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Short Communication

Toxic and Essential trace Elements Regularly Measurement and Monitoring Should be Considered in Chronic Kidney Disease Patients Undergoing Maintenance Dialysis

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Abstract

People with Chronic Kidney Disease (CKD) receive maintenance dialysis as an effective treatment. Accumulation of toxic elements and loss of essential metals through dialysis is not considered a serious issue by doctors. Therefore, physicians do not order trace elements for dialysis patients in routine or regular evaluations. Revisioning the reference range of trace elements in CKD patients and equipping clinical laboratories with facilities to measure these elements is another aspect of care and management of CKD patients. Therefore, we suggest revising the clinical guidelines for the management of CKD patients based on the facts about the role of trace and toxic elements on patient morbidity.

Keywords: Maintenance Dialysis; Trace Elements; Chronic Kidney Disease; Morbidity;

Introduction

Chronic Kidney Disease (CKD) is a non-communicable disease with high prevalence. Advances in medical care have improved the survival of CKD patients [1]. The best available intervention for CKD patients is dialysis (hemodialysis or peritoneal dialysis), but it is associated with complications that lead to poor quality of life [2]. Unfortunately, when it comes to the care of CKD patients, most efforts are focused on maintenance interventions rather than improving their quality of life.

Measurement and assessment of toxic elements in dialysis patients is only a research interest among clinical scientists, while it should be a clinical demand in therapeutic and monitoring guidelines. We cannot simply determine the direct effect of toxic elements on the morbidity and mortality of dialysis patients because of their many non-specific targets in the human body.

What is Simpler is More Complex

Researchers have reported that toxic element overload affects various biochemical mechanisms and physiological processes. For example, toxic elements interfere with glycolysis, Krebs cycle, uptake and absorption of minerals, metabolism of various essential elements such as iron, phosphate, calcium, zinc, and copper. They reduce cell proliferation and differentiation. In addition, they alter the normal metabolism of parathyroid hormone, male and female sex hormones, norepinephrine, cortisol, thyroid hormones, and insulin [3-7]. However, it is difficult to draw a causal map to

explain the direct effect of toxic elements on the biochemical or physiological process, and the physiopathology of the disease in dialysis patients, because what is simpler is more complex.

Trace or toxic elements are simple agents compared to many other chemicals or biomolecules in the human body or circulation. Simple and small ions, such as unbound metals, enter cells and tissues more easily than complex structures. The immune system does not react with ions such as toxic heavy metals. After passing through the cell membrane, toxic metals are replaced in biomolecular structures such as metalloenzymes and disrupt biochemical processes such as Krebs cycle, electron transport chain, fatty acid biosynthesis, etc. Also, they accumulate in both soft and solid tissues and stimulate inflammatory responses [6,8]. Therefore, toxic metals are simple agents that affect complex biological processes. Simpler agents seem to have diverse targets, more complex metabolism, and interaction network.

Maintenance Dialysis is Not so Efficient in Removing the Toxic Metals from Blood Circulation

Today, there are significant challenges regarding the status of toxic elements in CKD patients receiving maintenance dialysis:

a) Are there good facilities for measuring toxic and essential trace elements in clinical laboratories (automation aspect)?

b) What is a good reference range or upper limit for a toxic element in the circulation?

c) Does a CKD patient lose an essential element during maintenance dialysis (supplementary regimen therapy)?

d) Do toxic elements accumulate in the organs of CKD patients undergoing dialysis treatment (detoxification)?

Although there are several scientific reports on the importance of assessing essential and toxic elements in dialysis patients, perhaps doctors do not have a positive view of their measurement and monitoring in CKD patients. Mi Kyung Song [9] stated that: "Decisions About Dialysis and Other Life-Sustaining Treatments Should Not Be Made Separately". Such a title for a scientific article also indicates the importance of life-threatening factors that we think toxic elements are in this category. In our country, Iran, there are about 1000 active hospitals and more than 5000 active clinical laboratories. Unfortunately, we do not have detailed information on the number of clinical laboratories equipped with trace element (metal) measurement equipment such as atomic absorption spectrometry or Inductively Coupled Plasma (ICP) apparatus. However, we think there are less than 10 clinical laboratories with devices to determine a limited number of metals such as lead. We think that this is a global issue that exists at least in low- and middle-income countries. The lack of suitable facilities for determining trace elements (toxic or essential) is related to the doctor's request, which is according to clinical guidelines for the management of CKD patients [10]. Despite this, food and drug quality control laboratories in Iran are well equipped with such facilities, but their working structure is not suitable for clinical purposes.

We think that trace elements should be measured regularly in dialysis patients to determine their overload or deficiency and necessary preventive or therapeutic interventions. For example, many hemodialysis patients suffer from aluminum, arsenic, and lead overload compared to non-CKD subjects [8,11-15]. Unfortunately, the chronic or long-term effects of toxic element overload in hemodialysis patients have not been well evaluated. This is due to the difficulty of monitoring dialysis patients, conducting cohort studies, and multifaceted complications in these patients.

Another issue is the precise definition of reference values of toxic and essential metals in CKD patients undergoing dialysis intervention. Unfortunately, the toxic levels of heavy metals defined for dialysis patients are far from the upper limit of the normal population. Rahimzadeh, et al. [8] stated that aluminum levels in normal people are less than 10μ/L, in dialysis patients less than 60μ/L, and critical toxicity is when the aluminum level exceeds 100μ/L. Nevertheless, we know that metabolic pathways, physiological process, and biological mechanisms are similar in CKD patients and normal population. Therefore, different definitions for the cut-off point and the upper limit of trace elements, in these two populations are not rational and need to be revised. Also, toxic levels occur only in a small number of patients and in rare cases, while overload status is common in most dialysis patients.

It appears that toxic metal overload status persists for long periods of time without reaching toxic levels (according to currently defined cut-off points) that are associated with clinical manifestations. We may have reported non-toxic but excessive levels of a metal in the circulation of a hemodialysis patient, but the patient suffers from accumulation of that element in internal tissues, and this is not considered in routine clinical evaluations. Long-term overload of toxic elements and insufficiency of essential elements affect the metabolic pathways and bring complications such as sickness and constant unwellness.

Another challenge is the loss of essential elements during maintenance dialysis. Increased levels of trace elements occur after dialysis due to blood concentration. If we measure trace elements in the dialysis ultrafiltrate, we will see that some elements are lost during maintenance dialysis while their blood levels are within the normal range or even above the upper limit. We have reported such findings in our previous studies [10,15]. If we assume that tissue stores of trace elements can compensate for their reduced blood levels, then we can expect unchanged or increased levels of toxic and essential elements. To solve the problem of loss of essential elements, after accurate measurement, supplemental formulations can be used. For example, doctors rarely request measurements of cobalt, manganese, and copper, even though these metals are

essential for certain enzymes with critical roles in cell growth and development [16-18]. Therefore, supplementary formulations may be needed in management of CKD patients.

The last challenge is the need of alleviating the overload of toxic elements in dialysis patients. Such treatment is necessary to reduce toxicity and possibly improve morbidity. It may be necessary to consider chelator drugs such as penicillamine in the treatment protocols of dialysis patients. However, the effectiveness of such treatments must be demonstrated in clinical studies before adding this preventive intervention to the therapeutic guidelines of CKD patients.

Conclusion

Overall, the need to monitor toxic and trace elements should be reconsidered in clinical guidelines when managing CKD patients and those on maintenance dialysis. Essential trace elements should be prescribed for CKD patients. In addition, the toxic metal overload should be reduced in the CKD patient's body by chelators, if necessary, based on the results of accurate clinical laboratory methods. Achieving these goals requires access to appropriate measurement facilities with accurate and precise results, defining more sensitive cut-off points regarding the lower and upper limits of the blood levels of essential and toxic elements in CKD patients. Therefore, there are unclear aspects about the biology and physiopathology of trace and toxic elements that require extensive studies to obtain better guidelines for increasing life expectancy in CKD patients.

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Conflicts of Interest

The authors declare no conflict of interest.

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