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ORIGINAL ARTICLE

Investigating toxic aluminium levels in haemodialysis patients after "Day Zero" drought in Cape Town, South Africa

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ABSTRACT

Introduction: Aluminium is the most abundant metallic element in the earth's crust and can be consumed through water, medications, and by using metallic cooking utensils. Aluminium levels become a concern when they are above biological exposure limits and can present with multiple clinical complications. When patients have chronic kidney disease and are on haemodialysis, impaired aluminium excretion can lead to its accumulation. Significantly elevated serum aluminium levels were noted in patients with chronic kidney disease (stage 5) on haemodialysis at Groote Schuur Hospital, Cape Town, South Africa. This coincided with one of the worst water crises ever experienced in this metropolitan area, with extreme water restrictions being imposed and alternative water sources being accessed.
Method: A multidisciplinary task force performed a systematic evaluation of aluminium concentrations throughout the dialysis water system. Additionally, a thorough investigation was performed to assess the quality of the laboratory results.
Results: Possible areas of contamination and potential sources of exposure were excluded. The laboratory results were verified, and potential sources of error were excluded. The investigation verified that aluminium was truly elevated in the serum of patients, and concluded that dialysis was not the cause. Subsequently, patients' results have declined to baseline, making it possible that there was increased environmental exposure during the drought.
Conclusion: This report serves as a reminder to clinicians of acceptable serum aluminium levels in people on dialysis, and in the water system. Furthermore, it highlights the importance of a multidisciplinary collaborative team approach for the investigation of unexpected results or changes in trends.

Keywords: Aluminium; toxicity; haemodialysis; contamination; kidney; disease.

INTRODUCTION

Aluminium is the most abundant metallic element in the earth's crust [1]. Ubiquitous, it is found *inter alia* in water. Aluminium intake is increased in certain settings, including the use of aluminium cooking utensils [2] and medications – for example, aluminium-containing phosphate binders, liquid erythropoietin, and intravenous iron. Aluminium consumption is a concern in the setting of renal dysfunction where aluminium excretion is impaired [3].

Patients with chronic kidney disease (CKD) stage 5 on haemodialysis (CKD-5D) are exposed to copious quantities of water, approximately 120 to 160 litres per week. Therefore, water for dialysis needs to be carefully processed, including the use of sand and carbon filters, softeners that exchange calcium and magnesium for sodium, and reverse osmosis (RO). RO forces water through a semi-permeable membrane at high pressure

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to remove microbiological contaminants and dissolved ions, such as aluminium. The Association for the Advancement of Medical Instrumentation (AAMI) has established chemical and microbiological standards for dialysis water [4].

International guidelines recommend annual aluminium testing in CKD-5D patients and three-monthly in those receiving aluminium-containing medications [5]. Toxicity results in several clinical effects including dementia, osteomalacia, low bone turnover, microcytic anaemia, cardiomegaly, and increased all-cause mortality [6]. Aluminium levels in the non-exposed normal population should be <10 μg/L (0.37 μmol/L) [5]. The threshold concentration for aluminium indicating toxicity in dialysis patients remains unclear. The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that aluminium levels be assessed at least once per year and that levels should be <20 μg/L (0.74 μmol/L) [7]. Moreover, the dialysate fluid concentration of aluminium should be <10 μg/L (0.37 μmol/L)[8]. The South African National Standard for drinking water (i.e., water from the city) should be <300 μg/L (11 μmol/L) [9].

Aluminium toxicity in CKD-5D patients has declined over time due to the use of fewer aluminium-containing medications, advancements in dialysis and improved filtering systems[10]. After years of acceptable aluminium levels in CKD-5D patients at Groote Schuur Hospital (GSH), Cape Town, South Africa, significantly elevated results were noted in 2019 on routine annual testing (Figure l). No patient had complaints suggesting aluminium toxicity. Amongst other potential explanations, patient exposure, sample contamination, and laboratory error were considered. Consequently, a multidisciplinary task force was created to verify the validity of the results and perform a systematic evaluation of aluminium concentrations throughout the water system (see Figure 2).

The current protocol at the GSH Nephrology Unit requires routine annual surveillance of serum aluminium concentrations in CKD-5D patients. However, during the investigation, the surveillance frequency was increased. Aluminium analysis is conducted annually on municipal water, and the RO water system undergoes twice-yearly aluminium analysis, once as aluminium alone and the second as an annual full chemical analysis. A stepwise approach was used to determine the cause of the rise in serum aluminium levels seen in our patients.

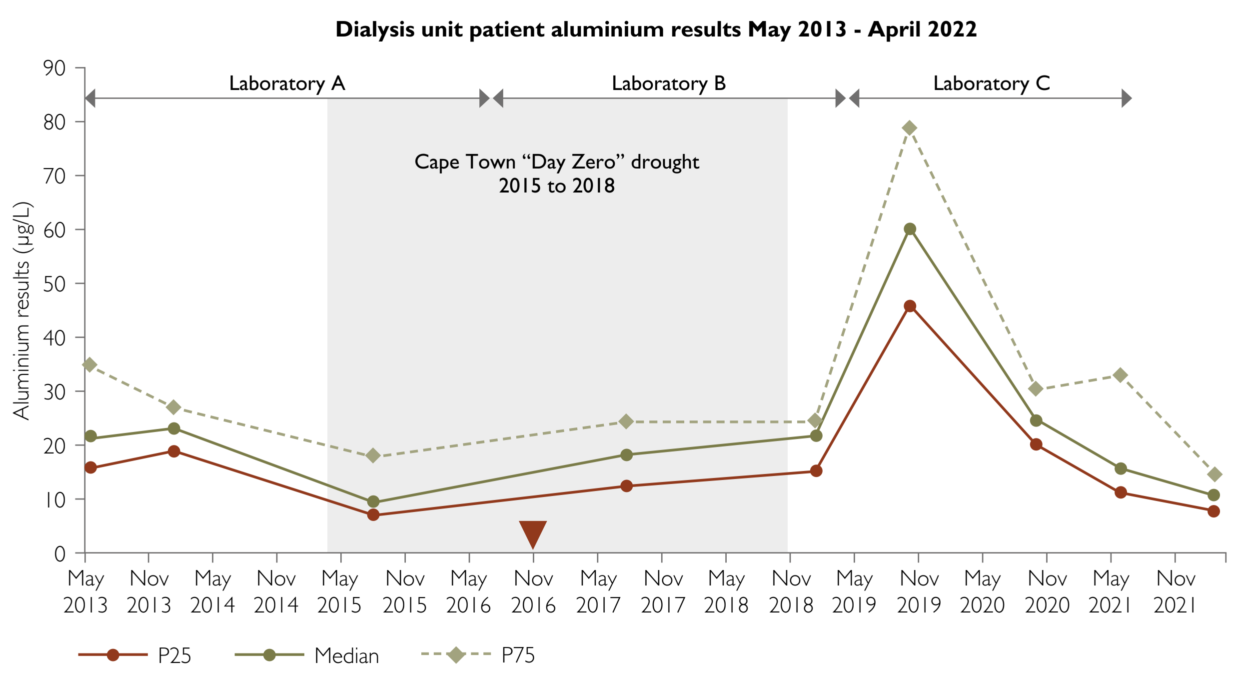

Figure 1. Aluminium results from May 2013 to April 2022. Dialysis unit patient aluminium surveillance results expressed as medians and interquartile ranges (presented as P25 and P75) for the period May 2013 to April 2022. A peak in aluminium values was noted in November 2019, soon after a multi-year drought (shown in grey) depleted the reservoirs of South Africa's second-most populous city, Cape Town, impacting millions of people. Subsequently, aluminium levels have decreased to baseline. In November 2020 and July 2021, aluminium was tested at two laboratories (Laboratory B and Laboratory C, respectively) as part of the troubleshooting exercise to further evaluate the quality of the results. The thick arrow indicates where results from Laboratory A (November 2016) were omitted due to laboratory error (all results returned values of zero).

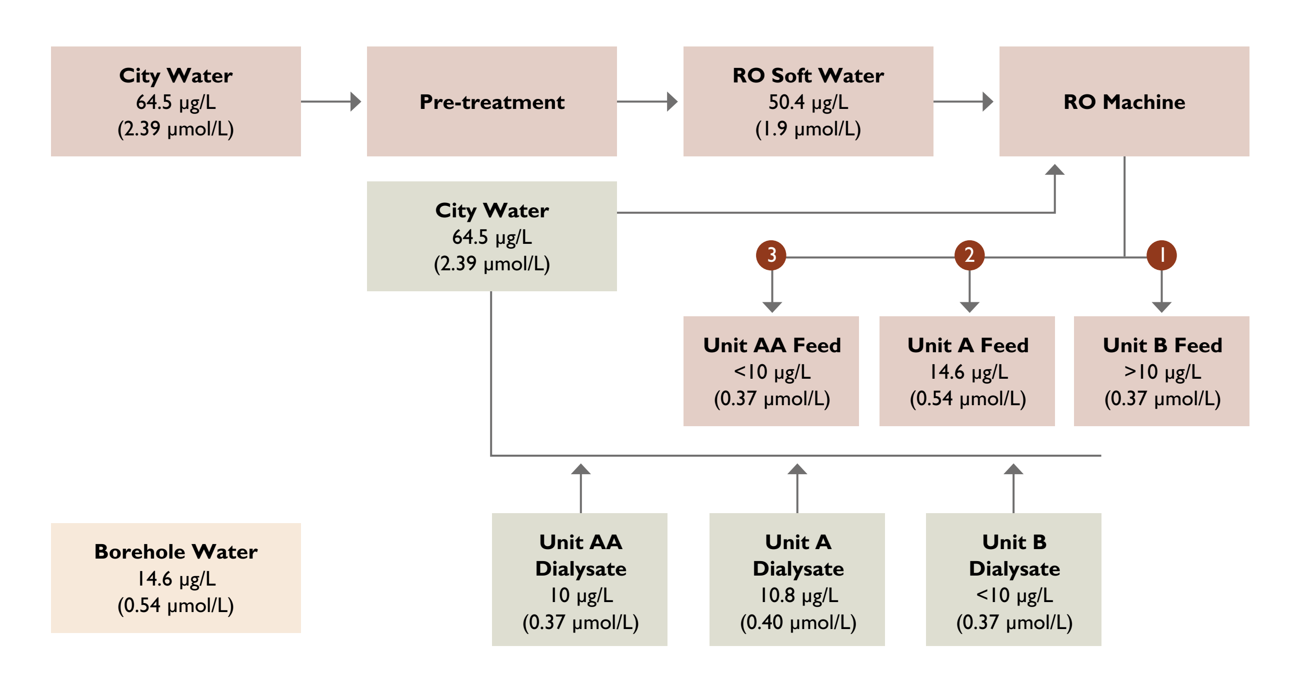

Figure 2. **Sources of water for aluminium testing.** Schematic diagram representing the water circuit in the Dialysis Unit. Points of sampling and the respective values for aluminium are shown. City water was tested as the source, and borehole water was tested for comparison, although borehole water was not used in the unit during the drought.

METHODS

Step 1: Result verification and method comparison

An audit of retrospective data of CKD-5D patients' aluminium levels was performed for the period May 2013 to April 2022 (Figure 1). From 2013 to the present, aluminium levels were routinely measured at one of two different laboratories (referred to here as Laboratory A and Laboratory B). Laboratory A was used from 2013 until it had instrumentation problems in November 2016, reporting all aluminium levels as zero. After this event, Laboratory B was used. After the peak in 2019, Laboratory A was again used, and a method comparison was performed with Laboratory B. An additional laboratory, Laboratory C, was then used for a second method comparison of patient results, and investigation of the water system (compared to Laboratory A). Laboratory D is the dialysis unit's routine laboratory to assess the quality of the RO water.

Aluminium was analysed via atomic absorption spectrophotometry (AAS, PerkinElmer, USA) in Laboratory A. Laboratories B, C and D used inductively coupled plasma mass spectrometry (ICP-MS, Agilent Technologies, USA). To eliminate laboratory error as an explanation for the results, we communicated in detail with all three laboratories, and all quality reports (external quality assurance and internal quality control) were assessed and were within acceptable limits.

Step 2: Systematic approach for water testing from source through RO to patient

Figure 2 represents specific water points within the unit analysed to determine if the patients' elevated results were due to exposure during dialysis. Both city and borehole water were analysed. The primary source comes from the city water that feeds directly into the RO machine. Figure 3 represents potential sites of contamination.

For patient samples, five millilitres of blood were collected into Serum Vacutainer® Becton Dickinson (BD) (Franklin Lakes, NJ, USA) blood collection tubes for trace element testing. These tubes are the standard ones used for trace element testing, are metal-free, and were compared to standard serum tubes by analysing patients' samples in both tubes, as well as RO water in both tubes. Trace element testing tubes are only slightly more expensive than standard serum tubes, approximately R1.80 ($0.10) more per patient. To avoid contamination and other pre-analytical factors from influencing test results, all samples were handled carefully and consistently, following the instructions of the laboratory.

Step 3: Investigation of medication used

Aluminium-containing medication use was excluded with the pharmacy's assistance. No aluminium-based antacid (Gaviscon©, Amphogel© etc.) or phosphate binder (Alutab©) were dispensed during the study period. Salicylates

Source	Al Concentration
A. Butterfly needle	<10 μg/L (0.37 μmol/L)
B. Metal-free blood collection tube	<10 μg/L (0.37 μmol/L)
C. Acid-washed water collection container	<10 μg/L (0.37 μmol/L)
D. Collection device	<10 μg/L (0.37 μmol/L)
E. Metal tap	21.9 μg/L (0.81 μmol/L)

Figure 3. Sources of potential contamination. Sources of potential contamination investigated are shown (A to E), along with the aluminium values. The metal tap outside the unit was evaluated for comparison but is not part of the testing circuit.

contain aluminium but few patients in the unit received salicylates, and there was no increase in salicylate prescription during this period.

Statistics

The Shapiro–Wilk test was used to assess normality. Descriptive statistics are presented as medians and interquartile ranges (IQR). For the method comparison, linear regression, difference plots, and Lin's concordance correlation coefficient were determined. Statistical analysis was performed using Microsoft Excel® (Redmond, Washington, USA).

Ethics consideration

This analysis was performed as part of an investigation for which University of Cape Town Human Research Ethics Committee approval was not required.

RESULTS

Patient aluminium results from 2013 to 2022

Over a 9-year period, 807 patient aluminium results were analysed and monitored. These are presented in Figure 1 and demonstrate stable results from 2013 until 2018. Results are omitted for 2016, when a laboratory error returned aluminium levels of zero for all patients included. The figure also shows the sudden and unexpected peak in 2019, and a progressive decline to baseline during 2020, 2021 and 2022. This trend indicates potential patient exposure to aluminium.

Notably, a small ($n = 5$) method comparison experiment performed subsequently to the peak in 2019, and using patient samples, demonstrated that Laboratory B results tended to be positively biased when compared with Laboratory A. This positive bias was also observed in a concurrent inter-laboratory experiment ($n = 5$) using quality control material. Linear regression of these results gave an r value of 0.92, with a Lin's coefficient of 0.43, in keeping with the observed bias. However, the dramatic peak in results in 2019 did not seem to be fully explained by the observed bias (approximately 60%).

Aluminium analysis in the water circuit of the dialysis unit

The aluminium results from the RO system from 2016 to 2021 were all within acceptable limits, measured at four different laboratories (Table 1). Laboratories have different methods of reporting, and generally, if results are below their detection limits of 10 μg/L (0.37 μmol/L), they will report it as <10 μg/L (0.37 μmol/L). In November 2019 the RO water was measured at 24.8 μg/L (0.90 μmol/L); although not as low as in previous years, this is still within acceptable limits (i.e., <300 μg/L (11 μmol/L)). In 2020, this testing was omitted due to the COVID-19 pandemic. In 2021, the RO system was analysed by three laboratories, as part of this troubleshooting exercise. All were found to be acceptable. The city water had higher aluminium results than borehole water in 2021 (Figure 2). The different points tested within the dialysis unit all had acceptable aluminium levels [<10 μg/L (0.37 μmol/L)].

Table 1. Aluminium results in RO water.

	Nov-16	Nov-17	Nov-19	Jul-21	Jul-21	Sep-21
	Lab A	Lab B	Lab B	Lab A	Lab C	Lab D
RO water	16 µg/L (1.11 µmol/L)	<10 µg/L (0.37 µmol/L)	24.8 µg/L (0.92 µmol/L)	<10 µg/L (0.37 µmol/L)	<10 µg/L (0.37 µmol/L)	<10 µg/L (0.37 µmol/L)
Pre-RO	Not analysed	97.4 µg/L (3.6 µmol/L)	61.3 µg/L (2.3 µmol/L)	50.4 µg/L (1.9 µmol/L)	25.8 µg/L (0.95 µmol/L)	64.8 µg/L (2.4 µmol/L)

Table 2. Comparison of standard serum tubes with trace element tubes.

	Trace element tube Al µg/L (µmol/L)	Standard serum tube Al µg/L (µmol/L)
Patient 1	9.80 (0.36)	15.1 (0.56)
Patient 2	45.9 (1.70)	54.7 (2.03)
Patient 3	12.6 (0.47)	15.6 (0.58)
Patient 4	15.1 (0.56)	21.9 (0.81)
Patient 5	12.6 (0.47)	17.2 (0.64)
Patient 6	14.4 (0.53)	21.2 (0.79)
Patient 7	7.90 (0.29)	12.5 (0.46)
Patient 8	11.2 (0.42)	13.8 (0.51)
Patient 9	8.40 (0.31)	11.4 (0.42)
Patient 10	9.30 (0.35)	14.8 (0.55)
Patient 11	8.10 (0.30)	13.9 (0.52)
Patient 12	8.40 (0.31)	15.3 (0.57)
Patient 13	11.00 (0.41)	14.3 (0.53)
Water	0.8 (0.03)	12.00 (0.45)

Potential sources of aluminium contamination

All results from potential contamination sites after the RO system were within acceptable limits (Figure 3). For comparison, a water sample was collected from a metal tap outside of the dialysis circuit, and aluminium levels were elevated. Additionally, the results show that the trace element tubes had significantly lower aluminium results than the standard serum tubes (Table 2).

DISCUSSION

When elevated aluminium levels were detected, the multidisciplinary task force systematically investigated the problem, looked for potential areas of contamination, and excluded laboratory errors. The abnormal aluminium levels coincided with the worst drought Cape Town has seen for more than 82 years[11]. The "Day Zero" drought was named after the day when the municipal water supply for this major city was estimated to run out. The quality of the city and borehole water was not assessed at the time of the drought, but rather retrospectively when trying to understand potential sources of contamination.

During the time of the drought, the RO membrane did not require changing, and the particle filters were changed every three months, as per protocol. Furthermore, the analysis demonstrated sufficient removal of aluminium, and other contaminants, from the water.

Although the RO water had a higher-than-normal aluminium result (compared to previous years) during this period, the levels are insufficient to attribute to the elevated patient levels of aluminium. However, this does support the theory that patients were exposed to water with higher than the normal aluminium concentrations during the drought period. There is limited information regarding how the city water was treated during stage 5 water restrictions (total water usage limited to 87L per day per person) when the available municipal water was extremely low, but there is evidence that reliance on groundwater increased[12,13]. Additionally, many people accessed water from springs and boreholes [14]. Indeed, it is common for the people of Cape Town to access the large network of publicly accessible spring water collections informally[14]. Cape Town is also reliant on groundwater for its rapidly growing population, and this groundwater is at considerable risk of being polluted[15]. This may explain the higher than normal baseline aluminium levels [13,14] seen in our local setting (see Supplementary Figure 1).

Increased environmental exposure to aluminium from alternative sources – such as cooking utensils and pots – during this crisis period cannot be excluded. It is apparent in several studies that these containers are popular in developing countries and that leaching of various metals, including aluminium, can take place[15]. This theory does not explain the universal rise in aluminium recorded in the unit.

The investigation verified that aluminium was truly elevated in the patients, and we can accurately state that the increase was not because of increased aluminium exposure in the unit. Several potential sources of exposure and contamination were excluded, as well as laboratory error. The cause of this elevation in patients, however, is yet to be determined. Were the patients exposed to significant levels of aluminium from city/spring water during the drought? We were unable to confirm this, but results have subsequently declined to baseline since the end of the drought, without specific intervention.

CONCLUSION

Considering that climate change is an important concern, further droughts are likely to occur and may lead to similar problems. This article, therefore, serves to remind clinicians and dialysis units of the importance of monitoring aluminium levels and acceptable targets. Furthermore, it highlights the importance of a multidisciplinary collaborative team approach for the investigation of unexpected results or changes in trends.

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Conflict of interest

The authors have no conflict of interest to declare.

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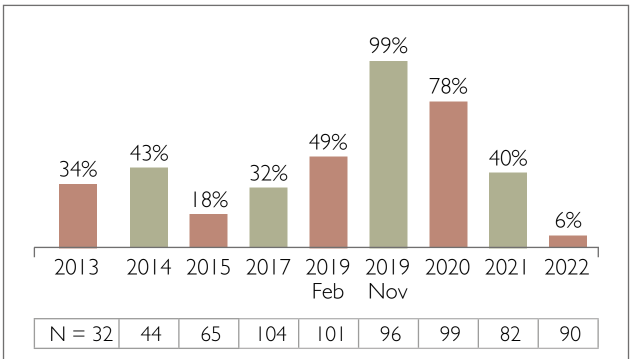
APPENDIX 1: SUPPLEMENTARY MATERIALS

Percentages of patients with aluminium levels >20 µg/L are available via the supplementary materials on the *African Journal of Nephrology* website.



Supplementary Figure 1. Patients with aluminium levels >20 µg/L (percentage per year).