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Analysis of trace metals in single droplet of urine by laser ablation inductively coupled plasma mass spectrometry

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ABSTRACT

Inductively coupled plasma mass spectrometry (ICP-MS) is now widely accepted as a universal and sensitive analytical technique in different research fields. In this project, we applied the technology to the analysis of complex matrix composition by using urine samples from Fabry disease patients and controls. The aims of the project were: (1) to develop a new and rapid analytical procedure for the determination of trace metal concentrations in single droplets of urine using laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS); and (2) to establish preliminary results for trace metal concentrations in Fabry disease patient urine samples and controls. The processing of samples required only drying a homogeneous urine sample. Different supports (or sample substrates) were used: Teflon sheets, Whatman 903 filter paper, Urine Kid paper and glass slides. In order to establish the merits of the analytical method developed, matrix-matched synthetic laboratory standards spiked with analytes of interest were prepared at low concentrations ($\mu g\,L^{-1}$ level). The precision and accuracy of the analytical method were <20% (LA-ICP-MS) for trace metals in 1 μL urine laboratory standards (at analyte concentrations of 300 ng mL^{-1}). The limit of detection varied from 0.003 to 0.58 $\mu g\,g^{-1}$ for lithium, boron, titanium, vanadium, chromium, manganese, cobalt, copper, zinc, arsenic, rubidium, strontium, molybdenum, silver, cadmium, barium, lead, and uranium. LA-ICP-MS allowed the quantification and comparison of different trace metals in urine samples from a Fabry disease patient and from a reference control individual. This method may be applicable to forensic science, particularly when only a small amount of dried urine sample is available for investigation.

1. Introduction

The investigation of nutrient (essential) and toxic elements of body fluids is challenging for analytical chemistry especially the determination of concentrations at the trace and ultratrace levels [1]. Urine is one of the most frequently investigated medical matrices in this field [2–5] because samples can be collected easily and in a non invasive way for the evaluation of possible contamination by toxic metals or also long-lived radionuclides The limits of the use of ICP-MS as a sensitive analytical technique may be demonstrated using urine with complex matrix composition. The analysis of urine by ICP-MS has been reported by several authors [2–5]. The investigation of suspected deficiencies of elements and the assessment of suspected occupational, environmental or acute exposure to toxic elements have also been proposed [6–12]. The potential role of ICP-MS determination in clinical chemistry is still under investigation. Although the actual ICP-MS analysis itself is not time-consuming, the preparation steps are usually both time-consuming and labour-intensive.

Laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) is a sensitive and powerful analytical technique used for the detection of essential and toxic trace elements in solid samples including biological specimens (e.g., tissue sections, teeth, bones, single hair strands, blood, droplets of urine and others). Compared to ICP-MS, LA-ICP-MS has the advantages of direct solid sampling, rapid analysis at low limits of detection and small sample size requirements. Recently, the elemental quantification of

Abbreviations: CHUS, Centre hospitalier universitaire de Sherbrooke; Gb_3, globotriaosylceramide (also known as ceramide trihexoside, or CTH or GL-3); ICP-MS, inductively coupled plasma mass spectrometry; LA-ICP-MS, laser ablation inductively coupled plasma mass spectrometry; LOD, limit of detection; RSD, relative standard deviation.

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dried deposit of biological tissues solubilized with formic acid for LA-ICP-MS determinations was proposed [20].

Fabry disease is an X-linked lysosomal storage disorder caused by deficiency of α-galactosidase A. This enzyme deficiency results in the accumulation of globotriaosylceramide (also known as GL-3, ceramide trihexoside, CTH, and Gb_3) in several organs, including the heart, nervous system, and kidney [13]. Many Fabry patients are not diagnosed until adulthood when irreversible kidney or cardiac damages have occurred. Many authors have proposed the application of mass spectrometry methods to the quantitative analysis of Gb_3 [14–17] in biological fluids. Urine sample collections are not invasive for adults and young children. Efficient methods for Gb_3 detection in urine samples have been recently published [14,15,18,19].

To our knowledge, LA-ICP-MS technology for rapid screening and direct detection of trace elements in urine samples from Fabry disease patients has not been investigated. Therefore, the aims of this work were: (1) to develop a LA-ICP-MS methodology for direct detection and quantification analysis of trace metal concentrations using single droplets of urine; and (2) to establish preliminary results for trace metal concentrations in urine samples from a Fabry disease patient compared to a control individual using LA-ICP-MS.

2. Materials and methods

2.1. Ethics approval

This project was approved by the Research Ethics Board (REB) of the Faculty of Medicine and Health Sciences and the Centre hospitalier universitaire de Sherbrooke (CHUS).

2.2. Fabry patient and control urine specimen collection

After informed consent was obtained, random urine samples were collected from one Fabry disease patient in whom the diagnosis had been confirmed by demonstrating marked enzyme deficiency of α-galactosidase A in leucocytes or by *GLA* mutation analysis and from a control reference individual. Samples were coded, with the key code kept at CHUS, in Sherbrooke, Quebec.

2.3. Chemicals and reagents

All chemicals used were analytical reagent grade. Sub-boiling distillation of nitric acid from Merck was used. High purity deionised water (18.2 MΩ cm) obtained from a Milli-Q system was used for all dilution of mixed metal standard solution and urine samples. ICP multi-element standard stock solution IV (Merck) was used for preparation of matrix-matched laboratory standards for analysis of single droplets of urine.

2.4. Instrumentation and experimental parameters

An ICP-MS spectrometer (XSeries 2 from Thermo Scientific, Bremen, Germany) operating at standard mode was coupled with a laser ablation system UP-266 New Wave – wavelength of Nd: YAG laser: 266 nm (Cambridge, UK). The experimental parameters of the LA-ICP-MS measurements were optimized to obtain maximum ion (M^+) intensity and minimum intensity of oxide (MO^+) and double charge (M^{++}) ions. The ablated material was transferred into the inductively coupled plasma (ICP) using argon as the carrier gas. Maximum ion intensity was observed at a RF (radio frequency) ICP power of 1400 W and carrier gas flow rate of 0.87 L min^{-1} for the transport of ablated material to the ICP-MS. The experimental parameters for LA-ICP-MS are summarized in Table 1.To obtain the elemental concentrations of digested control and Fabry disease urine samples, a quadrupole-based inductively coupled plasma mass spectrometer (ICP-QMS, Agilent 7500, Tokyo, Japan) operating at standard mode equipped with a Cetac ASX-510 Autosampler (Cetac Technologies, Omaha, USA) for automation of the multielement trace analyses was used. Optimized experimental parameters of ICP-MS are summarized in Table 2.

Table 1
Optimized experimental LA-ICP-MS parameters for single urine droplet analysis.

ICP-MS (XSeries 2)	
RF power (W)	1400
Carrier gas (L min^{-1})	0.92
Isotopes measured	^{7}Li, ^{11}B, ^{24}Mg, ^{51}V, ^{52}Cr, ^{55}Mn, ^{57}Fe, ^{59}Co, ^{63}Cu, ^{65}Cu, ^{64}Zn, ^{66}Zn, ^{75}As, ^{85}Rb, ^{88}Sr, ^{98}Mo, ^{107}Ag, ^{111}Cd, ^{137}Ba, ^{208}Pb
Dwell time (ms)	100
Laser ablation	
Method	Single line scan
Repetition frequency (Hz)	20
Spot size (μm)	160
Scanning speed (μm s^{-1})	50
Pulse energy (mJ)	0.084

2.5. Processing and analysis of urinary specimens

Prior to ICP-MS determination, frozen urine samples from a control individual and from a Fabry patient were gradually thawed, first at 4 °C in a refrigerator for several hours and finally at room temperature. Urine samples were homogenized in an ultrasonic bath before sample preparation. The processing flowsheet is presented in Fig. 1. Each sample was divided into two parts: (1) the first part was used for urine droplet preparation; and (2) the second part was used for the ICP-MS solution for trace metal determinations. For urine droplet processing, samples were prepared by depositing 1, 2, 5, and 10 μL of urine sample on four different substrates: Urine Kid paper, Whatman filter paper no. 903 (10 cm × 10 cm) (Whatman-GE Healthcare), glass slide and Teflon sheet. After drying each droplet of urine with an infrared lamp, samples were analyzed by LA-ICP-MS according to the experimental parameters presented in Table 1. For the ICP-MS solution determinations, digested urine samples were diluted, acidified (to 1% HNO_3 final concentration) and spiked with the internal standard (Rhodium (Rh), at 10 ng mL^{-1} final concentration). Diluted urine samples were analyzed for each trace element via an external calibration strategy.

Table 2
Optimized ICP-MS experimental parameters for urine analysis.

ICP-MS (Agilent 7500 ce)	
RF power (W)	1480
Sample uptake rate (ml min^{-1})	0.3
Gas flow rate (L min^{-1})	
Coolant gas flow	14
Auxiliary gas flow	1.4
Nebulizer gas flow	1.1
Ion sampling depth (mm)	5
Ion lens setting	Adjusted to maximum ion intensity
Nebulizer	Concentric nebulizer
Spray chamber	Scott-type double pass spray chamber
Sample/skimmer diameter orifice	Nickel 1.0 mm/0.4 mm
Scanning mode	Peak-hopping
Dwell time (ms)	50
Isotopes measured	^{7}Li, ^{24}Mg, ^{31}P, ^{34}S, ^{39}K, ^{40}Ca, ^{47}Ti, ^{51}V, ^{52}Cr, ^{55}Mn, ^{56}Fe, ^{60}Ni, ^{63}Cu, ^{64}Zn, ^{75}As, ^{85}Rb, ^{88}Sr, ^{98}Mo, ^{103}Rh, ^{111}Cd, ^{137}Ba, ^{208}Pb
Integration mode	Peak area
Points per spectral peak	1

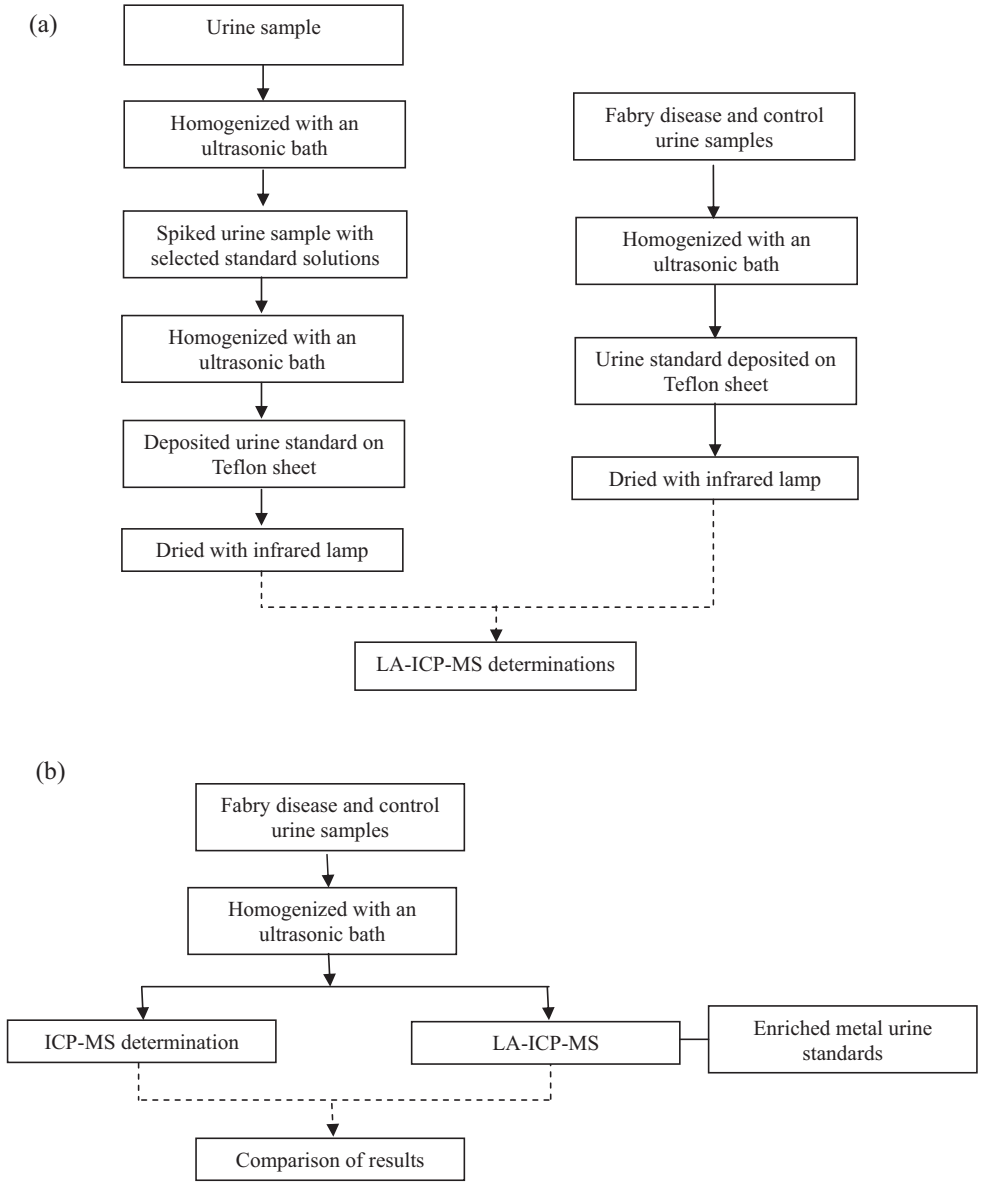

Fig. 1. Experimental flowsheet for sample preparation via calibration strategies (a) and measurement of single droplets of urine by LA-ICP-MS and ICP-MS determination in order to check the accuracy of the LA-ICP-MS method (b).

2.6. Calibration strategy and sample analysis

Matrix-matched laboratory urine standards with well-defined elemental concentrations were prepared for single droplet of urine analysis (see Fig. 1). Three mixed metal stock standard solutions containing the elements of interest (Li, Mg, V, Ti, Cr, Fe, Ni, Cu, Zn, As, Rb, Sr, Mo, Ba, Pb and U) in defined concentrations were prepared. Three aliquots of urine samples were spiked with selected standard solutions. A fourth aliquot was not spiked and was used for blank correction. All standards were homogenized in an ultrasonic bath then transferred to a Teflon sheet and dried under an infrared lamp. The urine standards were scanned first with three lines at the central position of the urine droplet (three replicates). A similar procedure was applied to the control and Fabry urine droplets using the same experimental conditions as used for the analysis of standards. Each point of the calibration curve was the average signal obtained by ablating at least three times. LA-ICP-MS internal standardization was done using the measurement of $^{13}C^{+}$ ion intensities. The calibration curve was obtained by plotting the observed ratio of analyte ion intensities to $^{13}C^{+}$ intensities versus the metal concentrations added in prepared laboratory urine standard solutions. The limit of detection (LOD) for each element of interest was based on three times the standard deviation above the mean for 10 consecutive measurements of the method blank (3σ).

3. Results and discussion

3.1. Type of substrates for droplet of urine preparation

In order to select the best type of substrates for single droplet of urine preparation, four supports were tested: Whatman filter paper, Urine Kid paper, glass slide, and Teflon slide. Signal intensities of elements of single urine droplet deposited on these four supports using LA-ICP-MS are shown in Fig. 2. These results show ion intensities for $^{13}C^{+}$ in Fig. 2 (a) and $^{64}Zn^{+}$ in Fig. 2 (b) for droplet of urine samples deposited on these four supports. We observed that signal intensities of elements of droplets of urine depend strongly on the support used. When one μL of urine sample was deposited on Urine Kid paper and Whatman filter paper, low ion intensities of analytes were detected. When Teflon sheets

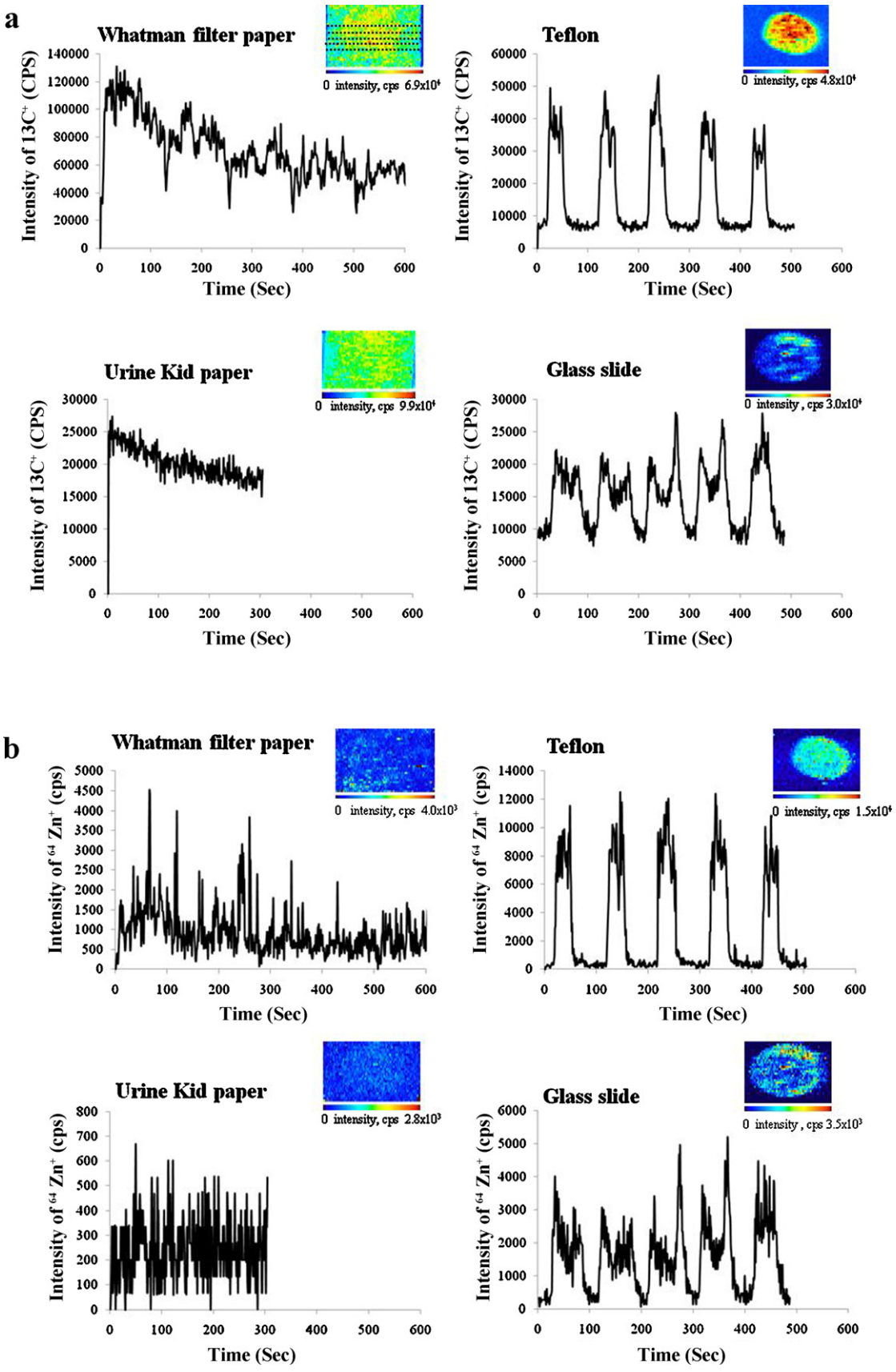

Fig. 2. Signal intensities of ^{13}C (a) and ^{64}Zn (b) for droplets of urine samples deposited on 4 different substrates measured by LA-ICP-MS.

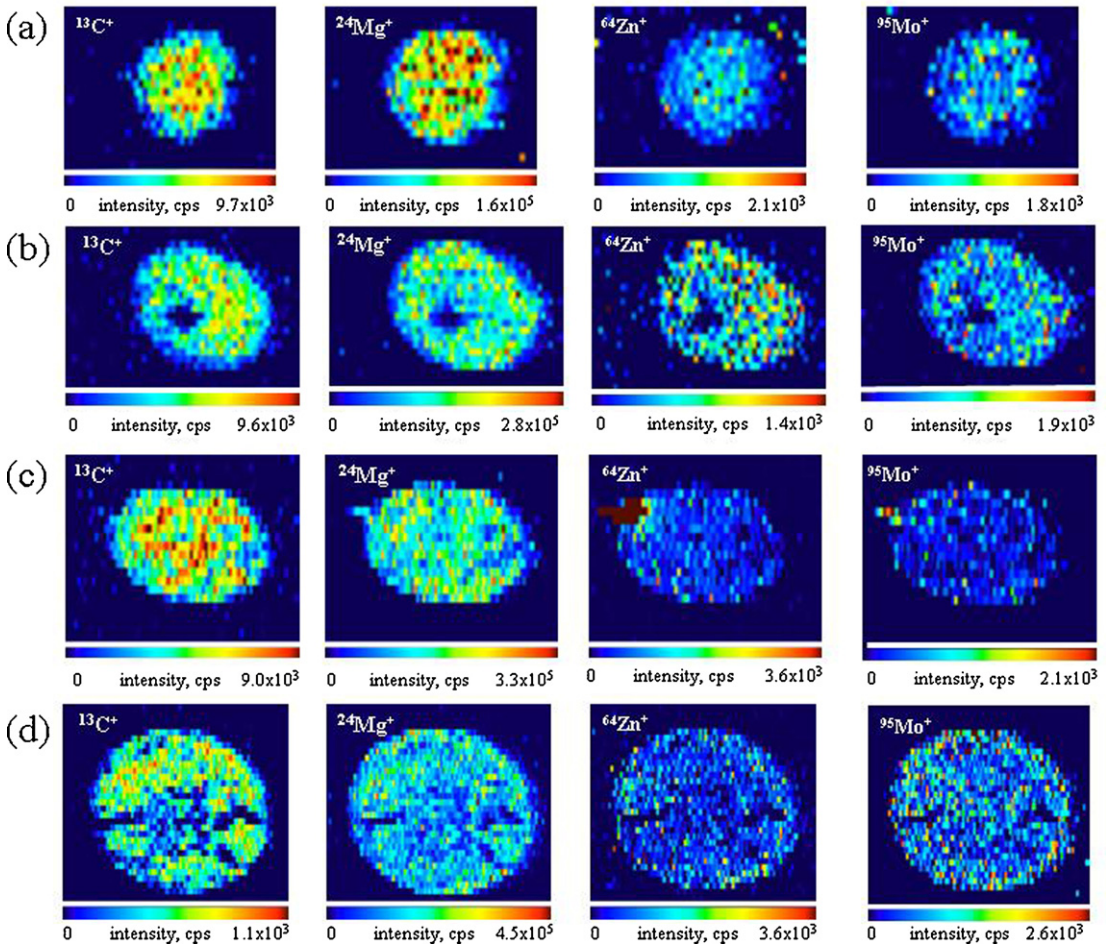

Fig. 3. Elemental imaging of Fabry disease droplets of urine using different volume size deposited on Teflon sheet by LA-ICP-MS: 1 μL (a); 2 μL (b); 5 μL (c); and 10 μL (d).

and glass slides were used as the sample supports, ion intensities of metals (such as Zn) were detected with relatively high intensities (Fig. 2). The low response with Urine Kid filter paper and Whatman filter paper might be due to a strong sample dispersion and high background from paper substrates. No significant background and no strong sample dispersion were detected for the analytes of interest during ablation using Teflon or glass slides. This confirms that these two supports do not generate contamination levels that could compromise the sensitivity of the analysis. Moreover, the size of the urine droplet deposited on Teflon was smaller than the one deposited on the glass slide. We concluded that Teflon was the optimum sample support because it provided good ion intensities of analytes and low background levels even with a small quantity of urine.

3.2. Sample volume investigation for droplet of urine preparation

The effect of urine sample volume on signal intensity of analytes and droplet size was further investigated. Elemental imaging by LA-ICP-MS of Fabry disease patient droplets of urine using different volumes of urine (1, 2, 5, and 10 μL) deposited on a Teflon sheet is presented in Fig. 3 for selected isotopes: ^{13}C, ^{24}Mg, ^{64}Zn, and ^{95}Mo. Volumes of droplets of urine in the range of 1–20 μL were prepared (all data not shown). Significant differences in dried spot size were found when different volumes of urine were used. The droplet size is determined by the volume of urine sample. We noticed that owing to a high urine salt content, the suspended nucleated particles were distributed over the surface of the Teflon sheet, which altered its surface tension resulting in a propensity for the precipitate to adsorb onto the Teflon surface during the evaporation of the sample. When we increased the volume of urine sample, we obtained slightly larger droplet size and lower ion intensities of analytes. We thus selected one μL as the optimum volume for each sample to be deposited on the Teflon sheet because it provided a smaller droplet, relatively good homogeneity, and higher analyte ion intensity. Moreover, several droplets could be deposited over a limited surface area of the Teflon substrate sheet.

3.3. Quantification of trace metal concentrations in single droplets of urine

The urine standards containing known amounts of added metals deposited on Teflon sheets were fixed with double-sided adhesive tape and analyzed directly by line scanning using LA-ICP-MS. Urine standards were scanned with three lines at the central position of the droplet. Each concentration of urine droplet standards was measured in triplicate. In order to compensate for ablation efficiency, ^{13}C was used as the internal standard. Fig. 4 shows the calibration values representing the ratio of analyte ion intensity compared to $^{13}C^+$, plotted against the spiked concentrations in urine standards. Good linear correlation coefficients for the calibration curves ($R^2 > 0.99$) were obtained from the metal enriched urine droplet standards. In addition, the concentration values extrapolated by the calibration curves were similar to the measured values obtained from acid digestion using ICP-MS. The linear regression coefficient of the calibration (R) curves and the LODs experimen-

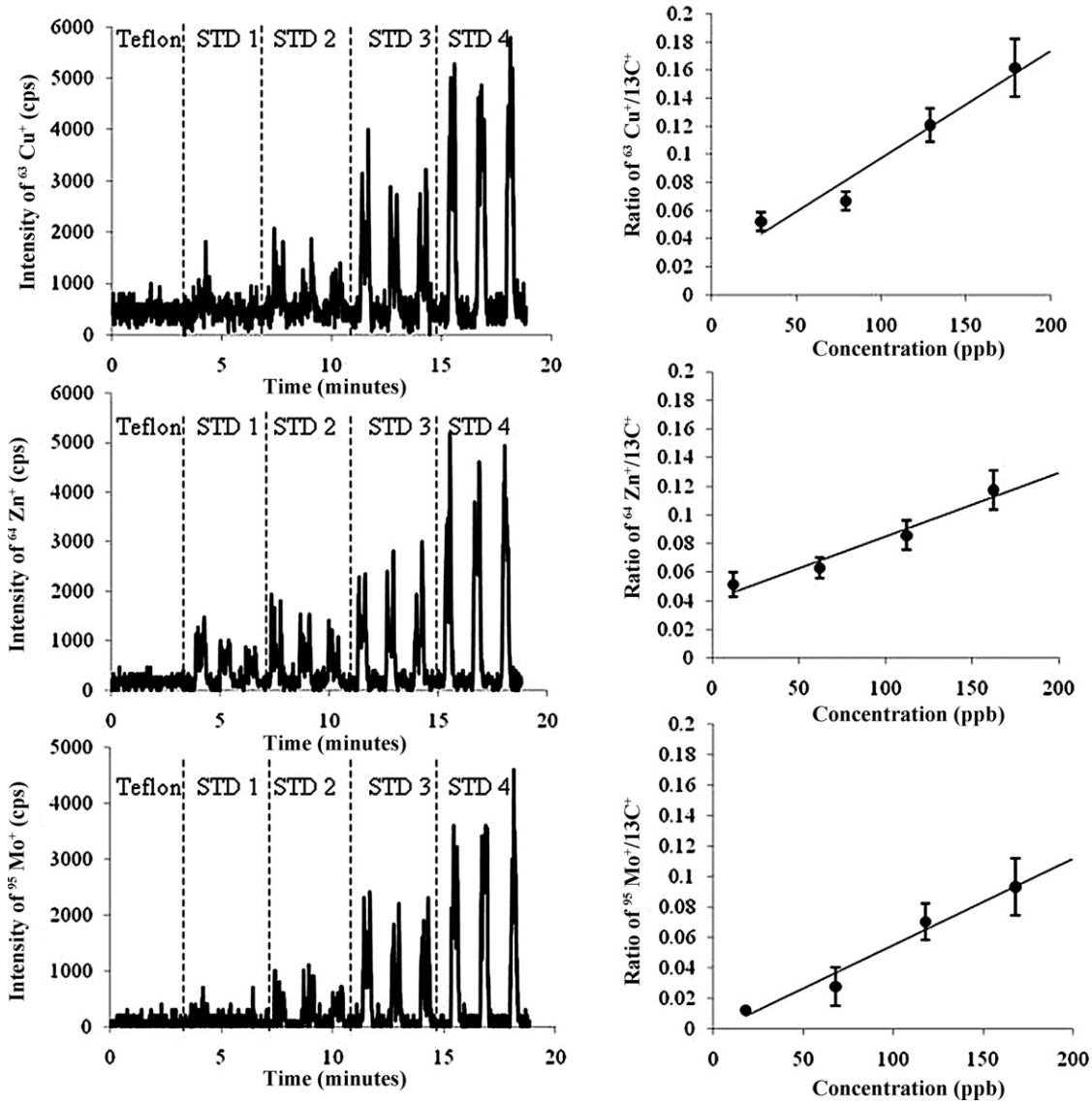

Fig. 4. Signal intensities of analytes in metal enriched droplets of urine standards and calibration curves.

tally determined by LA-ICP-MS are summarized in Table 3. It shows that the values of the linear correlation coefficient are typically between 0.97 and 0.99. The limits of detection varied between 0.003 and 0.58 $\mu g\,g^{-1}$ for Li, B, Ti, V, Cr, Mn, Ni, Cu, Zn, Ga, As, Rb, Sr, Mo, Ag, Cd, Ba, Pb, and U. According to these results, LODs for Mg is much higher than those of other elements owing to instrumental background and isobaric interferences of polyatomic ions on isotopes measured.

3.4. Element concentrations in single droplet of urine from a Fabry disease patient compared to a control sample

The LA-ICP-MS method developed was applied to monitor the concentrations of elements in urine samples from a Fabry disease patient compared to a control individual. After evaluation of all analytes under study (added in the urine standard solutions), we found that only a few elements (B, Mg, Cu, Ti, As, Rb and Mo) were detected by LA-ICP-MS in single droplet of urine from the Fabry patient and the control. In order to evaluate the precision and accuracy of the method, urine samples were analyzed by both solution ICP-MS and LA-ICP-MS. Elemental concentrations obtained by LA-ICP-MS and ICP-MS after acid digestion by measurements

Table 3
Linear regression equations, linear correlation coefficients (R) for calibration curves, and limit of detection (LOD) using metal enriched urine standards in LA-ICP-MS; x is in $ng\,g^{-1}$.

Analytes	Linear regression equations	R	LOD ($\mu g\,g^{-1}$)
^{7}Li	$y = 0.001x + 0.6311$	0.7852	0.586
^{11}B	$y = 0.0003x + 0.0044$	0.9885	0.214
^{24}Mg	$y = 0.0013x - 5.6831$	0.9944	1.8
^{48}Ti	$y = 0.0029x - 0.5184$	0.9480	0.205
^{51}V	$y = 0.0032x + 0.1584$	0.9985	0.026
^{52}Cr	$y = 0.0017x + 0.3138$	0.9879	0.180
^{55}Mn	$y = 0.0017x + 0.2097$	0.9577	0.110
^{60}Ni	$y = 0.0004x + 0.0399$	0.9727	0.120
^{63}Cu	$y = 0.0008x + 0.0194$	0.9795	0.024
^{64}Zn	$y = 0.0005x + 0.0402$	0.9802	0.111
^{69}Ga	$y = 0.0011x + 0.0008$	0.9945	0.004
^{75}As	$y = 0.0005x + 0.0059$	0.9886	0.003
^{85}Rb	$y = 0.0015x - 0.0046$	0.6449	0.528
^{88}Sr	$y = 0.0026x + 0.0644$	0.9606	0.078
^{95}Mo	$y = 0.0005x - 0.001$	0.9842	0.008
^{107}Ag	$y = 0.0005x - 0.0048$	0.9880	0.002
^{111}Cd	$y = 0.0001x - 0.0008$	0.9752	0.021
^{137}Ba	$y = 0.0003x + 0.002$	0.9854	0.022
^{208}Pb	$y = 0.0005x + 0.0032$	0.9268	0.031
^{238}U	$y = 0.0018x - 0.0082$	0.9972	0.003

Table 4
Concentration of metals in urine samples obtained from one control individual and from one Fabry disease patient analyzed by LA-ICP-MS (measuring one urine droplet; calibration was performed with metal enriched urine droplet standards) and ICP-MS after acid digestion of samples.

Analytes	Concentration of metals in urine samples			
	Control individual		Fabry disease patient	
	LA-ICP-MS	ICP-MS	LA-ICP-MS	ICP-MS
mg L^{-1} (ppm)				
Na	1163 ± 250	1800 ± 60	2120 ± 120	2090 ± 60
Mg	16 ± 6	13 ± 2	52 ± 10	62 ± 6
Ca	28 ± 8	19 ± 2	45 ± 9	35 ± 5
μg L^{-1} (ppb)				
Ti	320 ± 30	292 ± 8	497 ± 50	528 ± 30
Cr	<180	14 ± 2	<180	53 ± 5
Fe	668 ± 120	736 ± 44	–	2125 ± 60
Ni	<120	10 ± 2	<120	18 ± 2
Cu	29 ± 10	38 ± 5	95 ± 15	67 ± 11
Zn	28 ± 9	16 ± 4	323 ± 30	393 ± 10
Rb	304 ± 40	480 ± 11	1502 ± 150	1426 ± 60
Sr	<90	32 ± 3	<90	87 ± 8
Mo	23 ± 5	24 ± 2	16 ± 8	23 ± 2
Ba	<22	3 ± 1	<22	7 ± 2
Pb	<31	3 ± 1	<31	4 ± 1

of 1 μL droplet of urine (via the calibration with metal enriched urine droplet standards) are presented in Table 4. The proposed LA-ICP-MS method resulted in a precision mostly less than 20% RSD for all metals detected, whereas the precision by ICP-MS varied from 3 to 10% RSD. Lower precision of data and differences in the metal concentrations obtained from LA-ICP-MS compared to ICP-MS measurements after acid digestion can be explained by inhomogeneous analyte distribution on dried droplet of urine and possible interference problems.

We systematically evaluated Fabry disease urine samples compared to controls (as discussed in another paper of this Special Issue [21]) and found no statistically significant differences in detectable trace metals using the LA-ICP-MS method compared to ICP-MS (p-values were 0.8687 for Fabry disease patients and 0.2627 for controls, respectively). Several elements, like Li, B, V, Ag, Cd, U were not detected in a single droplet of urine (1 μL) by LA-ICP-MS using the urine laboratory standards, but could be measured by ICP-MS. Generally, LODs of ICP-MS were significantly lower than those of LA-ICP-MS due to higher elemental sensitivities, mainly because the volume of urine sample introduced compared to the amount of laser ablated material into the ICP mass spectrometer is larger.

4. Conclusions

A simple procedure and rapid determination of trace metals in single droplets of urine using LA-ICP-MS was developed. Matrix matched synthetic laboratory standard enriched with analytes of interest were prepared for external calibration. The proposed method is convenient for high sample throughput. LODs of trace elements were measured from μg g^{-1} to ng g^{-1} ranges. The processing of samples is simple and rapid and minimizes possible contamination which could affect the sensitivity. Our results demonstrate the possibility of applying single urine droplet analysis using LA-ICP-MS as an easy quantification strategy for elemental monitoring of urine from patients and controls. Single droplets of urine dried on a Teflon substrate could be useful for rapid screening of toxic and essential metals and for systematic investigation of samples from diseased-patients compared to controls. It could also be applicable to forensic medicine studies and clinical research.

Future studies are intended to: (1) improve the analytical sensitivity either by application of more sensitive double focusing sector field ICP-MS or by increasing the laser ablation and transport efficiency of ablated material into the plasma; (2) evaluate other supports (or sample substrates); and (3) to evaluate this methodology with larger cohorts of Fabry disease patients and controls.

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