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Original Research Article

# Assessment of Serum Trace Element (Zinc & Magnesium) Status in Chronic Kidney Disease Patients on Hemodialysis

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**Abstract:**

In chronic kidney disease (CKD), the concentrations of trace elements are altered as a result of impaired renal function, endogenous toxicities, dietary restrictions and therapeutic measures. Thus hemodialysis patients are at theoretical risk of deficiency or toxicity of trace elements due to removal or addition by dialysis, the composition of source water used for hemodialysis, and residual kidney function. The aim of the study was to investigate whether CKD patients undergoing hemodialysis were prone to disturbances in trace element (zinc & magnesium) homeostasis, and if present, whether these disturbances were related to hemodialysis. This was a two-part study designed to determine and compare serum zinc and magnesium levels between 50 CKD patients undergoing hemodialysis at S.R.G. Hospital, Jhalawar (Rajasthan), and 50 healthy controls, and to determine and compare their concentrations in the same group of CKD patients before and after undergoing hemodialysis, by using Atomic Absorption Spectrometry at Jhalawar Medical College & Associated Hospitals, Rajasthan. Serum zinc in CKD patients (56.11±14.67 µg/dL) was lower as compared to controls (62.28±20.92 µg/dL), but the difference was statistically insignificant ($p=0.091$). Serum Zinc in CKD patients decreased significantly after undergoing hemodialysis (49.07±14.25 µg/dL) ($p<0.0001$). Serum Magnesium in CKD patients (3.13±0.74 mg/dL) was significantly higher than controls (1.57±0.52 mg/dL) ($p<0.0001$) which decreased significantly after undergoing hemodialysis (2.48±0.52 mg/dL) ($p<0.0001$). We concluded that regular monitoring of trace element status, especially in the light of trace element disturbances that were observed in CKD patients undergoing hemodialysis, becomes even more important for management of the disease, assessing the prognosis and improving the efficiency of hemodialysis.

**Keywords:** Chronic Kidney Disease (CKD), Hemodialysis, Zinc (Zn), Magnesium (Mg).



## Introduction

The Kidney Disease Outcomes Quality Initiative defines chronic kidney disease (CKD) as either kidney damage or decreased kidney glomerular filtration rate of less than 60 mL/min/1.73 $m^2$ for three months or more [1]. In 2017, the global prevalence of CKD was 9.1% (697.5 million cases), with approximately one-third of all CKD cases contributed by China (132.3 million) and India (115.1 million) [2]. Trace elements are being recognized as important factors in the development and progression of kidney disease [3]. In CKD, the concentrations of trace elements are altered because of endogenous toxicities, impaired renal function, dietary restrictions, and therapeutic measures [4]. Hemodialysis can lead to depletion of biologically significant substances from blood, if they are not present in the dialysate [5]. At the same time, even minute amount of source water contamination can cause clinical toxicity. Substances present in the dialysate, but absent in blood, may accumulate in the patient. Due to impaired renal clearance in these patients, toxicity of ingested trace elements might occur even when they are absent in the dialysate [6]. Thus CKD patients undergoing hemodialysis are theoretically at risk for deficiency or toxicity of trace elements, depending on food & medicine intake, residual kidney function, dialysate concentration, source water composition, dialyzer

membrane type & size, purification method and exchange during dialysis. Dialysis fluids play an important role in generating trace element dysfunction. [7].

We come across many CKD patients coming to S.R.G Hospital and Jhalawar Medical College of Rajasthan, due to the availability of hemodialysis here. The accurate determination of trace metals was limited by methodology previously. It resulted in a limited knowledge of the concentration of trace elements and its effect in many diseases, including renal disease. This situation has been resolved by the availability of Atomic Absorption Spectrometry (AAS) in the Department of Biochemistry, Jhalawar Medical College. The purpose of this study was to determine the levels of serum zinc and magnesium in CKD patients undergoing hemodialysis in the dialysis ward of S.R.G Hospital, Jhalawar (Rajasthan), and to compare them with those of healthy controls, and to assess the effect of hemodialysis on serum zinc and magnesium concentrations of CKD patients. Serum trace element levels in CKD patients have a great impact on overall health and their imbalance might lead to progressive decline in renal function, renal osteodystrophy, cardiovascular diseases, atherosclerosis, insulin resistance and anemia [8]. Deficiency or toxicity of trace elements, which was disregarded previously, has been observed as an important factor that induces complications in patients undergoing hemodialysis [9]. Thus, determination of serum zinc and magnesium was important in understanding their role in the pathophysiology, medical management, and prognosis of chronic kidney disease.

## Materials and Methods

This study was a two-part study conducted in 2020. First part of the study was designed to determine and compare serum zinc and magnesium levels between 50 CKD patients undergoing hemodialysis and 50 age & sex matched healthy controls. The second part of the study was designed to establish the effect of hemodialysis on serum zinc and magnesium concentrations, by determining and comparing their levels in the same group of CKD patients, before and after undergoing hemodialysis. CKD patients were selected from the dialysis ward of S.R.G. Hospital, Jhalawar, (Rajasthan), while the healthy controls were selected from the general population. All the test subjects were selected after excluding any other pre-existing conditions that might influence the serum trace element concentrations. All test subjects participated in the study after signing informed consents. The dialysate fluid used for hemodialysis was prepared by reconstitution of a 2-part dry citrate dialysate powder with purified water, pre-treated by reverse osmosis for removal of contaminants. The composition of dialysate fluid was standard for all patients undergoing hemodialysis.

**Table 1: Composition of dialysate fluid. Dialysis Unit, S.R.G. Hospital, Jhalawar (Rajasthan)**

| **Dry citrate powder concentration (Part – A)** | | **Dry citrate powder concentration (Part – B)** | |
|---|---|---|---|
| Sodium | 85.0 mEq/L | Sodium | 55.0 mEq/L |
| Potassium | 2.0 mEq/L | Bicarbonate | 35.0 mEq/L |
| Calcium | 3.0 mEq/L | Chloride | 20.0 mEq/L |
| Magnesium | 1.0 mEq/L | | |
| Citrate | 2.0 mEq/L | | |
| Chloride | 91.0 mEq/L | | |
| **Reconstitution:** Dilution ratio 1:83:34 (1 part of Part-A, 83 parts of Part-B, 34 parts of purified water) | | | |

Venous blood samples were collected using aseptic procedure in sterile tubes and serum was separated using centrifugation. For trace element decontamination, all the laboratory glassware used in the analysis were first acid washed by soaking in 0.1 mol/L nitric acid for 24 hours, and rinsed six times with deionized water and allowed to dry before commencing the analytical procedure [10]. Trace element analysis was performed on Thermo Scientific Atomic Absorption Spectrophotometer iCE 3000 AA01163803 v1.30® using air-acetylene flame, in the Department of Biochemistry, Jhalawar Medical College, Jhalawar (Rajasthan). For analysis of serum zinc, three working standard solutions of increasing zinc concentration i.e. 0.5 µg/L, 1 µg/L, and 1.5 µg/L were prepared in accordance with the instrument parameters for the given wavelength (213.9 nm), and the serum was diluted 10 times. For analysis of serum magnesium, three working standard solutions of increasing magnesium concentration i.e. 0.1 mg/L, 0.3 mg/L, and 0.6 mg/L were prepared in accordance with the instrument parameters for the given wavelength (285.2 nm), and the serum was diluted 100 times. After checking the parameters, firstly, optical set-up was done for alignment of the hollow cathode lamp, followed by blank testing for zero setting of the instrument, followed by calibration using the working standards, and lastly the samples were analysed. Statistical analysis of data was done by the help of SPSS software (version 20.0). Chi-square test, Unpaired–t test and Paired–t test were used in data analysis. Observations were reported

in terms of (Mean ± SD) and P value <0.05 was considered as significant.

## Results

The mean age of CKD patients was (40.54±12.60 years) whereas the mean age of controls was (37.46±7.54 years). Statistical analysis using unpaired–t test showed that p–value was 0.141, therefore the age difference in both groups was statistically insignificant. The percentage of males in case group was 54%, whereas the percentage of females was 46%. The percentage of males in control group was 66%, whereas the percentage of females was 34%. Statistical analysis using chi–square test showed that p-value was 0.221, therefore the difference in sex distribution in both groups was also statistically insignificant.

Table 2 and Fig 1 show the comparison of serum zinc concentration between controls and cases. The mean serum zinc concentration in healthy controls was found to be (62.28±20.92 µg/dL) whereas the mean serum zinc concentration in CKD patients was found to be (56.11±14.67 µg/dL). Statistical analysis using unpaired-t test showed that p–value was 0.091, therefore the difference in serum zinc concentration in both groups was statistically insignificant. Table 2 and Fig 2 show the comparison of serum magnesium concentration between controls and cases. The mean serum magnesium concentration in healthy controls was found to be (1.57±0.52 mg/dL) whereas the mean serum magnesium concentration in CKD patients was found to be (3.13±0.74 mg/dL). Statistical analysis using unpaired-t test showed that p-value was < 0.0001, therefore the difference in serum magnesium concentration in both groups was statistically significant.

**Table 2: Comparison of mean values of serum zinc & magnesium levels between healthy controls & CKD patients**

| **Study Group** | **Mean Serum Zinc Level (µg/dL)** | **P-Value** |
|---|---|---|
| Healthy controls | 62.28 ± 20.92 | 0.091 |
| CKD patients | 56.11 ± 14.67 | |
| **Study Group** | **Mean Serum Magnesium Level (mg/dl)** | **P-Value** |
| Healthy controls | 1.57 ± 0.52 | **< 0.0001*** |
| CKD patients | 3.13 ± 0.74 | |

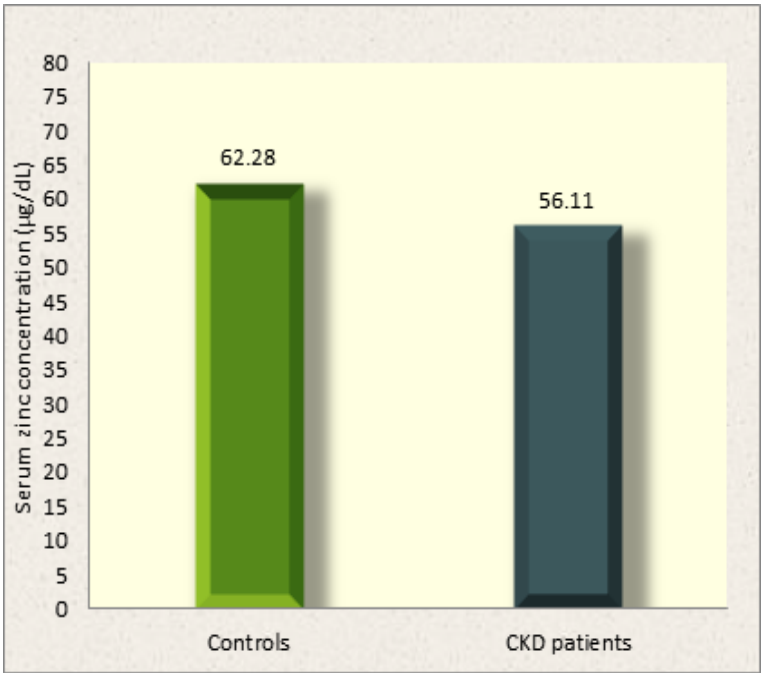


**Figure 1: Comparison of serum zinc between controls and CKD patients**

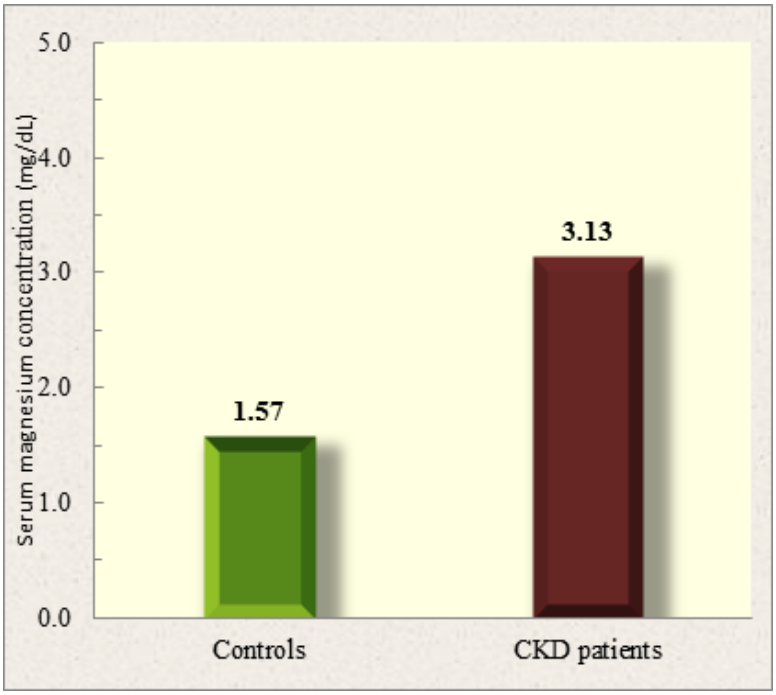


**Figure 2: Comparison of serum magnesium between controls and CKD patients**

Table 3 and Fig 3 show the comparison of serum zinc concentrations before and after hemodialysis in CKD patients. The mean serum zinc concentration in pre-dialysis CKD patients was (56.11±14.67 µg/dL), whereas the mean serum zinc concentration in post-dialysis CKD patients was decreased to (49.07±14.25 µg/dL).

Statistical analysis using paired t-test showed that p-value was < 0.0001 therefore the difference in serum zinc concentration in both groups was statistically significant. Table 3 and Fig 4 show the comparison of serum magnesium concentration before and after hemodialysis in CKD patients. The mean serum magnesium concentration in pre-dialysis CKD patients was (3.13±0.74 mg/dL), whereas the mean serum magnesium concentration in post-dialysis CKD patients was decreased to (2.48±0.52 mg/dL).

Statistical analysis using paired-t test showed that p-value was < 0.0001, therefore the difference in serum magnesium concentration in both groups was statistically significant.

**Table 3: Comparison of mean values of serum zinc & magnesium levels in CKD patients before & after undergoing hemodialysis**

| **Study Group** | **Mean Serum Zinc Level (µg/dL)** | **P-VALUE** |
|---|---|---|
| Pre-dialysis CKD patients | 56.11 ± 14.67 | **< 0.0001*** |
| Post-dialysis CKD patients | 49.07 ± 14.25 | |
| **Study Group** | **Mean Serum Magnesium Level (mg/dl)** | **P-VALUE** |
| Pre-dialysis CKD patients | 3.13 ± 0.74 | **< 0.0001*** |
| Post-dialysis CKD patients | 2.48 ± 0.52 | |

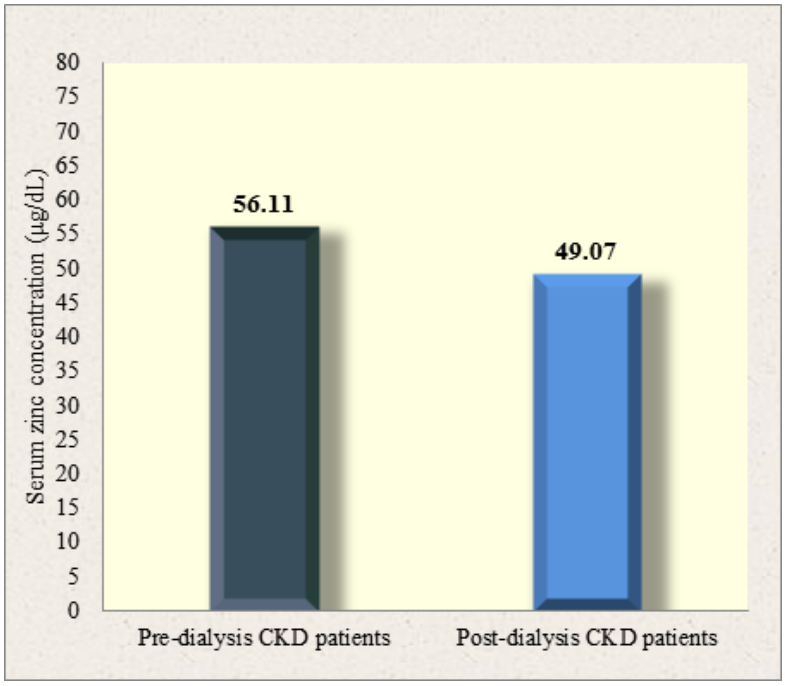


**Figure 3: Comparison of serum zinc in CKD patients before & after undergoing hemodialysis**

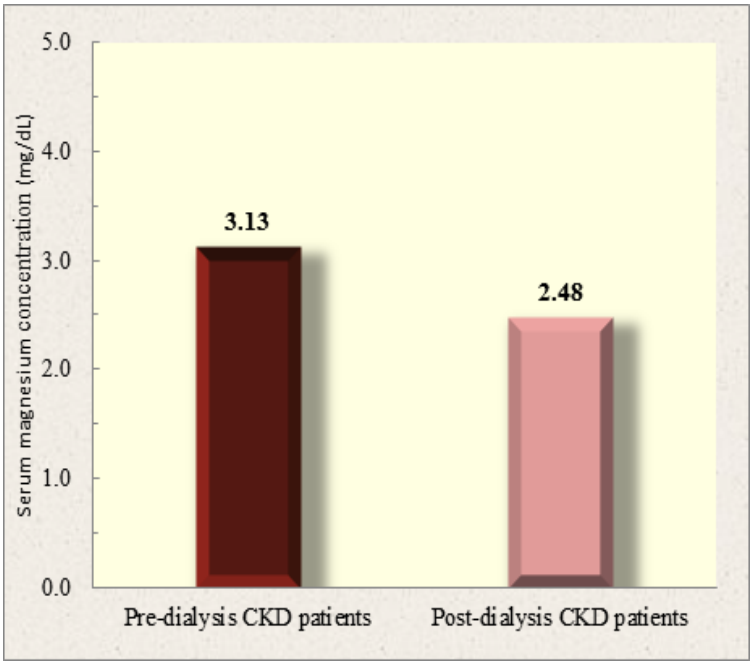


**Figure 4: Comparison of serum magnesium in CKD patients before & after undergoing hemodialysis**

## Discussion

**1. Serum Zinc Status:** In present study, both groups were statistically matched in age and sex distribution. From the analysis of serum trace elements in the study subjects, it was observed that CKD patients have lower serum zinc concentration (56.11±14.67 µg/dL) than healthy controls (62.28±20.92 µg/dL), but the difference was statistically insignificant as shown by Table 2 and Fig 1. Similar results were reported by earlier investigators [3, 11] whereas others reported an opposite trend [12, 13]. However, an interesting fact appeared to come to light, even though the differences in mean value in both groups was statistically insignificant, it was observed that subjects of both groups had serum zinc concentrations below the lower limit of reference interval for serum zinc (65-144 µg/dL) [14]. This indicated that the population of the area, in general had low concentration of serum zinc. The reasons for occurrence of low serum zinc could be diverse.

The major biological role of zinc is to act as a co-factor for more than 300 metalloenzymes including enzymes involved in anti-oxidant defence mechanisms such as superoxide dismutase, and enzymes involved in maintenance of acid-base homeostasis, such as carbonic anhydrase [15]. The exacerbation of zinc deficiency in CKD patients could, in part be explained due to increased oxidative stress encountered in CKD [16], which demands more consumption of zinc containing metalloenzymes such as superoxide dismutase. Loss of cellular architecture in nephrons due to glomerulosclerosis, tubulointerstitial fibrosis and tubular atrophy, occurs in CKD [17], consequently leading to depletion of zinc containing enzymes, particularly carbonic anhydrase, which is found in the cell membrane and cytoplasm of proximal convoluted tubules and collecting ducts of the nephron respectively. Since ZnT transporters are responsible for transport of zinc from intracellular to extracellular environment [18] therefore any reduction in the intracellular zinc pool could in theory, explain the observation of low serum zinc concentration in CKD patients. About 80% of plasma zinc is associated with albumin, and most of the rest is tightly bound in □2-macroglobulin [19]. Since proteinuria is the major dysfunction in the development of CKD, therefore loss of plasma proteins could explain the deficiency of zinc in CKD patients. Low zinc concentration in CKD patients can also occur due to shift of zinc into red blood cells under acidosis, caused by disturbed acid-base homeostasis. Almost all zinc in a red cell is present in the form of carbonic anhydrase, so that red cell concentration is about 10 times higher than in plasma [14]. This indicates that CKD patients are prone to shifting of zinc from extracellular to intracellular pool. This problem could be further accentuated by development of anemia in later stages of CKD, which results from erythropoietin deficiency [17]. Therefore decreased red cell production might cause even more depletion of intracellular pool of zinc, consequently leading to zinc deficiency. Lastly, CKD patients are subjected to frequent hemodialysis, which could also be attributed to zinc loss as a result of unregulated exchange. Further investigation into this particular cause corroborated this theory. After analysing the effect of hemodialysis on the trace element status of CKD patients, it was observed that serum zinc concentration in CKD patients, which was already below the lower limit of reference range for serum zinc, was further significantly reduced in these patients after undergoing hemodialysis (49.07±14.25 µg/dL) as shown by Table 3 and Fig 3. Some reports demonstrated a reduction in serum zinc concentration [11, 12] similar to our study while others have reported an increase [3, 20]. The decrease in serum zinc concentration after undergoing hemodialysis could be explained by unregulated exchange during dialysis. This can be due to the use of excessively purified water containing negligible amount of zinc, or use of completely zinc free dialysate, which filters out zinc from the patient's blood rendering them deficient in zinc.

**2. Serum Magnesium Status:** Regarding serum magnesium status, it was observed that CKD patients have higher magnesium concentration (3.13±0.74 mg/dL) than healthy controls (1.57±0.52 mg/dL), and the difference was statistically significant as shown by Table 2 and Fig 2. Many researchers have reported similar findings [8, 12] and some have reported opposite results [3]. The mean value of serum magnesium in CKD patients indicated that their concentration is above the reference interval for serum magnesium (1.7-2.4 mg/dL) [14], and suggested that CKD patients are hypermagnesemic. Contrasting to this result, the mean value of serum magnesium in healthy controls was below the lower limit of reference interval for serum magnesium. High serum magnesium concentration in CKD patients observed in our study could be attributed to multiple causes. Kidneys primarily regulate magnesium excretion [21]. Since 70% of magnesium is excreted via kidneys, from proximal convoluted tubules and thick ascending limb of loop of Henle, it could be possible that due to glomerulosclerosis, tubulointerstitial fibrosis and tubular atrophy that occur in CKD, there might occur, impairment of magnesium excreting capacity of kidneys. In CKD, uremia further diminishes the capacity of kidney to remove the trace elements from the body resulting in their accumulation and exerting toxic effects. Another possible explanation for hypermagnesemia in CKD patients as observed in our study is that almost 15% of extracellular magnesium is complexed with phosphate, citrate and other anions [14]. Since imbalance in phosphate excretion and hyperphosphatemia is a common occurrence in CKD [17] it can have significant effect on serum magnesium levels, consequently leading to hypermagnesemia. Also, since many hospitalized patients are regularly prescribed antacids, enemas and parenteral fluids which contain exceptionally high concentration of magnesium [14] the resulting hypermagnesemia observed in our study, could in part be attributed to excessive medicinal intake in chronically ill patients. Furthermore, CKD patients are subjected to frequent hemodialysis, which could also be attributed to magnesium overload as a result of unregulated exchange. Investigation into this was undertaken in the second half of this study and as shown by Table 3 and Fig 4, it was observed that hemodialysis was effective in significantly decreasing the elevated serum magnesium in CKD patients (2.48±0.52 mg/dL). However, some investigators have reported a decrease in serum

magnesium in post-dialysis CKD patients [12, 22] whereas others have reported an increase [20]. But despite the reduction by hemodialysis, it was not sufficient, and the mean serum magnesium concentration continued to be on the higher end of the reference interval (1.7-2.4 mg/dL). The decrease in serum magnesium concentration after undergoing hemodialysis could be explained by the fact that patients undergoing hemodialysis are exposed to very high volumes (>300 L per week) of dialysate. Therefore, even minute levels of trace element contamination of the source water could lead to tiny concentration gradients between plasma and dialysate, potentially leading to clinically relevant toxicity [6]. This can be related to the fact that the dialysate used in our hospital setting had magnesium concentration of 1 mEq/L. This could be slightly more than what is required for the correction of hypermagnesemia in CKD patients.

## Conclusion

Therefore, from our assessment of the results of this study, we have concluded that trace element status in CKD patients, as well as in healthy population plays a significant role in maintaining the state of good health. The occurrence of abnormal levels of serum trace elements in patients as well as in general population demands further investigation into this cause and regular monitoring of trace elements status is an unavoidable step towards achieving a holistic approach to health. Moreover, the occurrence of trace element imbalance due to hemodialysis warrants the need to further investigate trace element composition of the dialysate and the source water used for reconstitution, but was currently beyond the scope of this study.

In our judgment, the trace element status of CKD patients undergoing hemodialysis depends upon multiple factors, and varies with different hospital settings. This can be verified by ambiguity of observations, and the fact that different researchers across the world have reported different patterns. Therefore, regular assessment of trace element status in CKD patients undergoing hemodialysis, monitoring of dialysate salt concentration, source water trace element concentration, become even more important in the light of trace element disturbances that were found to occur in these patients. Not only will it improve the management and prognosis of CKD patients, but will also help in understanding the cause of unregulated trace element exchange that was found to occur during the process of hemodialysis, by paving the way for further studies aimed at identification and correction of this problem, in order to improve the efficiency of the dialysis process itself.

## Limitations

Primary limitation of this study was small sample size of CKD patients on hemodialysis, due to limited number of available dialyzers in the hospital. Other limitation was lack of availability of dialysate fluid for trace element analysis and consequently no data was available on trace element concentration in the dialysate fluid before & after hemodialysis. Despite these limitations our study findings were able to provide a clear assessment of the trace element status in CKD patients, highlighting the role of hemodialysis in trace element imbalance that was found to occur in these patients.

## Acknowledgment

The authors acknowledge that the study involved human participants & therefore ethical approval was obtained from the Office of Institutional Ethical Committee of Jhalawar Medical College & Associated Hospitals, Jhalawar (Rajasthan) through Approval letter number: 29/96 Dated: 06.09.2019. Prior written informed consent was taken from all test subjects. No funding was received for conducting the study.

## Author contribution

**Dr. Shantnu Singh Shekhawat:** Study conception & design, literature survey, specimen collection & analysis, data collection & analysis, manuscript writing.

**Dr. Ajay Kumar Bhargava:** Project supervision & mentoring, literature review, data interpretation, critical manuscript revision.

**Dr. Sujeet Kumar Jangir:** History taking, data collection, specimen collection & analysis.

**Sumit Kumar:** History taking, data collection, specimen collection & analysis.

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