collection period of 8 weeks. A total of 168 urine samples were collected. Volunteers were asked to record food consumption data throughout the sample collection period and fill a general food frequency table adapted from Pestitschek et al. [12]. Corning® polypropylene 300 mL sample collection containers (Corning, NY, USA) were used for the collection of the urine samples; subsamples (3× ca. 5 mL) were taken and stored at −80 °C.

2.2. Total selenium determination by ICPMS

Portions (500 μL) of the urine samples were subjected to microwave-assisted acid digestion in 12 mL quartz digestion tubes using nitric acid under previously described conditions [13]. The digests were made up to 10 mL with water (18.2 MΩ cm) and the total selenium concentration was determined using an inductively coupled plasma mass spectrometer (ICPMS, Agilent 7500ce from Agilent Technologies, Waldbronn, Germany) operated in the octopole reaction cell mode with hydrogen as the reaction gas and 1% CO_2 in argon as an optional gas to provide a four-fold increase in sensitivity, applying the conditions previously described [8]. Selenium quantification was based on the ^{78}Se isotope using germanium (^{72}Ge) as an internal standard. The LOD (limit of detection, based on blank + 3 SD_{blank}) was within the range 6–15 ng L^{-1} over the course of the study. Our method for measuring total selenium concentrations in urine was validated by analyzing the certified reference material NIES CRM No. 18 Human Urine (National Institute of Environmental Studies, Tsukuba, Japan; certified Se concentration: 59 ± 5 μg L^{-1}; found Se concentration: 58 (1) μg L^{-1}, mean (SD), n = 4). For the urine samples, Se concentrations were normalized according to each sample's specific gravity determined with a Leica TS 400 total solids refractometer (Leica Microsystems, Buffalo, NY, USA). The following equation was used for normalization:

$$C_{norm} = \frac{(\text{spec.grav}_{\text{mean}} - 1)}{\left(\text{spec.grav}_{\text{sample}} - 1\right)} \times C_{\text{sample}}$$

2.3. Determination of selenium metabolites in urine by HPLC/ICPMS

Our speciation analysis focused on the known excretion products of selenium; namely, selenosugar **1**, selenosugar **2**, selenosugar **3**, and trimethylselenonium (TMSe) (Fig. 1). Two sets of chromatographic conditions were used to separate and determine the four species as previously described [14]. Briefly, for the determination of selenosugar **1** and selenosugar **2**, we used reversed-phase chromatography on a Waters Atlantis C18 column (4.6 × 150 mm; Waters Corporation, Milford, MA, USA) employing a mobile phase of 20 mM ammonium formate adjusted with formic acid to pH = 3.0 and containing 3% methanol, at a flow rate of 1.0 mL min^{-1}, and column temperature of 30 °C. For the determination of selenosugar **3** and TMSe, cation-exchange chromatography was performed on a Hamilton PRP-X200 column (4.1 × 250 mm; Hamilton, Reno, NV, USA), using 20 mM ammonium formate adjusted with formic acid to pH = 3.0 as the mobile phase, with a flow rate of 1 mL min^{-1} at a column temperature of 30 °C. We applied 1% CO_2 in argon as an optional gas for the ICPMS detector for the cation-exchange chromatography. Injection volume was 20 μL for both chromatographic conditions. Urine samples were filtered through 0.2 μm nylon syringe filters, and the filtrates directly injected onto the column without dilution; the selenium species were detected using ICPMS

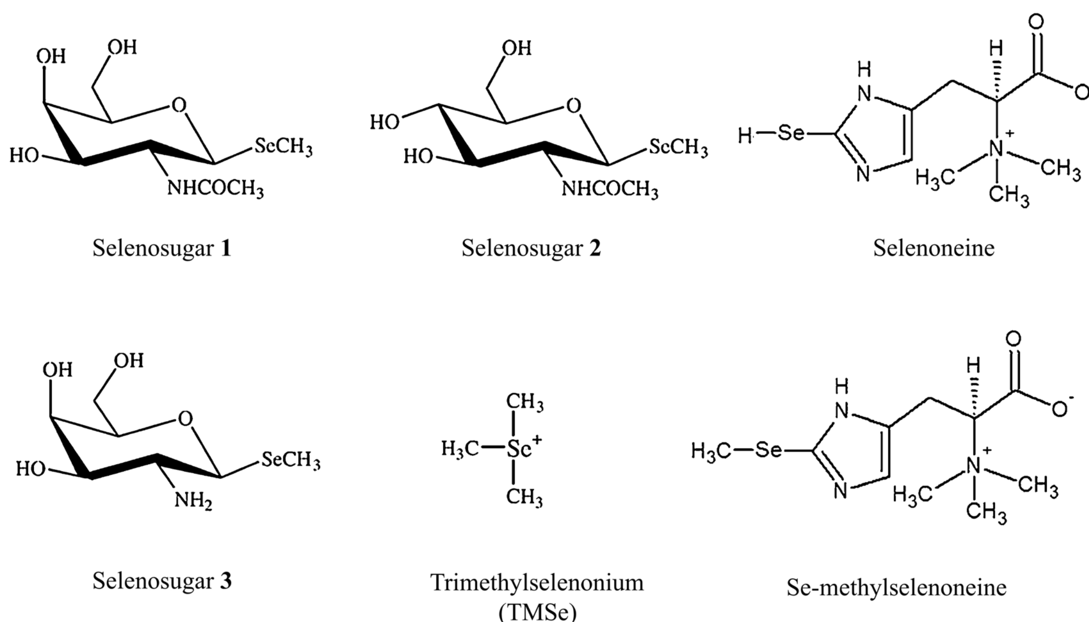

Fig. 1. The chemical structures of selenium species relevant to this study.

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