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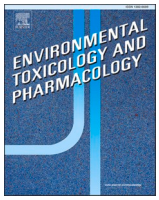

A time-course investigation of the human urinary excretion of the hydrogen sulfide biomarker trimethylsulfonium

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ABSTRACT

Hydrogen sulfide is a toxic gas but also recognized as an endogenously produced metabolite in humans playing key roles. We previously identified trimethylsulfonium, which can be a methylation product of hydrogen sulfide but the stability in the production of trimethylsulfonium has not been investigated. In the present work, the intra- and inter-individual variability in the excretion of trimethylsulfonium over 2 months in a group of healthy volunteers was investigated. Urinary levels of trimethylsulfonium (mean: 56 nM, 95% CI: 48–68 nM) were > 100-fold lower than the conventional hydrogen sulfide biomarker thiosulfate (13 μM, 12–15 μM) and the precursor for endogenous hydrogen sulfide production cystine (47 μM, 44–50 μM). There was no correlation between urinary trimethylsulfonium and thiosulfate. Higher intra-individual variability in the excretion of trimethylsulfonium (generally 2-8 fold) than that for cystine (generally 2-3 fold) was found. Trimethylsulfonium displayed significant inter-individual variability with two concentration clusters at 117 nM (97–141) and 27 nM (22–34). In conclusion, the observed inter- and intra-individual variability must be considered when using urinary trimethylsulfonium as a biomarker.

1. Introduction

Hydrogen sulfide is a highly toxic gas associated with occupational (Loso et al., 2021; Park et al., 2020) or environmental (Fazlzadeh et al., 2018; Somma et al., 2017) exposure. However, hydrogen sulfide is being also increasingly recognized as an endogenous metabolite naturally produced in humans at low concentrations resulting from naturally occurring enzymatic activities on the amino acid cysteine (Kimura, 2011). This endogenously produced hydrogen sulfide plays key biochemical roles in cell signaling that are relevant under normal physiological as well as pathological conditions, and therefore hydrogen sulfide has been referred to as the third gaseous signaling molecule following nitric oxide and carbon monoxide (Li et al., 2011; Wang, 2003). Notably, it was reported that altered hydrogen sulfide concentration is implicated in various pulmonary diseases (Chung, 2014; Suzuki et al., 2021). In particular, alteration in hydrogen sulfide levels has been referred to as a hallmark of COVID-19 (Dominic et al., 2021; Yang, 2020) and numerous reports suggested that sulfide-releasing agents can be potentially used as therapeutic agents (Citi et al., 2020; Datzmann et al., 2021). Given the high volatility and difficulty in measuring hydrogen sulfide in tissues and biofluids, the need arises for reliable biomarkers to probe its occurence in vivo resulting from not only exogenous or environmental normal physiological production.

Thiosulfate is an oxidation product of hydrogen sulfide, produced by enzymatic pathways that have been elucidated (Hildebrandt and Grieshaber, 2008) and is currently the conventional biomarker for acute hydrogen sulfide poisoning (Kage et al., 2002; Kage et al., 1997). However, we recently identified a methylated sulfur compound, trimethylsulfonium, in human urine and highlighted its great potential to serve as a novel biomarker for hydrogen sulfide (Lajin and Francesconi,

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Table 1
Geometric mean and its 95% CI in urine samples (n = 21) of each of the eight studied volunteers.

	V1	V2	V3	V4	V5	V6	V7	V8
Trimethylsulfonium (nM)	44 (36–55)	167 (124–224)	87 (74–102)	291 (236–360)	18 (15–22)	21 (15–31)	52 (33–80)	29 (17–47)
Cystine (μM)	67 (62–73)	42 (37–49)	42 (39–45)	28 (24–34)	44 (41–46)	43 (40–46)	40 (36–45)	88 (79–98)
Thiosulfate (μM)	18 (15–21)	15 (12–19)	14 (11–18)	12 (8.9–16)	20 (18–22)	15 (13–17)	7.9 (5.4–12)	8.9 (7.9–9.9)

All concentrations were adjusted to specific gravity. V1-4 were TMSe producers. V5-8 were TMSe non-producers, see text.

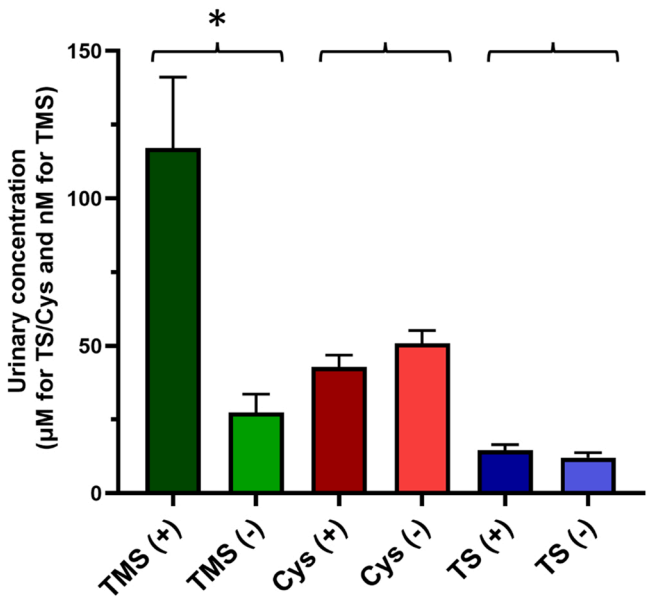

Fig. 1. The influence of the trimethylselenonium (TMSe) production phenotype on the urinary levels of trimethylsulfonium (TMS), cystine (Cys) and thiosulfate (TS). Each bar indicates the geometric mean and its 95% CI interval for all urine samples (n = 84 per group) from different volunteers grouped according to the TMSe production phenotype (indicated by + or -, see text). The difference in TMS levels between the TMSe producers (+) and TMSe non-producers (-) groups was statistically significant ($P < 0.001$, Mann-Whitney non-parametric test).

2016b). The levels of trimethylsulfonium in a large population of humans and in a large group of urine samples have not yet been characterized, and the long-term stability in the excretion of trimethylsulfonium has not been investigated, which is of paramount importance for the interpretation of the levels of this metabolite as biomarker of hydrogen sulfide.

The aim of the present work was to investigate the intra- and inter-individual variability in the urinary excretion of trimethylsulfonium in combination with cysteine, the precursor for endogenous hydrogen sulfide over a period of several weeks. Furthermore, correlation and comparison will be made with variability data for thiosulfate, the commonly used biomarker of hydrogen sulfide, which has been previously acquired in an earlier study (Lajin, 2022a).

2. Materials and methods

The study population and sample collection procedure were described in previous work (Lajin et al., 2016b). Briefly, A total of eight healthy volunteers (age range: 18–60, age mean ± SD: 37 ± 13 years, 5 females, 3 males) living in the city of Graz were recruited in the present study. Each volunteer donated 1 morning and 1 evening urine sample over 7 consecutive days followed by 1 morning urine sample over the next seven weeks as previously described. Informed consent was obtained from the participating volunteers and the study was performed in compliance with the declaration of Helsinki and approved by the ethical committee at the university of Graz (GZ: 39/46/63).

Urine analysis was performed with ultra-high performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (UHPLC-ESIMS/MS) as previously described in our previously developed and analytically validated method (Lajin et al., 2022b). An Agilent 1260 Infinity II LC system (Agilent Technologies, Waldbronn, Germany) was deployed for chromatographic separation, equipped with a quaternary 1260 Infinity II Flexible Pump (G7104C, max. pressure 800 bar), Multisampler (G7167A), and Multicolumn Thermostat (G7116A). Separation was performed on a Zorbax Eclipse Plus C18 RRHD column (50 mm × 2.1 mm, 1.8 μm particle size, Agilent Technologies, Waldbronn, Germany) connected with a guard column (5 mm × 2.1 mm, 1.8 μm). The outlet of the UHPLC column was connected to a triple quadrupole Ultivo® LC/TQ system (G6465B, Agilent technologies, Waldbronn, Germany)). Detailed chromatographic and mass spectrometric conditions can be found in previous work (Lajin et al., 2022b). Urine was directly injected without preparation apart from filtering through a 13 mm Nylon 66 syringe filter (pore size 0.22 μm BGB Analytik GmbH, Germany). All concentrations were normalized to specific gravity with the equation $C_{norm} = C_{sample} \times (spec.grav_{mean} - 1) / (spec.grav_{sample} - 1)$ in order to account for variability in fluid intake.

Comparisons in the urinary concentrations were performed based on the urinary concentrations calculated after adjusting to specific gravity and statistical testing was based on the the Mann-Whitney non-parametric test.

3. Results and discussion

The analytes described in this work were determined using an analytical method previously developed and validated (Lajin et al., 2022b). Additionally, as quality control measures, qualifier ions were employed to ensure selectivity, and the agreement between the quantifier and qualifier ions in the present study was within ± 1–5% for all samples measured (n = 168). Furthermore, a drift standard containing 50 nM trimethylsulfonium was repeatedly measured over the course of measurements to ensure measurement stability. The measured concentrations in the trimethylsulfonium drift standards were within the range of 49–53 nM. Additionally, a set of urine samples (n = 8) was reanalyzed to ensure repeatability and the results were within ± 3–14%. Finally, inhouse reference urine was analyzed and the measured concentrations of all target analytes included in the present work were within ± 10% of the expected concentrations. The in-house reference urine was stored for at least 2 years at − 20 °C and the agreement with the initially measured concentrations indicates long-term chemical stability in the urine matrix at these storage conditions.

The urinary levels of cystine, thiosulfate, and trimethylsulfonium in the total number of 168 urine samples, reported as geometric mean (95% confidence interval), were 47 μM (44−50), 13 μM (12−15), and 56 nM (48−68), respectively. Table 1 shows the levels of the three metabolites in each of the eight studied volunteers.

Although both thiosulfate and trimethylsulfonium are related to hydrogen sulfide, it is interesting to observe that trimethylsulfonium levels are > 100-fold lower than those of thiosulfate. The discrepancy

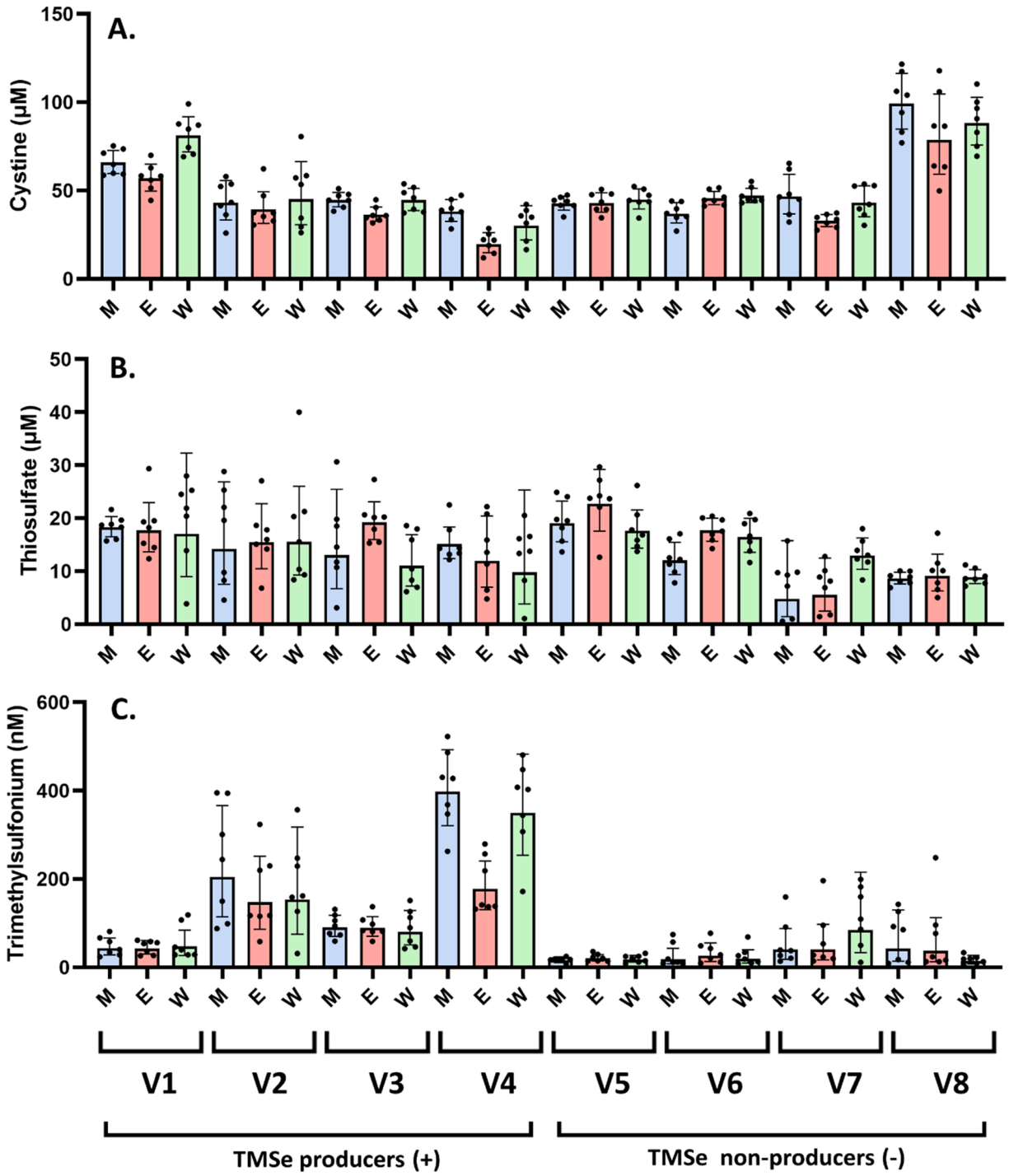

Fig. 2. Urinary levels of the studied sulfur compounds in the recruited volunteers. Each volunteer donated 1 morning urine and 1 evening urine over 7 consecutive days followed by 1 morning urine over 7 consecutive weeks. The graphs show the geometric mean and its 95% confidence interval along with individual datapoints for cystine (A), thiosulfate (B), and trimethylsulfonium (C). Each bar represents data for seven consecutive morning samples (M), seven consecutive evening samples (E), or seven consecutive weekly samples (W) from the eight volunteers' studies (V1–8). Trimethylselenonium (TMSe) production phenotype (indicated by + or -) which was previously found to correlate with trimethylsulfonium production status is shown (see text).

between the above reported micromolar urinary thiosulfate concentrations and nanomolar urinary trimethylsulfonium concentrations in our healthy volunteers, which are unexposed to exogenous (i.e. inhaled) hydrogen sulfide, could be explained when taking into consideration the multiple sources of endogenous hydrogen sulfide exposure in humans and the involved enzymatic activities contributing to the production of these two different metabolites. Specifically, hydrogen sulfide is produced at toxic levels by sulfate-reducing bacteria in the colon with a production rate reported in rats at ca. 0.1 μmol min^{-1} (Suarez et al., 1998). Concentrations in the human colon were reported to build up to millimolar concentrations (Blachier et al., 2010), which constitutes a major source of exposure to hydrogen sulfide in humans. The major route to protect against toxic buildup of hydrogen sulfide in human colon is enzymatic oxidation to sulfate and thiosulfate, which is carried out by rhodanese, an enzyme that displays high activity in the colonic mucosa (Levitt et al., 1999; Picton et al., 2002). On the other hand,

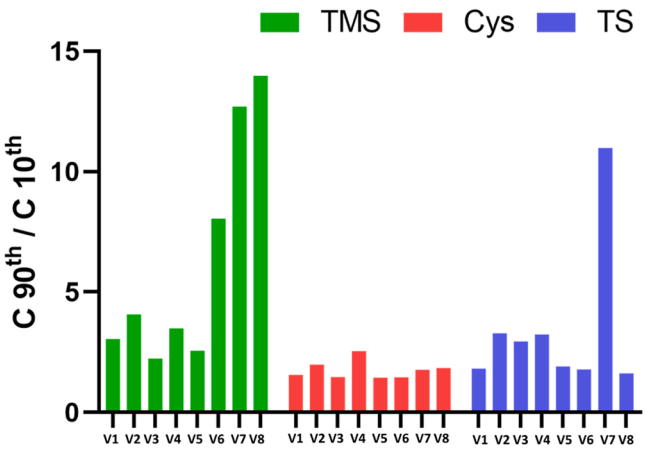

Fig. 3. The intra-individual variability in the urinary excretion of trimethylsulfonium (TMS), cystine (Cys) and thiosulfate (TS). The graph displays the ratios between the 10th and 90th percentile concentrations observed for the three metabolites in each of the eight volunteers (V1-V8) based on the total number of urine samples for each volunteer (n = 21) collected over the study period of 2 months. Note the higher variability for trimethylsulfonium and thiosulfate relative to cystine.

methylation of hydrogen sulfide in the colonic mucosa does not occur to a significant extent and in fact introduced methane thiol, which can also be produced by the bacteria in the colon, was reported to undergo demethylation and then oxidation to thiosulfate (Levitt et al., 1999). In other words, unlike trimethylsulfonium, urinary thiosulfate may predominately reflect the pronounced bacterial exposure to hydrogen sulfide in the colon over the endogenous hydrogen sulfide exposure due to enzymatic degradation of cysteine in tissues and this may at least partly explain the wide difference in the background concentration levels between trimethylsulfonium and thiosulfate in the studied volunteers. It is interesting to note that steady-state concentrations of hydrogen sulfide in mammalian tissues, produced by enzymatic degradation of cysteine, are within the low nanomolar range (10–20 nM) (Vitvitsky et al., 2012) which seems to be much more closely reflected by the nanomolar trimethylsulfonium levels in urine than the micromolar thiosulfate levels. This implies that trimethylsulfonium may be a more suitable biomarker for probing the levels of this gasotransmitter in tissues.

In an earlier investigation involving a small study cohort, we found association between the urinary levels of trimethylsulfonium and those of the selenium analogue trimethylselenonium (Lajin and Francesconi, 2016a). The rationale behind this previous investigation was that both trimethylselenonium and trimethylsulfonium are known to be produced by the same enzyme indolethylamine *N*-methyl transferase enzyme (INMT, also called thioether *S*-methyl transferase TEMT) from their respective substrates dimethylselenide and dimethylsulfide (Mozier

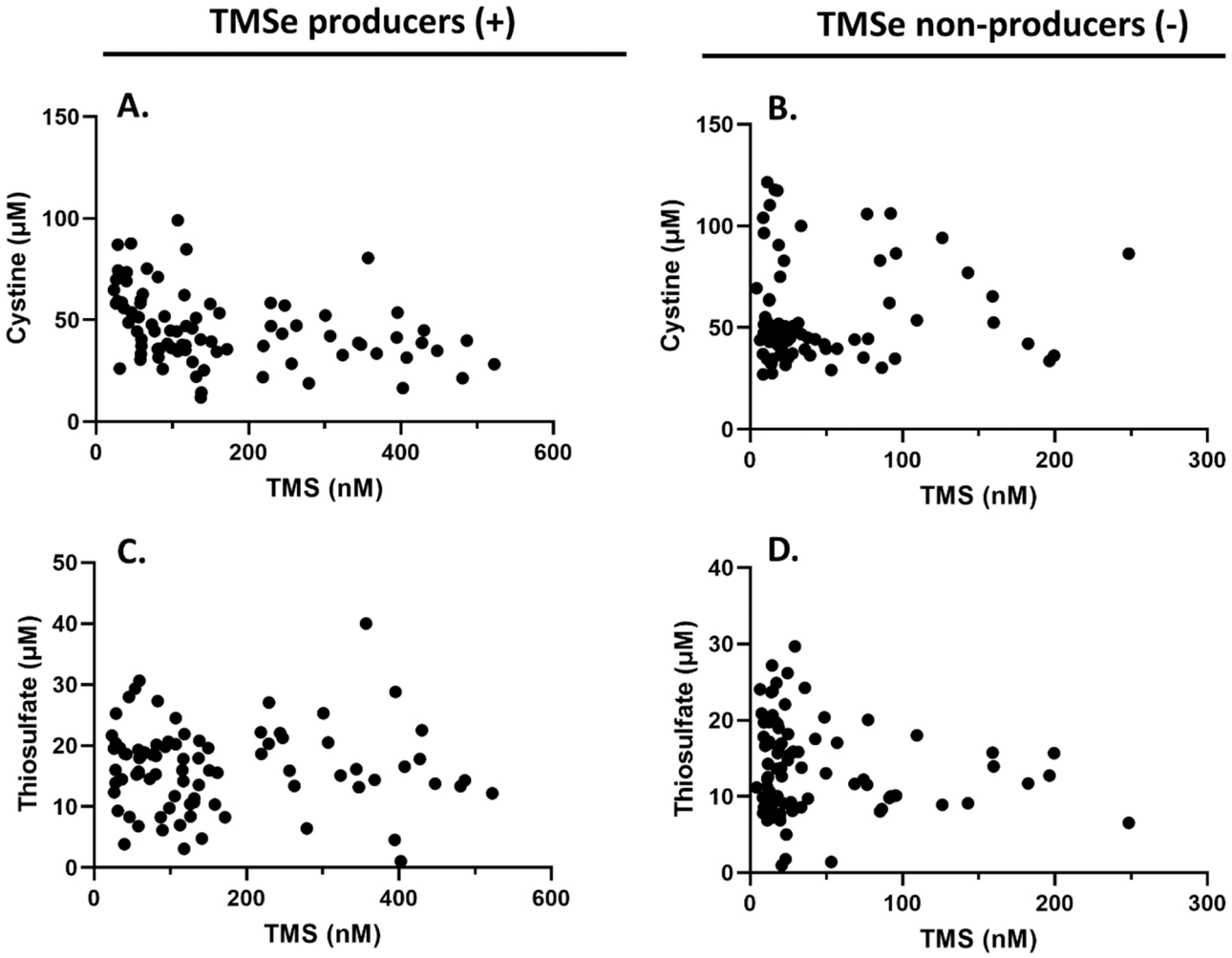

Fig. 4. Investigating the correlation between trimethylsulfonium excretion and cystine and thiosulfate excretion in volunteers grouped according to their TMSe production phenotype (see text). Graphs A and C are related to urine samples collected from TMSe producers. Graphs B and D are related to urine samples collected from TMSe non-producers.

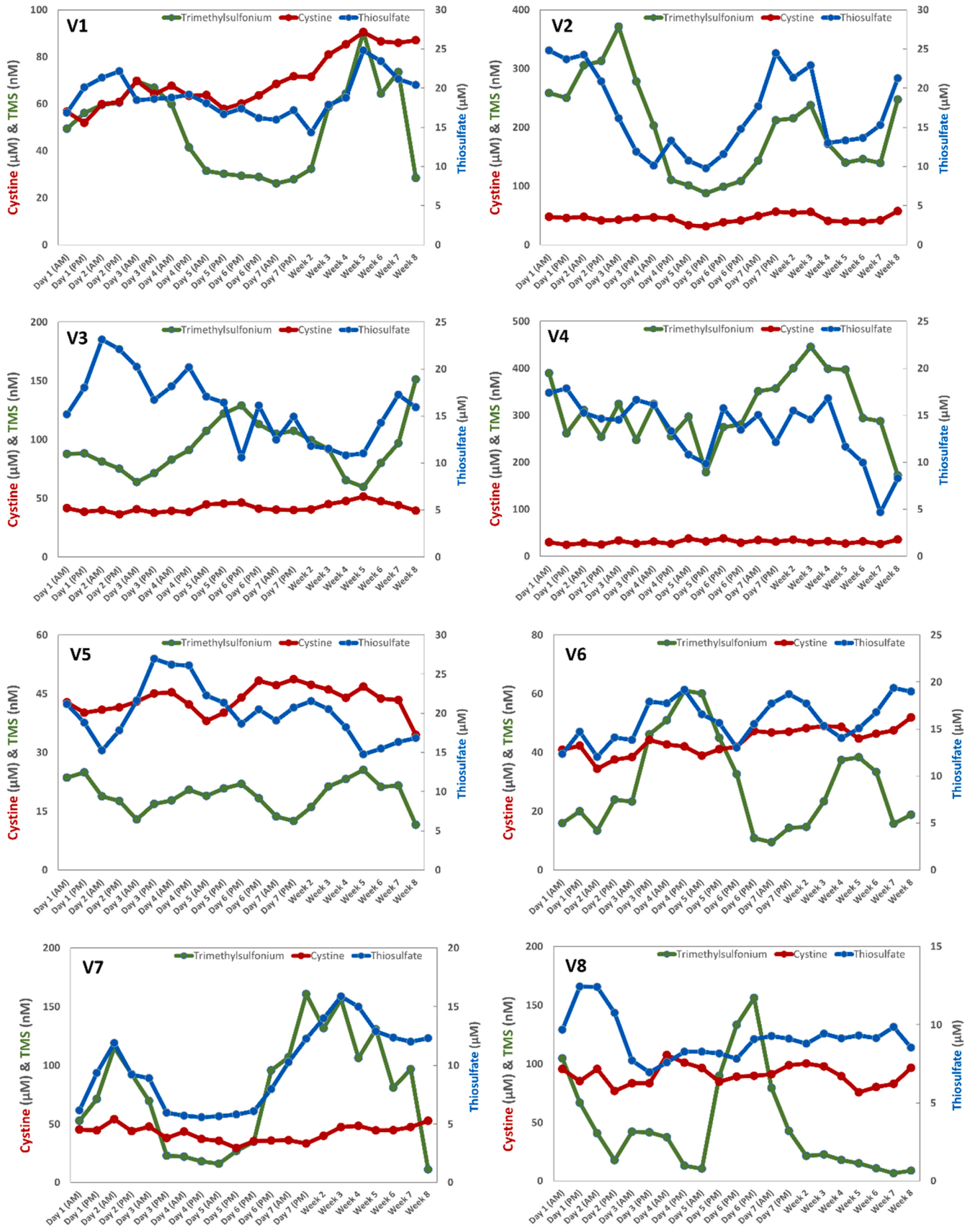

Fig. 5. The concentrations of trimethylsulfonium, cystine, and thiosulfate in urine of each of the eight studied volunteers over the entire sample collection period (2 months). Moving averages (n = 3) was used to facilitate the visualization of the time-concentration trends and the comparison between the three metabolites.

et al., 1988). Furthermore, genetic polymorphisms have been recently identified in the *INMT* gene (Kuehnelt et al., 2015). These polymorphisms have been found to explain the major inter-individual variability (up to 1000-fold) in the urinary excretion of trimethylselenonium which has been consistently observed and reported over the past two decades (Jäger et al., 2016; Kuehnelt et al., 2006; Lajin et al., 2016a). For this reason, we included the trimethylselenonium excretion phenotype in the present work, determined as previously described (Lajin et al., 2016c) and classified our volunteers into TMSe producers (volunteers 1–4) and TMSe non-producers (volunteers 5–8).

In the present work, trimethylsulfonium urinary levels were found to be significantly higher ($P < 0.001$) in the TMSe producers group (117 nM (97−141)) than in the TMSe non-producers group (27 nM (22−34)), which is a difference by < 10 fold (Fig. 1). However, confirming the previous finding (Lajin et al., 2016d), it is clear that this observed inter-individual difference (<10-fold) in the excretion of trimethylsulfonium is not as profound as the > 200-fold difference commonly reported for trimethylselenonium (e.g. 0.02 – 0.028 μg Se L^{-1} in TMSe non-producers Vs. 4.6–15 μg Se L^{-1} in TMSe producers (Kuehnelt et al., 2006)). This suggests that the activity of the INMT enzyme is less of a limiting factor for the production of trimethylsulfonium than that for trimethylselenonium and/or that the genetic polymorphisms responsible for TMSe variability have a larger impact on the methylation of the selenium than the sulfur substrate.

While the variability in thiosulfate excretion has been previously investigated (Lajin, 2022a), there is no previous report about the long-term week-to-week and month-to-month stability in the urinary excretion of trimethylsulfonium in humans. We found no evidence of a diurnal pattern for the excretion of trimethylsulfonium in urine (see combined morning (M) and evening (E) levels in Fig. 2), but there was significant day-to-day intra-individual variability in the excretion of trimethylsulfonium, despite adjusting the concentrations to specific gravity to account for variability in fluid intake. On the other hand, cystine, the dietary amino acid and the precursor for endogenous hydrogen sulfide production, displayed relatively high stability (Fig. 3).

Furthermore, a lack of correlation between the concentrations of thiosulfate and trimethylsulfonium was generally observed in the present study (Fig. 4). However, a notable exception was observed in volunteer 2 and to a lesser degree in volunteer 7 where urinary concentrations of thiosulfate and trimethylsulfonium were parallel (Fig. 5). On the other hand, a consistent decrease on day 4–7 and increase on day 5–7 in the urinary concentrations of trimethylsulfonium not mirrored by thiosulfate were observed in volunteer 1 and volunteer 8, respectively (Fig. 5). The origin of these various patterns is unclear and may warrant investigation in a larger number of volunteers. It is noteworthy however that the occurrence of both thiosulfate and trimethylsulfonium in human urine might reflect direct and independent exposure to their immediate precursors sulfite (Hildebrandt and Grieshaber, 2008) and dimethylsulfide (Mozier et al., 1988), respectively. For example, sulfite is a common preservative in food and alcoholic beverages (Cressey and Jones, 2009), whereas dimethylsulfide can be a thermal degradation product of S-methylmethionine which is found in some vegetables (Scherb et al., 2009). Moreover, food of the genus Allium (e.g. garlic) contains multiple sulfur compounds which can give rise to hydrogen sulfide and dimethylsulfide. These possible dietary contributions to the variability in the excretion of thiosulfate and trimethylsulfonium can be the subject of future investigations.

In conclusion, although trimethylsulfonium appears to be a promising new biomarker for hydrogen sulfide, the data in the present work indicates that when interpreting the levels of trimethylsulfonium, the clear inter-individual variability in its urinary excretion has to be accounted for by considering TMSe production phenotype or its associated genotype. Furthermore, significant intra-individual day-to-day and week-to-week variability in the excretion of trimethylsulfonium was also observed and the physiological and biochemical basis for this has to be elucidated. The intra-individual variability in trimethylsulfonium excretion observed in the present study can be at least partly accounted for through the collection of multiple urine samples per individual over several days when attempting to investigate the utility of trimethylsulfonium as a hydrogen sulfide biomarker in future studies.

CRediT authorship contribution statement

Bassam Lajin: Conceptualization, Methodology, Investigation, Validation, Funding acquisition. **Barbara Obermayer-Pietsch B:** Writing – review & editing. **Renato Somma:** Writing – review & editing. **Walter Goessler:** Writing – review & editing, Project administration, Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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