Analytica Chimica Acta 809 (2014) 1–8

Contents lists available at ScienceDirect

Analytica Chimica Acta

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

Accurate determination of ultra-trace levels of Ti in blood serum using ICP-MS/MS

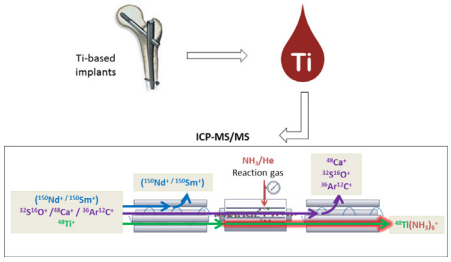
Lieve Balcaen[a], Eduardo Bolea-Fernandez[a], Martín Resano[b], Frank Vanhaecke[a,*]

[a] Ghent University, Department of Analytical Chemistry, Krijgslaan 281-S12, B-9000 Ghent, Belgium
[b] University of Zaragoza, Department of Analytical Chemistry, Pedro Cerbuna 12, E-50009 Zaragoza, Spain

HIGHLIGHTS

- Novel method for determination of Ti at ultra-trace levels in clinical samples (serum).
- Novel method based on $Ti(NH_3)_6^+$ reaction product ion formation and double mass selection using recently introduced ICP-QQQ instrumentation.
- Lowest limits of detection ever obtained using quadrupole-based instrumentation for Ti.
- Accurate determination of basal levels of Ti in blood serum.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 20 August 2013
Received in revised form
26 September 2013
Accepted 10 October 2013
Available online 19 October 2013

Keywords:
Blood serum
Titanium
Reaction cell inductively coupled plasma mass spectrometry
Implants

ABSTRACT

Ti is frequently used in implants and prostheses and it has been shown before that the presence of these in the human body can lead to elevated Ti concentrations in body fluids such as serum and urine. As identification of the exact mechanisms responsible for this increase in Ti concentrations, and the risks associated with it, are not fully understood, it is important to have sound analytical methods that enable straightforward quantification of Ti levels in body fluids (for both implanted and non-implanted individuals). Until now, only double-focusing sector field ICP-mass spectrometry (SF-ICP-MS) offered limits of detection that are good enough to deal with the very low basal levels of Ti in human serum. This work reports on the development of a novel method for the accurate and precise determination of trace levels of Ti in human serum samples, based on the use of ICP-MS/MS. O_2 and NH_3/He have been compared as reaction gases. While the use of O_2 did not enable to overcome all spectral interferences, it has been shown that conversion of Ti^+ ions into $Ti(NH_3)_6^+$ cluster ions by using NH_3/He as a reaction gas in an ICP-QQQ-MS system, operated in MS/MS mode, provided interference-free conditions and sufficiently low limits of detection, down to 3 ng L^{-1} (instrumental detection limit obtained for the most abundant Ti isotope). The accuracy of the method proposed was evaluated by analysis of a Seronorm Trace Elements Serum L-1 reference material and by comparing the results obtained with those achieved by means of SF-ICP-MS. As a proof-of-concept, the newly developed method was successfully applied to the determination of Ti in serum samples obtained from individuals with and without Ti-based implants. All results were found to be in good agreement with those obtained by means of SF-ICP-MS. The typical basal Ti level in human serum was found to be <1 μg L^{-1}, while values in the range of 2–6 μg L^{-1} were observed for implanted patients.

* Corresponding author. Tel.: +32 92644848; fax: +32 92644960.
E-mail addresses: Lieve.Balcaen@UGent.be (L. Balcaen), Eduardo.BoleaFernandez@UGent.be (E. Bolea-Fernandez), mresano@unizar.es (M. Resano), Frank.Vanhaecke@UGent.be (F. Vanhaecke).

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http://dx.doi.org/10.1016/j.aca.2013.10.017

1. Introduction

The determination of low levels of Ti in biological fluids has become a hot topic in the last 10–15 years, mainly because of the increased use of Ti in prostheses and dental implants and the awareness that metallic joint replacement devices can interact with the surrounding body fluids and tissues. As all metallic implants are subject to wear over time, increased serum and urine metal concentrations and, eventually, local and systemic metal storage may be the result [1–7]. Moreover, Ti is also widely used – often under the form of TiO_2 nanoparticles – as a white pigment in paints, coatings, plastics, food, toothpaste or in sunscreen [8]. In 2006, the International Agency for Research on Cancer (IARC) has classified TiO_2 dust as an IARC Group 2B carcinogen, which means that it is possibly carcinogenic to humans [8]. So far, there is no real evidence on the clinical consequences and potential adverse effects of Ti, released in the human body, but there is a clear need for more systematic research on this topic [9].

Over the years, many authors have reported on the basal Ti levels in human body fluids, with values ranging between 0.200 $\mu g\,L^{-1}$ and 200 $\mu g\,L^{-1}$ [5,6,10–13]. The very large spread on these results, indicates that there is a lot of confusion about the actual basal levels of Ti, which makes it also difficult to obtain reliable information on the possible release of additional Ti in the body. This controversy finds its origin in the fact that most of the analytical methods typically used for trace element determination – such as ETAAS (electrothermal atomization atomic absorption spectrometry) [14,15], ICP-OES (inductively coupled plasma – optical emission spectroscopy) [16] or ICP-QMS (inductively coupled plasma – quadrupole-based mass spectrometry) [3,17] – are not sensitive and/or selective enough to allow for an accurate quantification of the ultra-trace levels of Ti in complex matrices, such as human blood (serum). Although, owing to its sensitivity, ICP-MS can generally be seen as the method of choice for the determination of ultra-trace metals in clinical samples, the specific problem for Ti is the occurrence of spectral overlap affecting all Ti isotopes (Table 1) when samples with high Ca, P, S, C and Cl contents (such as clinical samples) have to be analyzed.

Nowadays, the most general way of dealing with spectral interferences is the use of a suited collision/reaction gas in a quadrupole-based ICP-MS instrument (chemical resolution), or of double-focusing sector field (SF)-ICP-MS (higher mass resolution). Sarmiento-González et al. showed that the interferences affecting the Ti isotopes could not be overcome by using H_2 or He as reaction/collision gases in an ICP-QMS instrument, equipped with an octopole reaction cell (or octopole reaction system ORS) [17]. Up to now, only by using a double-focusing SF-ICP-MS instrument, operated at a higher mass resolution ($R = 3000$), a method detection limit of <100 $ng\,L^{-1}$ could be obtained [20]. From the above, it must be clear that the shortness in suitable analytical methodologies severely hinders the research concerning Ti release in the body of people with Ti-based implants, particularly considering that the superior robustness and cost-efficiency of quadrupole-based ICP-MS devices makes these instruments to be more prevalent in routine labs than SF-ICP-MS devices.

It can be noted that very recently a new type of quadrupole-based ICP-MS instrument has become commercially available. This instrument is commonly referred to as a triple quadrupole (ICP-QQQ) set-up, although this terminology is not entirely correct. In fact, in such an instrument, an octopole-based collision/reaction cell is located in-between two quadrupole analyzers. This configuration permits to operate an ICP-MS instrument in MS/MS mode [21,22], which in principle offers superior potential to deal with spectral overlaps. Such instrument should therefore offer improved possibilities for the determination of Ti, although the number of publications reporting on the performance of this spectrometer is still very low and, to the best of the authors' knowledge, no papers reporting on Ti monitoring have been published yet.

Therefore, the main goal of this work is to explore the capabilities of an ICP-QQQ device and develop a novel analytical method that is both sensitive and selective enough to allow for the accurate determination of Ti concentrations in blood serum of non-exposed and exposed individuals.

2. Experimental

2.1. Instrumentation

All measurements were carried out with an Agilent 8800 triple-quadrupole ICP-MS instrument (ICP-QQQ/Agilent Technologies, Japan), equipped with a MicroMist nebulizer and a Peltier-cooled (2 °C) scott-type spray chamber for sample introduction. This instrument contains an octopole-based collision/reaction cell, located in-between two quadrupole analyzers. The octopole cell can be vented or pressurized with a collision gas (typically He) or a reaction gas (typically H_2, O_2 or NH_3/He), or a mixture of both (Fig. 1).

In this work, the possibilities of using O_2 and NH_3/He as reaction gases for the interference-free determination of Ti in a blood serum matrix, were evaluated. As the width of the first quadrupole bandpass can be varied from "fully open" down to "single mass width", an enhanced control over the chemical reactions taking place in the octopole cell is enabled (compared to other reaction/collision cell based instruments). This offers good prospects for the determination of elements which traditionally suffer from spectral interferences when measured with a quadrupole-based ICP-mass spectrometer. Typical instrumental settings and measurement parameters used throughout the experiments can be found in Table 2.

To validate the results obtained by means of ICP-MS/MS, all samples have also been analyzed by means of sector field ICP-MS, which – until now – can be seen as the method of choice for the determination of low levels of Ti in biological materials. For these analyses, a Thermo Element XR sector field ICP-MS instrument (ThermoScientific, Germany) was used, under the conditions specified in Table 2.

Table 1
Titanium isotopes with their natural isotopic abundance [18] and the most important isobaric and polyatomic interferences [19] (non-restrictive list).

Analyte	Abundance (%)	Isobaric interferences	Polyatomic interferences
$^{46}Ti^+$	8.25	Ca^+ (0.004[a])	$^{32}S^{14}N^+$, $^{14}N^{16}O_2^+$, $^{15}N_2{}^{16}O^+$
$^{47}Ti^+$	7.44	–	$^{32}S^{14}N^1H^+$, $^{30}Si^{16}O^1H^+$, $^{32}S^{15}N^+$, $^{33}S^{14}N^+$, $^{15}N^{16}O_2^+$, $^{14}N^{16}O_2{}^1H^+$, $^{12}C^{35}Cl^+$, $^{31}P^{16}O^+$
$^{48}Ti^+$	73.72	Ca^+ (0.187[a])	$^{32}S^{16}O^+$, $^{34}S^{14}N^+$, $^{33}S^{15}N^+$, $^{14}N^{16}O^{18}O^+$, $^{14}N^{17}O_2^+$, $^{12}C_4^+$, $^{36}Ar^{12}C^+$
$^{49}Ti^+$	5.41	–	$^{32}S^{17}O^+$, $^{32}S^{16}O^1H^+$, $^{35}Cl^{14}N^+$, $^{34}S^{15}N^+$, $^{33}S^{16}O^+$, $^{14}N^{17}O_2{}^1H^+$, $^{36}Ar^{13}C^+$, $^{36}Ar^{12}C^1H^+$, $^{12}C^{37}Cl^+$, $^{31}P^{18}O^+$, $^{31}P^{17}O^1H^+$
$^{50}Ti^+$	5.18	Cr^+ (4.345[a]), V^+ (0.25[a])	$^{32}S^{18}O^+$, $^{32}S^{17}O^1H^+$, $^{36}Ar^{14}N^+$, $^{35}Cl^{15}N^+$, $^{36}S^{14}N^+$, $^{33}S^{17}O^+$, $^{34}S^{16}O^+$, $^{35}Cl^{14}N^1H^+$, $^{34}S^{15}N^1H^+$

[a] Isotopic abundance (%) for isobaric interferences.