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Detection of inorganic substances in clinical and forensic medicine - an overview

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Chemicals production has been increasing exponentially for the past century, and it is expected to continue in the coming decades. Should we be concerned? Probably yes. Putting aside environmental and economic considerations, we will here focus on human health aspects. What are the uses of these trace elements? What is their impact on us? How can we monitor trace elements in our bodies? And how policies can play a role to ensure better health conditions? In this review, we will try to answer these questions.

1. Introduction

Trace elements have intrigued humans for millennia, long before they were fully identified or measurable through modern techniques. In the prehistoric period, arsenic copper (i.e. arsenical bronze) was at the heart of metallurgy processes in Mesopotamia [1]. Iron (in ochre pigments) and black manganese oxide were used in arts [2]. During Antiquity, trace elements also found a place in medicine and jewellery [3,4]. They have been used through the centuries in various area with limited knowledge concerning their toxicity, like arsenical and thallium compounds and some of them are still used in medicine nowadays [5,6]. Arsenic even owes its fame to its use in the 17th century as “succession powder”. In the form of arsenic trioxide (a white powder without specific smell nor taste), it provoked poisoning similar to diet intoxication and was undetectable in the body until the 19th century. The Marsh test, developed and published in 1836, marked an important step in forensic toxicology. Through it, murders could finally be proved by blood or hair samples analysis [7]. Nevertheless, this period was also agitated with the concept of “normal arsenic” [8]. In the beginning of the 20th century, two French chemists (Armand Gautier and Gabriel Bertrand) worked on this issue, transferring interests from toxicology to pharmacology and nutrition science.

Trace elements are also used in industrial processes, sometimes leading to dramatic consequences for the population. This happened in Minamata (Japan), with the Chisso industrial scandal, in the 1950s. As the mercury-contaminated wastewater of the plant was released directly into the sea, a huge health scandal exploded. Due to high seafood consumption in the region, the health of thousands of people has been affected and more than 900 deaths were reported. The decrease in mercury content in hair of patients and in the ecosystem was monitored during the removal of mercury-contaminated sludge for three decades [9].

Today, human activities involve extraction of never observed amount of trace elements from the earth, creating potential health risks in case of both acute and chronic exposure. This exposure can be direct and indirect – due to contamination of water, food crops and ambient air. In the central Africa Copperbelt region, positive impacts of mining on economy and development have been overshadowed by negative impacts on population health and livelihood (soil erosion and acidification, deforestation) [10]. In the early 2010s, Muimba-Kankolongo *et al.* [10] reported in their study average concentrations of 2361,1 µg/L for lead and 138,7 µg/L for arsenic in tap water analyzed in the Democratic Republic of the Congo, considerably exceeding the WHO recommendations of 10 µg/L [11]. The few participants' urine samples analyzed showed particularly high levels for the nine trace elements monitored (i.e. manganese, cobalt, nickel, copper, zinc, arsenic, cadmium, lead and uranium) [10].

2. Trace elements in modern medicine, an additional tool to guide policies

Nowadays, with increasing knowledge about the impact of trace elements on health, interest in monitoring essential trace elements in clinical settings is also growing. Essential trace elements such as copper, zinc or selenium should be ascertained for patients with specific needs, as in clinical nutrition protocols [12,13]. A deficiency or excess in elements considered to be essential to human life is likely to induce a pathophysiological process. Monitoring them can also help to detect genetic disorders of trace element metabolism. These can be responsible for both accumulation of essential trace element in tissues (e. g. hemochromatosis, Wilson's disease) and deficiency (e. g. acrodermatitis enteropathica, Menkes' disease) which have several clinical consequences [14,15].

Some micronutrients play key roles in immune defence, including mucosal defence mechanisms and immunoglobulin production. For example, altered micronutrient status has been linked with COVID-19 infection and disease severity [16,17]. In particular, plasma levels of zinc, selenium and copper were different between COVID-19 patients in intensive care unit and other persons infected by COVID-19 [16]. In addition, the associations of selected circulating micronutrients with anti-SARS-CoV-2 IgG and IgA seropositivity were assessed in the Swiss community using early pandemic data, highlighting deleterious impact of low zinc plasma level [17]. Accordingly, the need of trace elements supplementation in severe COVID-19 patients was risen in several meta-analysis studies [18,19]. The existing literature on this subject did not converge on a consensual response, as the results are suggestive but insufficient to address a clear benefit of this supplementation [20,21]. Nevertheless, the recent ESPEN guidelines recommend supplementation for plasma selenium < 0,4 µmol/L (< 32 µg/L) [13].

Trace element analysis can also be used as prevention tool. The need for metal-on-metal hip replacement surgery is evaluated by monitoring cobalt, chromium but also titanium, molybdenum or nickel. Abnormal levels of these elements would be indicative of increased wear [22]. Although acute intoxication is generally relatively easy to interpret, as concentrations are much higher than physiological reference values, chronic intoxication due to repeated exposure can be more challenging. In any case, as we are exposed to trace elements daily through our environment and diet, it is essential to know the reference values of trace element concentrations in clinic or forensic samples for a local control population.

The analysis of inorganic substances in conventional biological samples such as blood, urine and hair has been facilitated by the development of high-throughput inductively coupled plasma - mass spectrometry (ICP-MS and ICP-MS/MS), offering rapid analysis of several dozens of trace elements in a single run. Unfortunately, it is sometimes difficult to obtain local reference values for all elements. In Switzerland, for example, it was only in 2024 that values were published for many trace elements. Based on the Swiss Kidney Project on Genes in Hypertension (SKiPOGH) cohort, 24 trace elements could be analyzed in both urine and plasma of nearly a thousand participants [23]. With this idea of a nationwide biomonitoring project in Switzerland, the Federal Office of Public Health launched in 2020 a pilot phase for the "Swiss Health Study" [24], in line with the European HBM4EU study. In addition, by exploiting the deep-phenotyping of population-based studies and state-of-the-art ICP-MS, it is now even possible to study the role of trace elements in physiological and pathophysiological states from several thousand of biological samples. The ToxiLaus study for example gives the opportunity for investigating the link between trace elements and kidney function [25] or cardiovascular risk factors [26].

These studies might influence public health policies, as the topic of trace elements is becoming a social issue, generating growing interest in the media. We have previously witnessed that the political decision to ban lead use as a gasoline additive, with its phase-out since 1973, has led to a drastic reduction in blood lead levels worldwide [27]. It was a necessity due to its chronic exposure impact on population health, especially for children. Developmental deleterious effect and nervous system disorders in fetuses and children have been reported to be associated with trace elements, especially lead and mercury. The young and the elderly are particularly sensitive population groups. Arsenic, lead, cadmium and cobalt are associated with cardiovascular diseases, especially in elderly [28]. Among the several risks associated with chronic exposure, some evidence of the obesogenic effects of certain elements, such as cadmium, arsenic, mercury, and lead, have also emerged [29].

3. Analytical approaches and forensic aspects

Thanks to technological developments, several analytical approaches are now available for the measurement of trace elements, depending on the sample to be analyzed, the substances to be investigated and the sensitivity required. In cases of chronic exposure, speciation analyses are required, to be able to identify the chemical species of the element [30]. Because organic form of mercury and arsenic commonly occur in seafood, their presence in samples will not guide toxicologists to the same conclusions as the presence of inorganic forms alone.

For example, we had a case in our laboratory in which a 45-year-old woman presented with paraesthesia and abdominal pain. Clinical examination confirmed distal nerves involvement and excluded various causes. The case history revealed daily fish consumption for several months. Laboratory analyses showed arsenic and mercury blood concentrations higher than reference thresholds (respectively 34 µg/L vs. <10 µg/L for arsenic and 19 µg/L vs. < 5 µg/L for mercury). Urinary arsenic concentration was also high (310 µg/g creatinine for a tolerance value of < 25 µg/g creatinine). Speciation analyses, performed by coupling liquid chromatography to ICP-MS (HPLC-ICP-MS), allowed confirming methylmercury poisoning (17,5 µg/L vs. threshold of 5 µg/L) as inorganic mercury and arsenic concentrations were in accordance with tolerance values. Arsenobetaine concentration (330 µg/g of creatinine) is consistent with fish-consumption. Laboratory analyses 1 month after stopping seafood products consumption showed decreased levels of arsenic and mercury, in both blood and urine samples. The woman had a progressive recovery in a few months.

Speciation can be used to differentiate chromium oxidation states (Cr(III) and Cr(VI)), inorganic arsenic (AsIII et As(V)) and its metabolites (MMA and DMA) from arsenobetaine, or elemental mercury (Hg^0) from methylmercury [31]. And when laser ablation is coupled to ICP-MS (LA-ICP-MS), it becomes possible to obtain precise localization of trace elements in a structure [32]. Altogether, the implementation of trace element monitoring will certainly be increasingly used in forensic and clinical routine.

However, for forensic cases, an additional aim is to be able to correctly interpret data that can be obtained from postmortem samples - due to possible redistribution in fluids and tissues, alteration of content due to putrefaction [33], influence of storage time and conditions [34]. There is a literature gap between large ante-mortem population studies and the post-mortem case reports of intoxication. Therefore, it would be interesting to study trace elements distribution in postmortem samples in order to have reference values in forensic context. Some organs seemed to accumulate preferentially different trace elements, as Bellouard *et al.* [35] reported, like Al in lungs, Mn in liver or Cd in kidneys. A study is currently underway at our university center of forensic medicine to strengthen these results.

4. Conclusion

This review intended to raise awareness on the topic of trace elements in medicine, as understanding their impact on human health is essential for implementing appropriate policies. Exposure to trace elements can adversely affect human health and play a role in the onset of different pathologies. So far, only few studies have explored the combined effect of multiple trace elements on the risk of diseases. Knowing the trace elements concentrations is an important indicator of the health status but requires reference values. Therefore, determining these reference values in various biomatrices is of growing interest for assessing toxicological exposure to pollutants in unexposed and occupational populations.

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