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Relationship between mercury in kidney, blood, and urine in environmentally exposed individuals, and implications for biomonitoring

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ABSTRACT

Background: Individuals without occupational exposure are exposed to mercury (Hg) from diet and dental amalgam. The kidney is a critical organ, but there is limited information regarding the relationship between Hg in kidney (K-Hg), urine (U-Hg), blood (B-Hg), and plasma (P-Hg).
Objectives: The aim was to determine the relationship between K-Hg, U-Hg, B-Hg, and P-Hg among environmentally exposed individuals, estimate the biological half-time of K-Hg, and provide information useful for biomonitoring of Hg.
Methods: Kidney cortex biopsies and urine and blood samples were collected from 109 living kidney donors. Total Hg concentrations were determined and the relationships between K-Hg, U-Hg, P-Hg, and B-Hg were investigated in regression models. The half-time of K-Hg was estimated from the elimination constant.
Results: There were strong associations between K-Hg and all measures of U-Hg and P-Hg ($r_p = 0.65–0.84$, $p < 0.001$), while the association with B-Hg was weaker ($r_p = 0.29$, $p = 0.002$). Mean ratios between K-Hg (in μg/g) and U-Hg/24h (in μg) and B-Hg (in μg/L) were 0.22 and 0.19 respectively. Estimates of the biological half-time varied between 30 and 92 days, with significantly slower elimination in women. Adjusting overnight urine samples for dilution using urinary creatinine resulted in less bias in relation to K-Hg or U-Hg/24h, compared with other adjustment techniques.
Conclusions: The relationship between K-Hg and U-Hg is approximately linear. K-Hg can be estimated using U-Hg and gender. Women have longer half-time of Hg in kidney compared to men. Adjusting overnight urine samples for creatinine concentration resulted in less bias.

1. Introduction

Mercury (Hg) is released to the environment by natural sources, fossil fuel combustion, and industrial activities (Berlin et al., 2015; WHO, 1990; WHO, 1991). The main sources of Hg exposure for environmentally-exposed individuals are diet, where methyl-Hg (MeHg) from fish consumption predominates, and dental amalgam, which releases inorganic Hg (IHg) mainly as metallic mercury vapour (Hg^0). The central nervous system and the kidney are critical organs for IHg in humans, and adverse health effects have been found mainly from occupational exposure (Berlin et al., 2015; WHO, 1990; WHO, 1991).

After ingestion, about 95% of MeHg is absorbed in the gastrointestinal tract, while the uptake of Hg^0 is <1% and uptake is also limited for other IHg species. On inhalation, the absorption of Hg vapour in the lungs is about 80% (Berlin et al., 2015; WHO, 1990; WHO, 1991). After absorption, Hg is transported by blood and distributed to various tissues. Hg^0 is oxidized to Hg^{2+}. MeHg and Hg vapour both pass the blood-brain barrier, but ionic Hg species do not. Most IHg is deposited

Abbreviations: B-Hg, Concentration of mercury in blood; CI, Confidence interval; GFR, Glomerular filtration rate; GSD, Geometric standard deviation; Hg, Mercury; IHg, Inorganic mercury; k, Elimination constant; K-Hg, Mercury concentration in kidney in wet weight; $K\text{-}Hg_{tot}$, Total amount of mercury in kidney; LOD, Limit of detection; MeHg, Methyl-Hg; P-Hg, Mercury concentration in plasma; SD, Standard deviation; SG, Specific gravity; $T_{1/2}$, Biological half-time; U24, 24 h urine sample; U-Alb, Urinary albumin concentration; U-Alb/24h, Urinary 24 h excretion of albumin; U-Hg, Urinary concentration of mercury; U-Hg/24h, Urinary 24 h excretion of mercury; U-Hg/h, Urinary 1 h excretion of mercury; U-HgCrea, Urinary mercury concentration adjusted for creatinine concentration; U-HgSG, Urinary mercury concentration adjusted for specific gravity; U-Crea, Urinary creatinine concentration; UF, Urinary flow rate; UON, Overnight urine sample (first morning sample).

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in the kidney, while MeHg is more evenly distributed in the body, including the kidney (Berlin et al., 2015; WHO, 1990; WHO, 1991). Elimination of IHg occurs via urine and faeces, and urinary Hg (U-Hg) excretion is widely used to assess long-term exposure to and/or the body burden of IHg. MeHg is primarily excreted via bile and faeces (about 90%, as IHg) and to a limited extent in urine (about 10%, again as IHg) (Barregard, 1993; Berlin et al., 2015; Cherian et al., 1978; Johnsson et al., 2005; WHO, 1990; WHO, 1991).

When using U-Hg as a marker of Hg exposure or Hg body burden, ideally 24 h urine samples should be used. However, in practice spot urine samples are used, such as overnight samples adjusted for dilution (Barregard, 1993; Lee et al., 1996; Martin et al., 1996; Mason and Calder, 1994; Trachtenberg et al., 2010). Blood Hg (B-Hg) increases rapidly after exposure to IHg, but under stable exposure can reach a steady state and reflect the body burden (Berlin et al., 2015; WHO, 1991). Information on the relationship between kidney Hg, U-Hg, and B-Hg is very limited, and it is unclear if the relationship between U-Hg and kidney Hg is linear. The biological half-time of U-Hg has been estimated at 40–80 days (Berlin et al., 2015; Ellingsen et al., 1993; Sallsten et al., 1994; Skare and Engqvist, 1990), and has been assumed to also reflect the half-time of Hg in kidneys. The biological half-time of MeHg in whole body and blood has been estimated at about 70 and 50 days, respectively (WHO, 1990).

Attempts to quantify the levels of kidney Hg and the relationship between kidney Hg and Hg in urine, blood, and plasma (P-Hg) have been made using autopsy studies (Aalbers et al., 1987; Drasch et al., 1992; Falnoga et al., 2000; Johansen et al., 2007; Lech and Sadlik, 2004; Nylander et al., 1987; Nylander and Weiner, 1991; Weiner and Nylander, 1993) and by in vivo X-ray fluorescence (XRF) analysis (Bloch and Shapiro, 1981; Borjesson et al., 1995). However, most studies have been performed on occupationally-exposed individuals. Autopsy studies also have the disadvantages that levels may change post mortem and information on exposure sources may be lacking. For subjects with low environmental exposure, the XRF technique does not provide the needed accuracy (Bloch and Shapiro, 1981; Borjesson et al., 1995).

The present study of kidney donors is the first to provide data on Hg in kidney, urine, blood, and plasma among healthy environmentally-exposed individuals. The aim was to determine the relationship between Hg in kidney, urine, blood, and plasma among such individuals, to use this information to estimate the biological half-time of Hg in kidney, and to provide information useful for biomonitoring of Hg.

2. Material and methods

2.1. Study population and study design

In a study investigating metal concentrations in kidney, blood, plasma, and urine, 152 healthy kidney donors (65 men and 87 women) were recruited between 1999 and 2005 as described previously (Akerstrom et al., 2013a; Barregard et al., 2010). All gave their informed consent, and the study was approved by the Ethics Committee of the University of Gothenburg, Sweden. Before acceptance as a kidney donor, each participant had been examined with routine tests less than one year before the transplantation. Glomerular filtration rate (GFR) (mL/min/1.73 m^2 body surface area) was measured, in most cases as Cr-EDTA clearance or iohexol clearance (GFR was missing for one donor). The participants were admitted 1–2 days before the transplantation, and separate 24 h urine (U24) samples and timed overnight spot urine (first morning [UON]) samples were collected, with collection times and total volumes being recorded. Blood samples were also collected. Details of the sampling equipment used are provided elsewhere (Akerstrom et al., 2013a). The number of amalgam surfaces (total and occlusal) was recorded, and information about occupational history and fish consumption was obtained in a structured interview (Barregard et al., 2010).

In 109 participants (49 men and 60 women), a wedge kidney cortex biopsy was taken as part of the routine procedure at the Sahlgrenska University Hospital, and a part of this biopsy was available for metal analysis. In the other participants, a biopsy was either not available (N = 26) or was too small or of inadequate quality to be used for chemical analysis (N = 17). Blood and plasma samples were available for all participants, but 16 U24 and 5 UON samples were missing. For more background data, see Table 1, Fig. S1 in the Supplemental Material, Barregard et al. (2010), and Akerstrom et al. (2013a).

2.2. Chemical analysis and quality control

Total Hg concentrations in kidney (kidney cortex dry weight concentration), blood, plasma, and urine (U24-Hg and UON-Hg) were determined by cold vapour atomic fluorescence spectrometry (CVAFS) (Sandborgh-Englund et al., 1998a). The analysis of kidney biopsy samples has been described in detail elsewhere (Barregard et al., 2010). The samples were analysed in four different rounds together with external quality control samples and blank samples. The limit of detection (LOD), calculated as three times the standard deviation (SD) of the blanks, was 0.19–0.83 μg/g for kidney cortex concentration (dry weight), 0.18–0.20 μg/L for B-Hg, 0.03–0.10 μg/L for P-Hg, and 0.23–0.33 μg/L for U-Hg. For kidney samples, quality control samples (BCR No. 186, lyophilized pig kidney, certified reference material, Community Bureau of Reference [BCR], Brussels, Belgium) were analysed six times in each round. The results (±SD) were 1.91 ± 0.09 μg/g (N = 6), 1.94 ± 0.09 μg/g (N = 6), 1.75 ± 0.04 μg/g (N = 6), and 1.70 ± 0.10 μg/g (N = 6) versus the recommended 1.97 μg/g. For blood, plasma, and urine samples, Trace Elements Blood/Plasma/Urine, Seronorm AS, Billingstad, Norway, and Blood/Plasma Reference Material, Centre de Toxicologie du Quebec, International Comparison Program, Canada were used as quality control samples. Results versus recommended values (±SD) were 1.93 ± 0.10 μg/L (N = 5) versus 2.0 μg/L, 13.9 ± 0.57 μg/L (N = 5) versus 14.0 μg/L, 7.0 ± 0.20 μg/L (N = 2) versus 6.4 μg/L, 12.0 ± 0.54 μg/L (N = 4) versus 12.0 μg/L, 11.5 ± 0.03 μg/L (N = 2) versus 12.0 μg/L, 1.5 ± 0.24 μg/L (N = 4) versus 2.0 μg/L, 1.96 ± 0.10 μg/L (N = 4) versus 2.0–2.4 μg/L, and 13.2 ± 0.56 μg/L (N = 4) versus 14.0 μg/L for blood samples; 1.91 ± 0.12 μg/L (N = 5) versus 2.0 μg/L, 13.8 ± 0.25 μg/L (N = 5) versus 14.0 μg/L, 6.8 ± 0.14 μg/L (N = 2) versus 6.4 μg/L, 1.4 ± 0.06 μg/L (N = 5) versus 2.0 μg/L, 31 ± 0.07 μg/L (N = 4) versus 33 μg/L, 1.53 ± 0.007 μg/L (N = 2) versus 2.0 μg/L, and 1.97 ± 0.16 μg/L (N = 6) versus 2.0–2.4 μg/L for plasma samples; and 6.2 ± 0.73 μg/L (N = 5) versus 5.0 μg/L, 2.3 ± 0.13 μg/L (N = 3) versus 2.0 μg/L, 4.6 ± 0.14 μg/L (N = 3) versus 4.8 μg/L, and 2.14 ± 0.2 μg/L (N = 4) versus 2.0 μg/L for urine samples.

Table 1
Descriptive data for study participants with a kidney biopsy.

Background factor	All	Men	Women
Participants, N	109	49	60
Age, median (range)	51 (24–70)	52 (32–70)	50 (24–64)
Occupational exposure,[a] N	4	3	1
Amalgam surfaces[b]:			
No, N	7	3	4
Yes, median (range)	19 (1–58)	20 (1–58)	17 (1–53)
Fish meals,[c] N			
<1/month	14	9	5
>1/month but <1/week	42	25	17
1/week	33	17	16
>1/week	20	9	11

[a] Occupational exposures in all these cases were assessed by an occupational hygienist to be low or to have ceased more than ten years before this study.
[b] Information missing for four donors.
[c] Information missing for one donor.