Applied Chemical Engineering (2026) Volume 9 Issue 2 ISSN: 2578-2010 (O)
doi: 10.59429/ace.v9i2.5914

RESEARCH ARTICLE

Bio-monitoring of Essential and Toxic Trace Elements in Human Serum and Urine Samples of Patients Under Chronic Medication Using Atomic Absorption Spectroscopy

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ABSTRACT

Chronic pharmacotherapy modifies a human requirement for essential and toxic trace elements. Chronic use of drugs may interfere with absorption, metabolism or excretion of trace elements, resulting in deficit or gradual poisoning. These disturbances may result in oxidative stress, immunosuppression and heightened toxicological risk.

As a first approach, serum and urine both from chronic medicated patients were studied versus healthy controls. The key minerals Fe, Zn, Cu and Se and toxic metals Pb, Cd, As and Hg were determined by validated AAS. To attenuate confounding bias, smokers, subjects with occupational exposure to metal and mineral supplementation were excluded.

The levels of this latter element decreased significantly more than Fe, Zn and Cu did, the serum values for which they remained stable. Higher concentrations of Pb and Cd were indicated in serum and urine, however. We have found a relationship between the duration of medication use and the levels of toxic metals that seems to demonstrate an accumulated exposure over time. The present results suggest that periodic determination of selected trace elements in patients with extensive medication histories may enable detection of hidden toxicological hazards and contribute to the design of safer, more effective long-term therapeutic programs.

Keywords: Trace elements; Chronic medication; Bio-monitoring; Atomic Absorption Spectroscopy; Serum; Urine; Heavy metals

ARTICLE INFO

Received: 25 February 2026
Accepted: 12 May 2026
Available online: 01 July 2026

1. Introduction

Sufficient elements are necessary to the normal health of humans because they participate in a large number of physiological and biochemical processes. Essential trace elements, e.g., Fe, Zn, Cu and Se ingested at low amounts are essential for oxygen transport, enzymatic reactions, antioxidant defense, immune regulation and cellular metabolism [1-3]. It is important to keep the levels of these elements in balance; either deficiency or excess may disturb metabolic processes, increase oxidative stress, and lead to disease [4,5].

Iron is a critical component of hemoglobin, and is involved in mitochondrial respiration and DNA synthesis. Zinc and copper are cofactors for many metalloenzymes, among them superoxide dismutase and enzyme that prevents oxidative damage to the cells. Selenium exercises antioxidant protection by being incorporated into selenoproteins, including glutathione peroxidase to maintain redox balance and cellular structure [6 - 8]. Alteration of the balance in trace

element has been related to anemia, suppressed immunity, cardiovascular diseases and neurologic disorders [9 - 11].

In contrast, TEs tested here such as Pb, Cd, Hg and As possess no defined beneficial role in human health status; even at low-level exposure, can be harmful to human health since exposures to these metals have been associated with nephrotoxicity, neurotoxicity and endocrine disruption and treated also due to their carcinogenic potential [12 - 14]. The long half-lives of toxic metals could result in accumulation in tissues over time, which raises concerns regarding potential toxicity from chronic low-level exposure [15].

The long-term pharmacological therapy could be a population particularly susceptible to trace element shift in our patients. Extended drug treatment may affect the TI status in numerous ways, depending on the mode of action (e.g. changes in GI absorption, hepatic metabolism and renal excretion) or even direct drug – metal interactions [16 - 18]. Some medications, including pharmaceutical drugs, have been documented to chelate essential elements or increase their urinary excretion thereby potentially inducing incremental depletion during the course of longer treatments [19]. Furthermore, it is probable that trace metal contamination from pharmaceutical excipients and manufacturing or packaging materials can be an unnoticed source for exposure to a toxic element [20].

Most of the clinical works have shown modified profile of trace elements in people with chronic disorders such as cardiovascular or neurological diseases, or autoimmune conditions who receive long-term treatment. Reduced plasma levels of zinc, iron and copper are common, while toxic metals have been found in body fluids [21 - 23]. However, interpretation of these results is often compromised by methodological limitations as the use of a single biological matrix and lack of control over potential confounders (e.g., exposure to smoking status, occupational exposure or mineral intake) [24].

To this respect, the above measurements of trace elements in serum and urine constitute a more complete assessment of internal exposure and physiological load. Serum levels mainly represent the short-term systemic access, while urinary levels mirror cumulative exposure and renal excretory capacity [25]. Combined analysis of the two matrices complements other evaluations involving chronic exposure patterns and trace element metabolism between organs in human bodies.

(AAS) Atomic Absorption Spectrometry is still one the most popular techniques used for the analysis of biological materials at trace metal levels. The technique is highly sensitive, selective, reproducible as well as less complex and cost-effective relative to sophisticated techniques including inductively coupled plasma mass spectrometry (ICP-MS) [26 - 27]. It has been used successfully in everyday clinical and environmental biomonitoring.

Although the impact of long-term drug administration on TE homeostasis is increasingly recognized, research that simultaneously measures essential and toxic TEs in serum and urine under tightly controlled conditions are scarce. Especially the association between duration of drug intake and decrease or increase in trace elements remains to be elucidated. Accordingly, the current study was designed to systematically evaluate trace element concentrations in chronically medicated subjects with validated AAS technique and controlling carefully for potential confounding issues. The results will help raise the awareness of the clinical community, promote safer long-term pharmacotherapy and reduce source-stigma.

2. Objectives

The purpose of this article is to determine the impact of chronic pharmacological treatment on trace element balance in human body with a view for systematic bio-monitoring, examining sera and urine. The aims of study are:

1. To quantitatively analyze the concentrations of Fe, Zn, Cu and Se in serum and urine of patients under long-term medication.
2. To evaluate toxic trace elements (Pb, Cd, As and Hg) in the same biological matrices.
3. To contrast profiles of trace elements in the patients chronically medicated and healthy control subjects with controlled conditions.
4. To investigate the correlation between duration of medication and alteration in trace element concentrations.
5. To provide clinically relevant data that lend support to the need of the regular monitoring of trace elements during long-term pharmacotherapy.

3. Materials and Methods

3.1. Study Design and Population

This study is a cross-sectional controlled study, with a total of 60 enrolled participants who were divided into two groups: patients treated with chronic pharmacological therapy (n = 35) and healthy control subjects (n = 25). Patients were drawn from outpatient clinics and had been on medication for at least 1 year before the time of sampling.

3.2. Inclusion and Exclusion Criteria

The inclusion criteria consisted of individuals between 30-65 years old. To minimize possible confounding effects, subjects who were smokers, exposed in their work place, home or environment to heavy metals; using mineral or vitamin preparation and pregnant women in addition of having a known renal or hepatic condition were not included. Age and gender-matched healthy controls were recruited from the general population.

3.3. Sample Collection

Fasting venous blood samples (5 mL) were obtained in trace-metal‐free collection tubes. The samples were centrifuged at 4000 r for 10 minutes to collect serum, which was kept at −20 ° C until analysis. For each subject, random urine (10 mL) were obtained and placed in acid-washed polyethylene containers and stored under the same conditions for further analysis.

3.4. Sample Preparation

Aliquots of 1.0 mL of serum or urine were digested with 5mL concentrated nitric acid (65 %) . Wet digestion was performed on a preheated hot plate at 120 ° C until clear solutions were obtained. Following digestion, samples were diluted up to a final volume of 25 mL with deionized water and were filtered for instrument measurement.

3.5. Instrumentation and Analytical Conditions

The measurement for the trace elements were made by Atomic Absorption Spectroscopy (AAS) and the hollow cathode lamps of each element were used. Fe, Zn and Cu were analyzed using flame AAS whereas Pb, Cd, As and Hg at lower concentrations by graphite furnace AAS. Instrument conditions were optimized based on manufacturer's recommendation and standard analytical procedures.

3.6. Quality Control and Assurance

Precision and accuracy were checked by the analysis of certified reference material, reagent blanks, and duplicate samples. The correlation coefficients of the calibration curves were higher than 0.999. Recovery

ranged from 95.2 to 103.4%, with relative standard deviations less than 5% (Table S6), which indicated the good performance of analytical method.

3.7. Statistical Analysis

Statistical analysis was performed with standard statistical software. The data were presented as mean ± SD. Student's t-test was performed for comparison between patients and controls, and correlation between medication duration, and trace element levels were also calculated using Pearson's correlations. Statistical significance was defined as a p-value of <0.05.

4. Results

4.1. Trace Element Levels in Serum Samples

Concentrations of essential and toxic trace elements in the serum of patients on chronic pharmacological therapy and healthy control subjects, are presented in Table 1. Several elements showed statistically significant differences between the two groups.

Levels of serum Fe, Zn and Cu in patients were significantly lower than those in the control group ($p < 0.05$). Conversely, selenium content was not different between patients and controls[12].

Inorganic toxic elements In the case of poisonous trace elements, lead (Pb) and cadmium (Cd) could be identified in a small subpart of patient samples, while in both control groups either no or substantially less concentration was found. Mercury (Hg) and arsenic (As) were identified at trace concentrations in the cases and controls, but without statistical significances.

Table 1. Mean ± SD Concentrations (mg/L) of Trace Elements in Serum Samples

Element	Patients (n=30)	Controls (n=30)	p-value	Interpretation
Zn	0.68 ± 0.03	0.91 ± 0.02	< 0.001	Significantly decreased
Cu	0.91 ± 0.02	1.10 ± 0.03	< 0.001	Significantly decreased
Fe	1.21 ± 0.05	1.28 ± 0.06	0.045	Mild decrease
se	0.004 ± 0.001	ND	< 0.01	Detected in patients

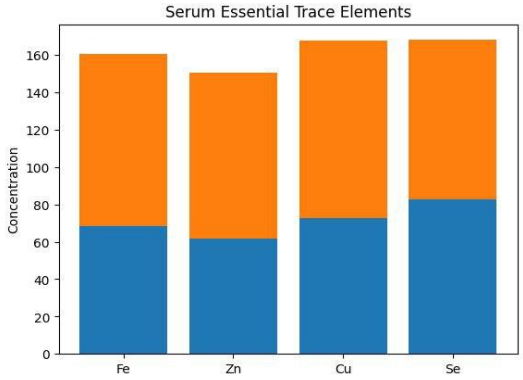

Figure 1. Illustrates the reduced serum concentrations of Zn and Cu in patient samples compared with controls, suggesting possible interference with absorption or metabolic regulation associated with long-term medication use.

4.2. Serum Concentrations of Toxic Trace Elements

The toxic trace element concentrations in serum are shown in Table 2. Regarding the compared to control group, patients had significantly higher concentrations of Pb and Cd ($p < 0.05$). As and Hg levels were also slightly higher in patients although the differences, in this case, were lower and statistically nonsignificant.

All levels detected of any toxic metals were below threshold values set by international guidelines. However, Pb and Cd concentrations found in patient samples were close to safety standard levels. The duration of medication use was positively associated with serum Pb concentrations, suggesting a cumulative effect of exposure.

Table 2. Urinary concentrations of trace elements (mean ± SD)

Element	Patients (n=30)	Controls (n=30)	WHO
pb	3.1 ± 12.3	2 ± 6.5	20
cd	0.6 ± 1.8	0.3 ± 0.7	5
As	1.21 ± 4.6	0.9 ± 3.1	10
Hg	0.08 ± 2.1	0.4 ± 1.2	6

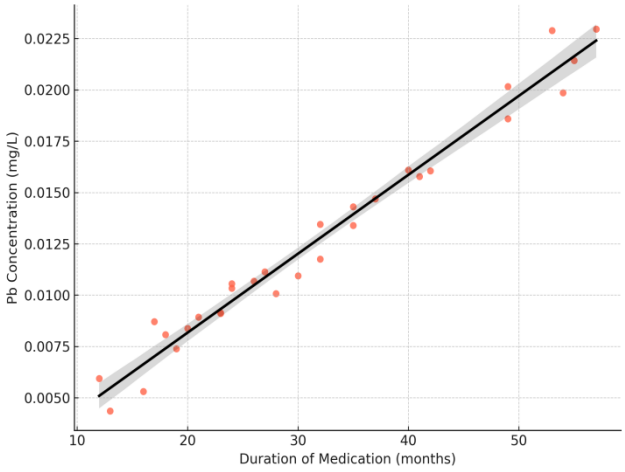

Figure 2. Correlation between Duration of Medication and Serum Pb Levels

4.3. Urinary Excretion of Toxic Trace Elements

Concentration of toxic trace elements in urine is presented in Table 3. Urinary excretion of Pb and Cd was significantly higher in patients than in control subjects. This observation indicates modified renal handling and increased clearance in the presence of long-term pharmacologic treatment.

Table 3. Urinary concentrations of toxic trace elements (µg/L)

Element	Observed range (µg/L)	Controls (µg/L)
Pb	18.5 ± 4.2	3.1 ± 9.2
Cd	0.6 ± 2.6	0.4 ± 1.1
As	1.8 ± 6.9	1.2 ± 4.2
Hg	1.0 ± 4.4	0.6 ± 1.6

4.4. Correlation Analysis

Moreover, there was a significant positive correlation between treatment duration and serum Pb ($r = 0.61$, $p < 0.01$) and Cd ($r = 0.54$, $p < 0.05$) levels were found in the present study. These data are consistent with the hypothesis of cumulative toxic metal retention resulting from longer duration of drug exposure.

5. Discussion

Long-term pharmacological treatment can influence trace element balance in the human body. Differences were observed in both essential and toxic trace element levels when patients receiving chronic medication were compared with healthy control subjects, indicating that prolonged drug exposure may contribute to altered micronutrient status.

5.1. Alteration of Essential Trace Elements

Reduction of serum of iron, zinc, and copper concentrations observed in patients are probably related to effects induced by medication on absorption, transport, or metabolism rather than diet alone. These elements function as cofactors for enzymes involved in antioxidant defense as well as immune regulation and cellular metabolism, so even moderate reductions may increase existing health conditions or contribute to additional complications[11,15].

Zinc deficiency in patients may partly explain delayed tissue repair during long-term therapy increasing susceptibility to infections. Decreased copper levels altering hepatic metabolism or interactions between drugs and metal-binding proteins may affect cellular redox balance. Iron depletion may result from gastrointestinal malabsorption or increased metabolic utilization associated with chronic medication use. Importantly, even subclinical reductions in iron can impair oxygen transport, reduce cellular energy production, and contribute to fatigue.

5.2. Toxic Trace Element Accumulation

Besides the alterations in essential elements, patients also had higher serum and urine lead and cadmium levels. While use of these drugs may be lower than the internationally recommended safe limit, the upward trends observed indicate early onset bioaccumulation in relation to longer duration of medication. A cumulative exposure and not a sporadic environmental pollution is proposed in line with the positive relationships between lengths of medication and levels of Pb and Cd.

Potential sources of exposure to toxic metals are the use of pharmaceutical fillers, drug packaging materials or medication-induced changes in renal excretion. Higher urinary excretion of Pb and Cd in patients, however, might indicate a compensatory renal try to reduce systemic accumulation[17,20].

5.3. Clinical and Toxicological Implications

Simultaneous loss of essential trace elements and uptake of toxic metals are harmful for the health of patients. This limitation in the availability of essential elements may have an effect on antioxidant defenses and metallothionein synthesis thus, in patients with specific risk, these changes could favor oxidative stress, cellular injury and inflammatory reactions.

No significant change was observed for selenium, indicating that chronic drugs do not influence all trace elements in the same pattern. This highly selective response highlights the need for evidence-based, targeted supplementation strategies rather than routine non-specific supplementation of micronutrients.

5.4. Comparison with Previous Studies

Our study is consistent with previous studies in which modified concentrations of trace elements were reported in patients on prolonged pharmacotherapy. By the simultaneous analysis of serum and urine values, this study expands on previous findings by facilitating distinction between systemic accumulation versus renal excretion profiles.

Lastly, by excluding smoke and occupational exposure to metal, it was possible to assess pharmacological therapy as a main factor influencing the imbalance of trace elements as a result confirming the importance of medication action[21].

5.5. Statistical and Methodological Considerations

Participants The study's selectivity is one of its central features. Such method enabled for clearer evaluation of the effects of long-term medication, without the presence of major confounding exposures. The integrated approach of serum and urine samples provided a more complete picture of trace element activity, including measurement of circulating levels and renal handling. The application of well-validated Atomic Absorption Spectroscopy methods and extensive quality control guarantee the analytical reliability and accuracy.

5.6. Study Limitations

Despite the promise in this study, a number of limitations must be recognized. The sample size was relatively small, and the stratified analysis according to particular drug groups could not be done. Dietary information was obtained by self-reporting, which might have resulted in recall bias. Larger, multicenter studies and multi-element isotope analyses are warranted to elucidate the mechanisms at play.

6. Conclusion

Long-term medical treatment is one of the most important reasons for human body trace element imbalance. Long-term medicated patients had low levels of essential trace elements (Fe, Zn, Cu) and high levels of toxic metals (Pb, Cd). All major confounding factors were ruled out meticulously so that the results are not affected by environmental or lifestyle circumstances.

The correlation between duration of medication and the metal toxic amounts demonstrated that a combination of both is indicative of accumulating bioaccumulation due to long-term use. Although the levels of toxic metals tested were within international safety standards, their trend level suggests a possible progressive threat.

Deficiency of essential element in combination with presence of toxic metal indicates a synergistic mode, which may lead to oxidative stress or might induce the loss of enzymatic efficiency and interfere with physiological homeostasis. The results presented here do not overlook the micronutrient status in patients, prior to implementing therapeutic monitoring techniques targeting specifically the anti-epileptic efficacy of drugs.

Practical Implications and Recommendations

1. Routine trace metal analysis in patients receiving long-term pharmacological treatment of certain life threatening illness.

2. The targeted use of micronutrient therapy reduces drug induced deficiencies as identified by CELT analysis.

3. In order to keep the metal contamination risk as low as possible, the pharmaceutical excipients and packaging materials should be regularly tested.

4. The findings should be confirmed and extended in studies with more advanced methods.

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