



Neutron activation analysis for determination of metal ions in biological fluids of patients after CoCrMo arthroplasty

Fotini Noli¹ · Pavlos Papadopoulos² · Pavlos Kolias³ · Eleftherios Tsiridis^{2,4} · Kyriakos Papavasiliou² · Fares Sayegh^{2,4}

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Abstract

Determination of metals and trace elements in patients with total knee or hip arthroplasty with CoCrMo alloy was performed. Blood, urine and cerebrospinal fluid (CSF) samples were analyzed and compared with samples from healthy people. Levels of Co, Cr as well as Na, Ca, Fe, Zn, Se, Rb, Sb and Br were determined by means of neutron activation analysis. The values of Cr and Co of the blood and urine measurements were elevated in patients with replacement, and according to the statistical analysis, significant differences of the elements Zn, Br, Co and Sb were found in the CSF ($p < 0.05$).

Keywords Metal ions · Total knee-hip arthroplasty · Blood · Urine · Cerebrospinal fluid · NAA

Introduction

Total hip and knee arthroplasty (THA) is one of the most commonly performed operation for patients with osteoarthritis leading to improvement of health-related quality of life [1–3]. Only in United States more than one million hip and knee replacements are performed each year according to the Agency for Healthcare Research and Quality and the number of individuals with total hip and knee arthroplasty is more than 7 million. Especially in the last years the number of replacements has increased for young and active patients. Regarding these reported data, of particular interest are the effects of such operations especially due to degradation products of total joint replacements [2–7]. In the case of the metallic components, there is an increasing

concern because of the production of metallic wear debris after arthroplasty. In most cases the implanted materials used for metal artificial joint are CoCrMo or TiAlV alloys [1]. As it is well known ions (some of them toxic) are released from the metallic implants in the body through processes of corrosive and mechanical wear [7–14]. Although cobalt (Co), chromium (Cr), titanium (Ti), aluminum (Al) and vanadium (V) are normal components of some enzymes, at high dosage they become toxic. Cobalt toxicity is associated to several symptoms as neurological, haematological and cardiological. Chromium is known to be less cytotoxic but more genotoxic than Co and causing anemia because may compete with Fe in binding to apo-transferrin. Aluminum toxicity has been linked to neurological conditions as well as the accumulation of Al in the brain has been reported as a possible cause of Parkinson's and Alzheimer's disease [1, 2]. The presence of implanted materials may also be reflected in the levels of other ions in biological fluids of patients with replacement. So, the quantification of metal ion concentrations is of great importance [14–22].

Although several articles have demonstrated elevated metal ion levels from the arthroplasty implants as Co and Cr in serum and urine, data concerning the levels of other metals in human organism and especially in cerebrospinal fluid (CSF) have not published in the literature to our knowledge [4–13, 23]. On the other hand, there are disagreements concerning the levels of the elements in CSF found by different researchers [24–28]. The reason for this is the very low

✉ Fotini Noli
noli@chem.auth.gr

¹ Department of Chemistry, Aristotle University, 54124 Thessaloniki, Greece

² Academic Orthopaedic Unit, Papageorgiou General Hospital, Aristotle University Medical School, Thessaloniki, Greece

³ Department of Mathematics, Aristotle University, 54124 Thessaloniki, Greece

⁴ Centre of Orthopaedics and Regenerative Medicine (C.O.R.E.) - Centre of Interdisciplinary Research and Innovation (C.I.R.I.), Aristotle University, Thessaloniki, Greece

concentrations of the trace elements in the CSF, the limited number of the samples and the limited sample volumes [25]. Michael et al. [24] have applied neutron activation analysis (NAA) for the determination of Co, Cr, Zn and Se in a variety of biological fluids, tissues and organs in patients with medical implants. Kjellin [25] determined trace elements in the CSF in neurological diseases using the same technique.

The aim of this study was to investigate the metal ions levels in biologic fluids of patients following total hip or knee arthroplasty by means of NAA. Levels of Co, Cr as well as Na, Ca, Fe, Zn, Se, Rb, Sb and Br were determined in whole blood, urine and CSF in active patients after CoCrMo arthroplasty and compared with data reported using different analytical techniques.

Experimental

Patients and samples

After giving signed written consent, ten patients enrolled in this study. Measurements of the metal ion levels were performed in the biologic fluids (blood, urine and cerebrospinal fluid) of eight patients who had undergone total hip or knee replacement in the past and two without any endoprostheses in his body. All of them had a primary total hip or knee arthroplasty with cobalt-chromium alloy during the period of February of 2001 till April of 2013. The average age of the patients in the study group was 62 (47–74) years at surgery. Four patients had undergone a total hip reconstruction and 4 patients had undergone total knee arthroplasty (TKA) in the past. At last one patient had undergone TKA bilateral. This cohort study is a subgroup of a larger cohort (100 patients) of arthroplasties, that will be the subject of future measurements.

Whole-blood and urine samples were collected in trace-element blood tubes on successive days of each patient's hospitalization for the surgery procedure at the Papageorgiou Hospital in Thessaloniki. The cerebrospinal fluid samples were collected at the time of epidural anaesthesia with anaesthesiologist assistance in special plastic tubes through a plastic catheter. In addition, they discarded 1 mL of CSF and then the samples were transported on ice [14, 15, 24, 25]. The weight and the volume of all these samples were recorded immediately after the collection. The blood and urine samples were dried at 50 °C at the Department of Chemistry at Aristotle University of Thessaloniki. Finally, a quantity of 100–120 mg was placed in special vials for analysis by INAA. The cerebrospinal fluid samples (5 mL) were centrifuged at 1300g for 10 min according to protocol [14, 22]. Then were placed in special vials (gradually adding a small amount of the sample) and dried at 45 °C leading

to dry residue (approximately 30 mg). All materials were cleaned with distilled HNO₃ and bidistilled H₂O.

Instrumentation

The metals and trace elements of the samples were determined by Instrumental Neutron Activation Analysis (INAA), at the 2 MW pool-type research reactor of the TU-Delft, The Netherlands. The system was calibrated using NIST-measurements. More details (neutron dose $4.5\text{--}5.3 \times 10^{16}$ n/cm² s, activation time 4–5 h) are given elsewhere [29]. After irradiation the activity of the samples was measured. According to protocol three sets of gamma-ray spectrometry measurements were performed considering the different half-life of the radioisotope. The first set was performed after 10 h from the end of irradiation and the third set 30 days approximately from irradiation.

Statistical analysis

Normality of elements concentration in blood, urine and cerebrospinal fluid was tested, using the Shapiro–Wilk test. The measurements of blood, urine and cerebrospinal fluid were treated independently. Welch's analysis of variance was used in order to analyze the differences between the three groups, regarding the blood, urine and CSF measurements. Welch's ANOVA is more powerful and robust compared to classical ANOVA when dealing with small samples or unequal variances. Post-hoc differences were tested using Games-Howell test [30, 31]. The significance level was set to $\alpha = .05$ for all statistical tests. All statistical analyses were performed using IBM SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results and discussion

The concentrations of the studied metals in blood and urine samples are given in Tables 1 and 2 respectively. The values of the elements Co, Cr as well as Na, Ca, Fe, Zn, Se, Rb, Sb and Br are presented whereas the levels of the elements As and Sn were lower than the LOD (limit of detection) in most of the cases and are not presented. The results for the above elements were comparable with relevant published data for blood and urine analyzed by NAA. Avino et al. [17] found similar values for the elements Na, Fe, Zn, Se and Rb in whole blood (slight lower in serum) and urine of healthy people by INAA whereas lower values of Co and Cr were found for non operated people in this research. Michael et al. [24] reported the following values $.16\text{--}.85 \mu\text{g L}^{-1}$ for cobalt in serum by NAA. Damie et al. found concentrations of $\text{Co} \geq .6 \mu\text{g L}^{-1}$ in serum of patients after arthroplasty during a thirty-month study. Clarke et al. also reported comparable

data to the results of the present study in serum of patients who had undergone total hip arthroplasty. These values (Co: .83–2.59 and Cr: 1.19–8.58 $\mu\text{g L}^{-1}$) were determined using atomic absorption spectroscopy 16 months after the operation. Furthermore Lhotka et al. found elevated cobalt and chromium blood levels in patients 4 years after hip arthroplasty. Higher concentrations up to 50 times for cobalt and 100 times for chromium were observed compared to the control group [4, 5, 8].

Table 3 presents the values of Na, Co, Zn, Sd and Br in cerebrospinal fluid. Selenium (Se) was detected only in the

control group (mean value 36 $\mu\text{g L}^{-1}$) while Ca, As and Sn only for the patients of the second (5-years prosthesis) group (mean value 21 mg L^{-1} , 63 and 170 $\mu\text{g L}^{-1}$ respectively). The levels of Cr were lower than the LOD (6.70 $\mu\text{g L}^{-1}$). Therefore the NAA can be used for determination of possible Co release in CSF but not for Cr because of insufficient sensitivity. This finding is in agreement with previous published data for Cr determination in biological fluids where Cr is referred as “difficult” element in NAA and can be determined using radiochemical neutron activation analysis [24, 32, 33]. Unfortunately, there are no data in the literature

Table 1 Descriptive statistics of concentration levels in blood

Element	Non operated				5 years				10 years			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Na (mg L^{-1})	2548	455.38	2226	2870	2270	111.07	2158	2417	2253.75	158.15	2053	2438
Ca (mg L^{-1})	72	4	69	74	132	20	111	155	56	16	41	78
Fe (mg L^{-1})	311	49	276	345	358	47	292	396	351	87	225	421
Zn (mg L^{-1})	5.10	.57	4.69	5.50	4.18	.47	3.51	4.59	4.90	.59	4.27	5.4
Rb (mg L^{-1})	1.84	.54	1.45	2.22	1.85	.14	1.70	2.03	1.76	.08	1.69	1.87
Br (mg L^{-1})	3.53	.47	3.19	3.86	3.30	.60	2.40	3.67	5.13	.59	4.27	5.63
Cr ($\mu\text{g L}^{-1}$)	5.30	.57	4.90	5.70	27.72	5.41	19.80	31.70	9.58	5.96	1.20	15.3
Co ($\mu\text{g L}^{-1}$)	.11	.01	.10	.11	3.70	2.70	.10	5.88	.18	.10	.10	.31
Se ($\mu\text{g L}^{-1}$)	83.65	.78	83.10	84.20	80.95	6.46	72.10	87.40	92.55	10.12	79.80	103.1
Sb ($\mu\text{g L}^{-1}$)	3.40	.28	3.20	3.60	6.00	.47	5.50	6.60	7.96	3.23	5.34	12.60

Table 2 Descriptive statistics of concentration levels in urine

Element	Non operated				5 years				10 years			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Na (mg L^{-1})	1866	606.70	1437	2295	2290	1234.40	1533	4135	1921.25	427.15	1533	2531
Ca (mg L^{-1})	133.7	5.94	129.5	137.90	39.18	13.74	24.50	55.50	28.40	8.66	16.30	36.70
Fe (mg L^{-1})	.07	.01	.06	.07	.60	.35	.17	.92	.07	.03	.03	.09
Zn (mg L^{-1})	.49	.03	.47	.51	.75	.16	.51	.88	1.16	.45	.65	1.71
Rb (mg L^{-1})	1.29	.08	1.23	1.34	.59	.24	.42	.94	.76	.07	.69	.86
Br (mg L^{-1})	2.72	.23	2.56	2.88	1.84	.30	1.46	2.17	3.22	.41	2.95	3.82
Cr ($\mu\text{g L}^{-1}$)	2.30	.00	2.30	2.30	9.53	.99	8.10	10.40	3.15	.62	2.40	3.80
Co ($\mu\text{g L}^{-1}$)	1.00	.42	.70	1.30	2.05	1.22	.30	3.10	.61	.58	.15	1.40
Se ($\mu\text{g L}^{-1}$)	33.30	5.09	29.70	36.90	10.03	1.35	8.72	11.80	19.00	2.41	16.90	22.10
Sb ($\mu\text{g L}^{-1}$)	.22	.09	.15	.28	.48	.25	.16	.75	.48	.18	.29	.66

Table 3 Descriptive statistics of concentration levels in CSF

Element	Non operated				5 years				10 years			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Na (mg L^{-1})	767.50	470.23	435	1100	994.25	91.27	879	1102	998	87.27	889	1098
Zn (mg L^{-1})	1.20	.01	1.20	1.21	1.06	.68	.12	1.61	.82	.12	.68	.93
Br (mg L^{-1})	.10	.00	.10	.10	3.48	1.33	2.52	5.44	4.59	.55	4.00	5.2
Co ($\mu\text{g L}^{-1}$)	2.22	.18	2.09	2.34	.69	.16	.49	.88	2.21	.16	1.98	2.35
Sb ($\mu\text{g L}^{-1}$)	5.26	.38	4.99	5.53	1.13	.26	.78	1.38	1.77	.11	1.65	1.90

for the cerebrospinal fluid concerning patients with arthroplasty, up to our knowledge. Moreover, the reported data for cerebrospinal fluid of healthy people are also limited, determined with different techniques and exhibit large variations. For example, concentrations of Na, K, Ca, Mg, Ba, Ti, Rb, Sr and As determined by ICP-MS in cerebrospinal fluid of patients with and without spinal cord stimulation, were published during a research in Sweden [14]. The values reported for Na (2000–2200 mg L⁻¹) in this research, were higher than these obtained in the present study (435–1100 mg L⁻¹) while the values for As (13–17 µg L⁻¹), were lower than our data (57–68 µg L⁻¹). Lower results were also reported by other researchers for As (.04–2.46 and 30 µg L⁻¹) and Se (.93–2.0, 13.5 and 19.1 µg L⁻¹) respectively [15, 21, 26]. The corresponding values for Co, reported in these papers determined by ICP-MS, were .13 and .0–.22 µg L⁻¹ while for Zn, 32 and 13–249 µg L⁻¹ respectively.

Ostachowicz et al. [19] reported quite higher values for Zn (78.3 mg L⁻¹) determined by XRF as well as for Na (2610 mg L⁻¹), Br (.52 mg L⁻¹) and Ca (26.3 mg L⁻¹). In our study the results for Ca were 14–27 mg L⁻¹ and obtained only for the patients with 5-years prosthesis. Gonzalez Romaris et al. [22] found mean value for Zn 170 µg L⁻¹ and for Ca 50 mg L⁻¹, determined by atomic absorption spectrophotometry-AAS.

In Table 4, literature data for concentration levels of elements, in CSF of control groups determined by different techniques, are presented for comparison. The large variations observed could be attributed to the very low concentrations of the trace elements in the CSF, the limited sample volumes and the fact that CSF samples from healthy humans are typically not available for determination of reference

values of metal species (the CSF by law can be sampled only after neurological indication). The age, quality of life and activities of the humans should be also considered [15, 25].

Taking into account these variations, it is concluded that for the CSF samples, comparisons can be done individually only for the control group of our research and patients with replacement in order to estimate the impact of the implant.

Statistical analysis

According to the Shapiro–Wilk test the concentration values of all elements were normally distributed for each group, except for sodium (Na) in the second group (5 years). Undetected concentrations of cobalt, antimony and chromium in blood and urine as well as of zinc in cerebrospinal fluid were replaced by the limit of detection (LOD) of each element. The mean value and standard deviation of concentration levels of each element in blood and urine are presented in Tables 1 and 2.

Significant differences for the blood tests were observed for Ca, Cr, Sb, and Br ($p < 0.05$). More specifically, for calcium concentration (see Fig. 1) and chromium concentration (see Fig. 2), the patients of the 5-years group had a significantly elevated concentration, compared to the other two groups ($p < 0.05$), which is in agreement with literature data [4–12, 23]. Antimony concentration (see Fig. 3) was significantly elevated in the second group (5 years prosthesis) compared to the first group ($p < 0.05$), while bromine concentration (see Fig. 4) was significantly higher in the third group ($p < 0.05$), compared to the second group (5 years prosthesis) and also higher than the first group, however the effect was borderline significant.

Table 4 Concentration levels of elements in the CSF

	Mean	Min	Max	Method	References
Na (mg L ⁻¹)		2000	2020	ICP-MS	[14]
Na (mg L ⁻¹)	2610			XRF	[19]
Zn (mg L ⁻¹)	78.3			XRF	[19]
Zn (µg L ⁻¹)	34.7			AAS	[27]
Zn (µg L ⁻¹)	170			AAS	[22]
Zn (µg L ⁻¹)		9	133	ICP-MS	[15]
Zn (µg L ⁻¹)		9	167	ICP-MS	[28]
Zn (µg L ⁻¹)		13	249	ICP-MS	[14]
Zn (µg L ⁻¹)	32.5			ICP-MS	[20]
Br (mg L ⁻¹)	.52			XRF	[19]
Br (mg L ⁻¹)	3.80			NAA	[25]
Co (µg L ⁻¹)		.04	.13	ICP-MS	[28]
Sb (µg L ⁻¹)	20.9			AAS	[26]
Sb (µg L ⁻¹)	1.00			NAA	[25]
Sb (µg L ⁻¹)	.09			ICP-MS	[20]
Sb (µg L ⁻¹)		.02	.17	ICP-MS	[28]

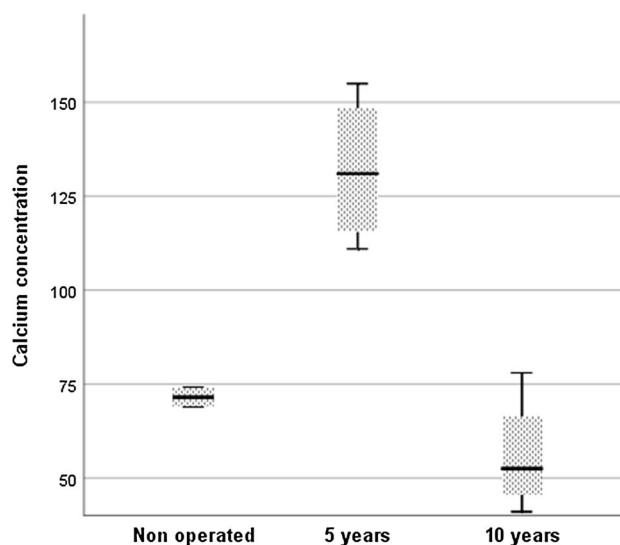


Fig. 1 Boxplot of calcium concentration (mg L⁻¹) of the blood measurement

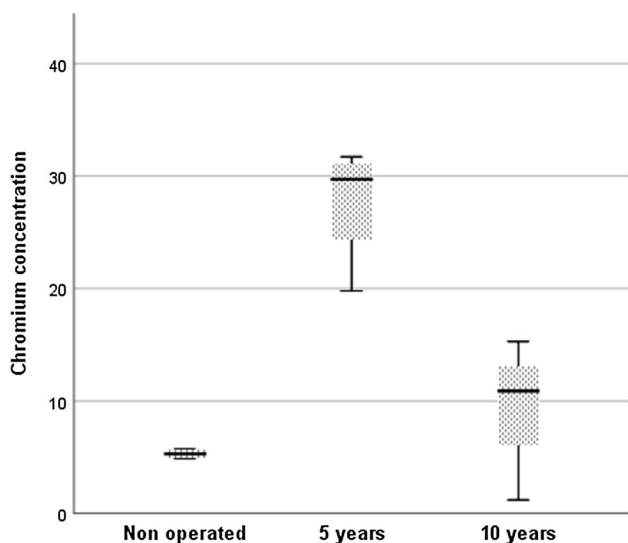


Fig. 2 Boxplot of chromium concentration ($\mu\text{g L}^{-1}$) of the blood measurement

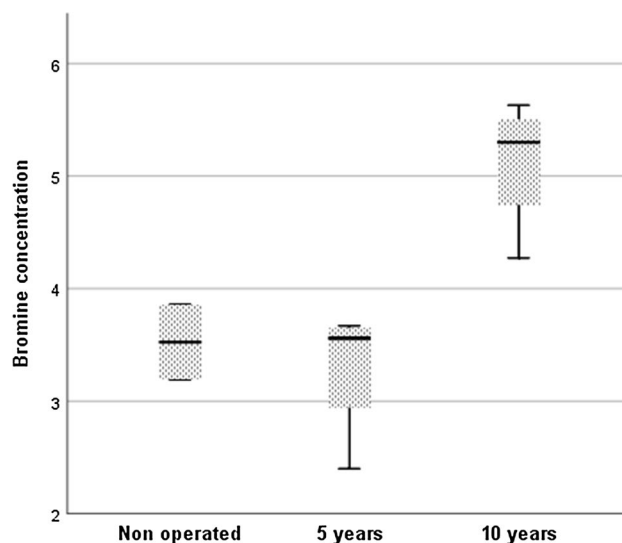


Fig. 4 Boxplot of bromine concentration (mg L^{-1}) of the blood measurement

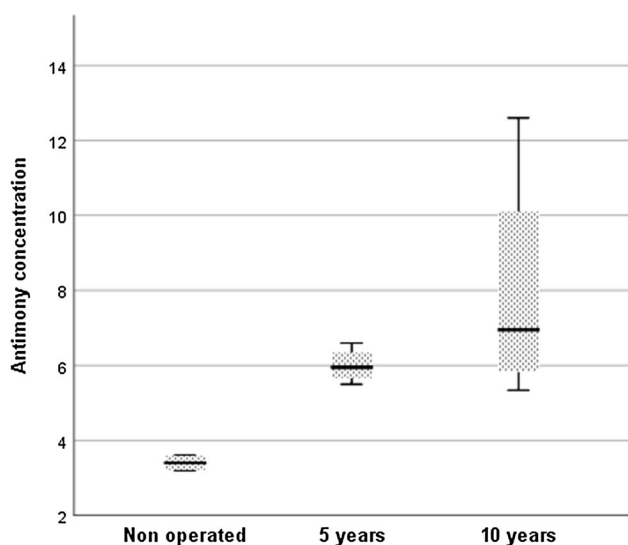


Fig. 3 Boxplot of antimony concentration ($\mu\text{g L}^{-1}$) of the blood measurement

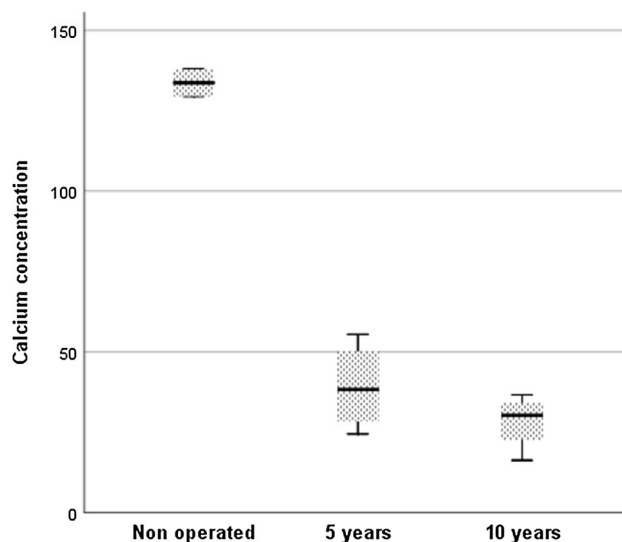


Fig. 5 Boxplot of calcium concentration (mg L^{-1}) of the urine measurement

For the urine tests, significant differences, regarding the concentration, were observed for Ca, Cr, and Br. More specifically, the calcium concentration of the non-operated patients was significantly higher (see Fig. 5) compared to the operated patients ($p < 0.05$), while chromium concentration (see Fig. 6) was significantly elevated in the second group (5 years) compared to the other two groups ($p < 0.05$). Finally, bromine concentration (see Fig. 7) was significantly higher in the third group ($p < 0.05$), compared to the second group (5 years prosthesis).

The mean values and standard deviations for Na, Zn, Br, Co and Sb in the cerebrospinal fluid are given in Table 3. Individuals in the 5- and 10-years groups had significantly elevated concentrations of bromine (see Fig. 8). Zinc was observed to be higher in the control group ($p < 0.05$) compared to the 10 years group. Cobalt and antimony were observed to be significantly lower in the cerebrospinal fluid of the 5 years group (Figs. 9, 10).

The different trend observed for the determined elements in blood, urine and CSF could be probably attributed to the fact that the behavior of each element varies in different biological

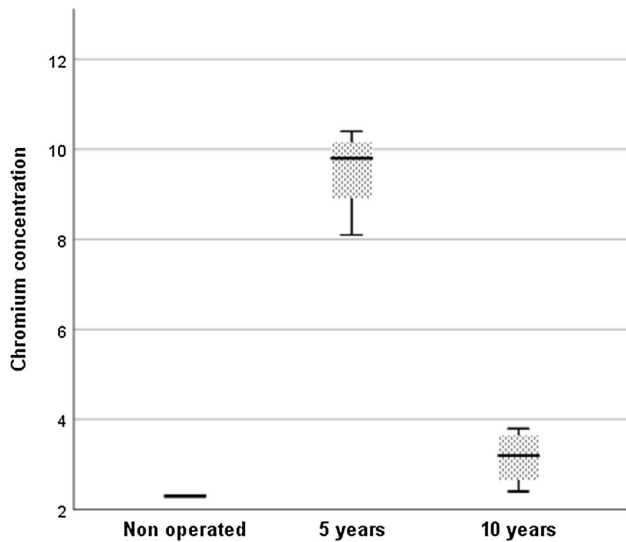


Fig. 6 Boxplot of chromium concentration ($\mu\text{g L}^{-1}$) of the urine measurement

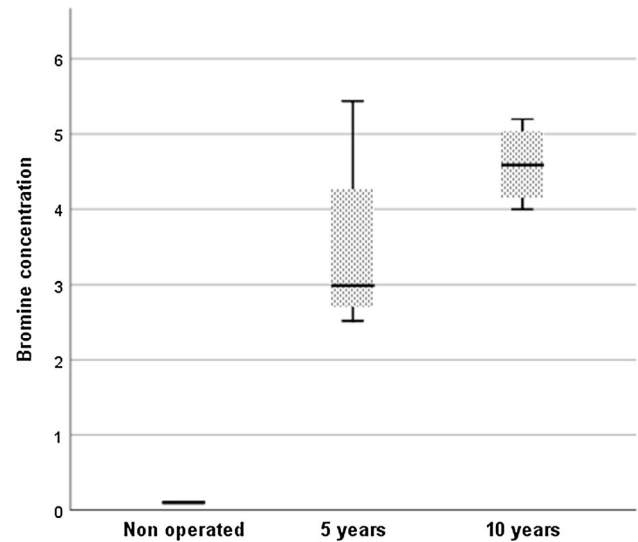


Fig. 8 Boxplot of bromine concentration (mg L^{-1}) of the CSF measurement

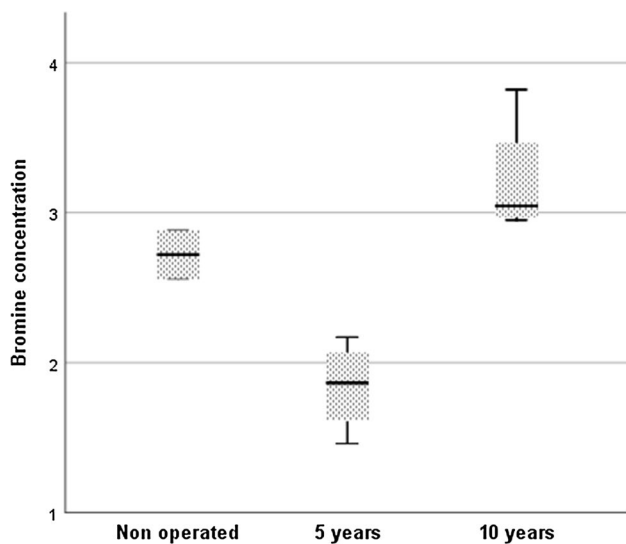


Fig. 7 Boxplot of bromine concentration (mg L^{-1}) of the urine measurement

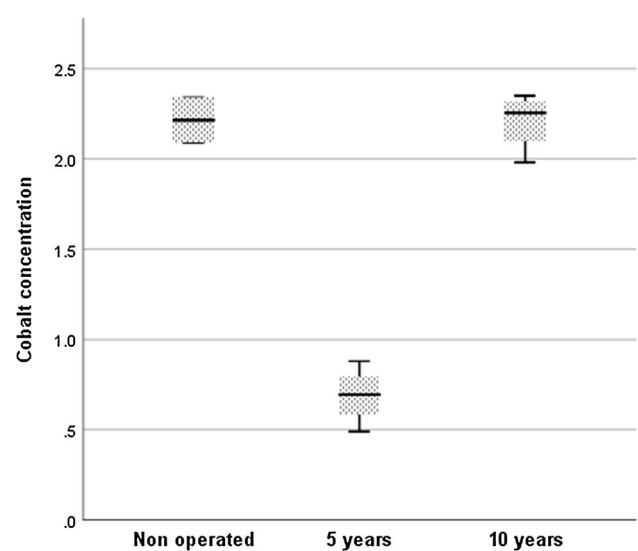


Fig. 9 Boxplot of cobalt concentration ($\mu\text{g L}^{-1}$) of the CSF measurement

fluids or organs. Michael et al. found different levels of Co and Cr in biological fluids, tissues and organs in patients with medical implants. Additionally the determination of the normal concentrations of trace elements is connected with pathological changes found in some cases and also the levels of some trace elements are affected after binding with proteins [24, 25, 34]. Generally, it is shown that the concentration of Co, in CSF, is decreased during the 5 years after replacement and later is increased reaching the initial values. The opposite

phenomenon was observed in the case of blood and urine, where Co and Cr ions released from the CoCrMo bio-implant, increased only in the first period after the replacement, due to corrosion phenomena, and then are stabilizing to normal values. These findings agree with other reported data concerning metals released from implanted biomaterials in blood, serum and urine [4–12, 23, 35].

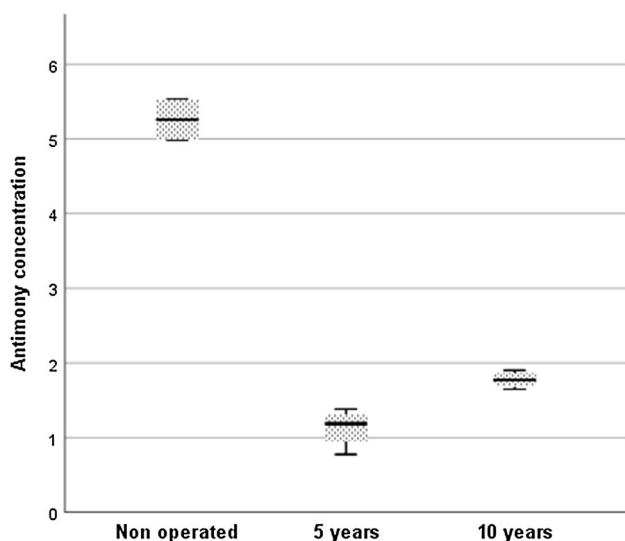


Fig. 10 Boxplot of antimony concentration ($\mu\text{g L}^{-1}$) of the CSF measurement

Conclusions

In the present study, the application of NAA for the investigation of metals and trace elements (Na, Ca, Fe, Zn, Br, Sb, Co and Cr) in blood, urine and CSF of patients with CoCrMo arthroplasty is demonstrated. The results compared to values obtained for healthy people (control group) and concerning the majority of the metals determined in blood and urine, are in agreement with literature data. Slight differences found between the distributions of trace elements in biological fluids in both groups. The concentration of Co and Cr, increased only in the first period after the replacement, as presented by the blood and urine measurements. For the elements Ca, Cr and Br significant differences for the blood and urine measurements were observed based on Welch's ANOVA.

In the case of CSF samples some imbalance between control and non-controls, were observed with significantly elevated concentrations of bromine in the 5- and 10-years groups and zinc in the control group. However due to the small number of patients and the limited published data, the explanation of these findings and connection to metals released mechanism is rather difficult. No conclusions could be drawn on the possible release of Cr and Mo from CrCoMo alloy prostheses to cerebrospinal fluid because of the insufficient sensitivity of NAA.

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References

- Sansone V, Pagani D, Melato M (2013) The effects on bone cells of metal ions released from orthopaedic implants. A review. *Clin Cases Miner Bone Metab* 10(1):34–40
- Michel R, Hofmann J, Lder F, Zilkens J (1984) Trace element burdening of human tissues due to the corrosion of hip-joint prostheses made of cobalt–chromium alloys. *Arch Orthop Trauma Surg* 103:85–95
- Afolaranmi GA, Tettey J, Meek RMD, Grant MH (2008) Release of chromium from orthopaedic arthroplasties. *Open Orthop J* 2:10–18
- Lhotka C, Szekeres T, Steffan I, Zhuber K, Zweymüller K (2003) Four-year study of cobalt and chromium blood levels in patients managed with two different metal-on-metal total hip replacements. *J Orthop Res* 21:189–195
- Clarke MT, Lee PT, Arora A, Villar RN (2003) Levels of metal ions after small- and large-diameter metal-on-metal hip arthroplasty. *J Bone Joint Surg Br* 85(6):913–917
- Savarino L, Granchi D, Ciapetti G, Cenni E, Nardi Pantoli A, Rotini R, Veronesi C, Baldini N, Giunti A (2002) Ion release in patients with metal-on-metal hip bearings in total joint replacement: a comparison with metal-on-polyethylene bearings. *J Biomed Mater Res* 63:467–474
- Jacobs JJ, Skipor AK, Patterson LM, Hallab NJ, Paprosky Black J, Galante JO (1998) Metal release in patients who have had primary total hip arthroplasty. *J Bone Joint Surg* 80-A(10):1447–1458
- Damie F, Favard L (2004) Metal serum levels in 48 patients bearing a chromium-cobalt total hip arthroplasty with a metal-on-polyethylene combination. *Rev Chir Orthop Réparatrice Appar Mot* 90(3):241–248
- Maezawa K, Nozawa M, Hirose T, Matsuda K, Yasuma M, Shitoto K, Kurosawa H (2002) Cobalt and chromium concentrations in patients with metal-on-metal and other cementless total hip arthroplasty. *Arch Orthop Trauma Surg* 122(5):283–287
- Sunderman W, Hopfer S, Swift T, Rezuze W, Ziebka L, Highman P, Edwards B, Folcik M, Gossling H (1989) Cobalt, chromium, and nickel concentrations in body fluids of patients with porous-coated knee or hip prostheses. *J Orthop Res* 7:307–315
- Schaffer AW, Pilger A, Engelhardt C, Zweymüller K, Ruediger HW (1999) Increased blood cobalt and chromium after total hip replacement. *Clin Toxicol* 37:839–844
- Brodner W, Bitzan P, Meisinger V, Kaider A, Gottsauner-Wolf F, Kotz R (2003) Serum cobalt levels after metal-on-metal total hip arthroplasty. *J Bone Joint Surg Am* 85:2168–2173
- Abdel-Gadir A, Berber R, Porter JB, Quinn PD, Suri D, Kellman P (2016) Hart AJ (2016) Detection of metallic cobalt and chromium liver deposition following failed hip replacement using T2* and R2 magnetic resonance. *J Cardiovasc Magn Reson* 18:29
- Korvela M, Linda A, Wetterhall M, Gordhb T, Andersson M, Pettersson J (2016) Quantification of 10 elements in human cerebrospinal fluid from chronic pain patients with and without spinal cord stimulation. *J Trace Elem Med Biol* 37:1–7
- Michalke B, Nischwitz V (2010) Review on metal speciation analysis in cerebrospinal fluid-current methods and results: a review. *Anal Chim Acta* 682:23–36
- Mitchell JD, East BW, Harris IA, Prescott RJ, Pentland B (1986) Short report. Trace elements in the spinal cord and other tissues in motor neuron disease. *J Neurol Neurosurg Psychiatry* 49:211–215
- Avino P, Capannesi G, Manigrasso M, Sabbioni E, Rosada A (2011) Element assessment in whole blood, serum and urine of

- three Italian healthy sub-populations by INAA. *Microchem J* 99:548–555
18. Nasrabadi MN, Forghani D, Shahabi I, Shirini R (2012) Determination of trace elements in blood samples of patients affected by multiple sclerosis from Iran by neutron activation analysis. *J Radioanal Nucl Chem* 293:479–482
 19. Ostachowicz B, Lankosz M, Tomik B, Adamek D, Wobruschek P, Strelciak C, Kregsamer P (2006) Analysis of some chosen elements of cerebrospinal fluid and serum in amyotrophic lateral sclerosis patients by total reflection X-ray fluorescence. *Spectrochim Acta Part B* 61:1210–1213
 20. Alimonti A, Bocca B, Pino A, Ruggieri F, Fortea G, Sancesario G (2007) Elemental profile of cerebrospinal fluid in patients with Parkinson's disease. *J Trace Elem Med Biol* 21:234–241
 21. Roos PM, Vesterberg O, Syversen T, Flaten TP, Nordberg M (2013) Metal concentrations in cerebrospinal fluid and blood plasma from patients with amyotrophic lateral sclerosis. *Biol Trace Elem Res* 151:159–170
 22. Gonzalez Romaris EM, Idoate Cervantes I, Gonzalez Lopez JM, Escanero Marcind JF (2011) Concentration of calcium and magnesium and trace elements (zinc, copper, iron and manganese) in cerebrospinal fluid: a study of a pathophysiological classification. *J Trace Elem Med Biol* 25S:S45–S49
 23. Black J, Maitin EC, Gelman H, Morris DM (1983) Serum concentrations of chromium, cobalt and nickel after total hip replacement: a six month study. *Biomaterials* 4(3):160–164
 24. Michael R, Loer F, Nolte M, Reich M, Zilkens J (1987) Neutron activation analysis of human tissues, organs and body fluids to describe the interaction of orthopaedic implants made of Co–Cr alloy with the patient's organism. *J Radioanal Nucl Chem* 113(1):83–95
 25. Kjellin KG (1981) Trace elements in the cerebrospinal fluid in neurological diseases. *Clin Toxicol* 18(11):1237–1245
 26. El Yazigi A, Al Saleh I, Al Meftty O (1984) Concentrations of Ag, Al, Au, Bi, Cd, Cu, Pb, Sd and Se in cerebrospinal fluid of patients with cerebral neoplasms. *Clin Chem* 30(8):1358–1360
 27. Kapaki E, Segditsa J, Papageorgiou C (1989) Zinc, copper and magnesium concentration in serum and CSF of patients with neurological disorders. *Acta Neurol Scand* 79(5):373–378
 28. Gerhardsson L, Lundh T, Minthon L, Londos E (2008) Metal concentrations in plasma and cerebrospinal fluid in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord* 25:508–515
 29. Bode P, Blaauw M (2012) Performance and robustness of a multi-user, multi-spectrometer system for INAA. *J Radioanal Nucl Chem* 291:299–305
 30. Games PA, Keselman HJ, Rogan JC (1981) Simultaneous pairwise multiple comparison procedures for means when sample sizes are unequal. *Psychol Bull* 90(3):594–598
 31. Brown MB, Forsythe AB (1974) The small sample behavior of some statistics which test the equality of several means. *Technometrics* 16(1):129–132
 32. Kuzelewska I, Polkowska-Motrenko H, Danko B (2016) Determination of chromium in biological materials by radiochemical neutron activation analysis (RNAA) using manganese dioxide. *J Radioanal Nucl Chem* 310:559–564
 33. IAEA, Vienna, 2001, IAEA-TECDOC-1215, ISSN 1011–4289
 34. Rubio JC, Garcia-Alonso MC, Alonso C, Alobera MA, Clemente C, Munuera L, Escudero ML (2008) Determination of metallic traces in kidneys, livers, lungs and spleens of rats with metallic implants after a long implantation time. *J Mater Sci Mater Med* 19(1):369–375
 35. Haynes DR, Crotti TN, Haywood MR (2000) Corrosion of and changes in biological effects of cobalt chrome alloy and 316L stainless steel prosthetic particles with age. *J Biomed Mater Res* 49:167–175

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