ORIGINAL ARTICLE

Role of drinking water with high Silica and Strontium in Chronic Kidney Disease: An Exploratory Community-based Study in an Indian Village

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Abstract

Background: Ground water is the ultimate and inevitable source of drinking water in rural India. Seepage of earth's crust elements into drinking water sources may lead to adverse health effects. Media reported unusually high kidney related disorders among the population in Uchapally village of Nellore district, Andhra Pradesh, India. **Objective:** The objective of the present study was to assess the role of drinking water in chronic kidney disease (CKD). **Methods:** A community based cross-sectional study was carried out among the population residing in two villages namely Uchapally with reported cases of renal diseases (Village-A; n=52) and Pedarajupalem with no reported cases of renal diseases (Village-B; n=50) from Nellore district, Andhra Pradesh, India. Blood and urine samples were collected to estimate the renal parameters. Glomerular Filtration Rate (GFR) as calculated by Modification of Diet in Renal Disease (MDRD) equation was used to assess the staging of CKD. **Results:** Majority of subjects in village-A were suffering from different stages of CKD. Blood urea and creatinine, intact parathyroid hormone and alkaline phosphatase levels were significantly ($p<0.01$) higher among the subjects in village-A. Silicon and Strontium levels in the drinking water samples from village-A were significantly higher as compared to the water samples from Village-B. The subjects from Village-A had a history of prolonged consumption of various non-steroidal anti-inflammatory drugs (NSAIDs). **Conclusion:** The high prevalence of CKD among the population in village-A could be attributed to the synergistic effect of chronic exposure to silicon and strontium through drinking water and prolonged consumption of NSAIDs.

Key Words

Ground water; Silica; Strontium; NSAIDs and Chronic kidney disease (CKD).

Introduction

The global End Stage Renal Disease (ESRD) patient population continues to grow at an alarming rate due to a number of factors. The etiology of chronic kidney disease sited in Indian studies was chronic interstitial nephritis apart from diabetes and hypertension (1-6). Chronic interstitial nephritis is presumed to be due to drugs or environmental toxins, and the possible environmental toxins

include water and food related toxins (7). It has been documented that environmental and occupational exposure to lead (Pb), cadmium (Cd), chromium (Cr), mercury (Hg), arsenic (As), silica (SiO2), strontium (Sr) and organic solvents, may lead to Chronic kidney disease (CKD) (8,9).

The surface water sources like ponds, lakes and shallow wells were the traditional water drinking water sources in rural India (8). However, the ever growing population and green revolution resulted in the imbalance of water sources at villages (9). This lead to increased dependency on ground water for irrigation and drinking needs and the groundwater is the only source of drinking water in entire rural and most parts of urban India (8).

Seepage of earth's crust elements such as silicon, strontium, heavy metals etc., into drinking water is a cause of concern. Silicon (Si), exists as silica (SiO2) in nature and has been identified as environmental nephrotoxin (8). Over decades, epidemiological studies documented a strong association between exposure to silica and kidney disease (10-12). In addition, experimental studies on animals have also shown that high levels of SiO2 in drinking water cause kidney disease (13). Similarly, it was also reported that inhalation of silica dust during the mining process leads to the development of nephropathy (11).

Strontium (Sr) resembles to calcium (Ca) in great extent, and more than 99% of the total body Sr is localized in bone (14). The role of Sr in bone metabolism is unclear, but studies on rat models demonstrated that low doses of oral administration of Sr is known to stimulate bone formation, while high doses may result in a defective bone (15, 16). In addition, Sr is known to interfere with Ca homeostasis and vitamin D metabolism, since these two processes are disturbed in CKD patients (17). The consumption of high Sr and low dietary Ca intake was known to cause osteomalacia, characterized by increased bone/body pains. Bone disorders, mineral disarrays, and vascular calcification are the three closely interrelated and common conditions in individuals with moderate to advanced CKD (18). On the other hand, exposure to environmentally abundant toxic heavy metals such as Pb, Cd, As and Hg are known to cause nephrotoxicity, while excreting through urinary system (9).

Rationale of the study: Print and electronic media reported unusually high kidney related disorders and four deaths with kidney disease among the population in Uchapally village of Nellore district, Andhra Pradesh, India. In this connection, with the instruction of the Ministry of Health, Gov of India and Indian Council of Medical Research (ICMR), New Delhi, a rapid exploratory cross-sectional survey was carried out by NIN and Nizam's Institute of Medical Sciences (NIMS), Hyderabad to assess the extent of the kidney disease among the population in Uchapally village.

Aims & Objectives

1. To assess the extent of chronic kidney disease among the population of Uchapally village.
2. To assess the role of drinking water in CKD among the population residing in Uchapally village located in mica belt.

Material and Methods

Study design & Location: A community based cross-sectional study was carried out during the month of October, 2006 in Uchapally (Village-A), where kidney disorders were reported and apparently normal Pedarajupalem (Village-B) village both located in mica belt of Nellore district, Andhra Pradesh, India. Both the villages belong to Podalkur block of Nellore district and were located >10 km away from one another, with 'tube-wells' were the only source of drinking water. As the apparently healthy individuals from Uchapally (village-A) have also been residing and consuming the water from same tube-wells, they were not considered as true controls. Therefore, we selected Pedarajupalem village for comparison and study the epidemiological variables attributing the kidney disease among the population of Uchapally village.

Selection of subjects from village - A: A total of 52 subjects i.e. 32 subjects with known history of kidney related disorders and 20 randomly selected apparently normal subjects were selected at a health camp for this rapid exploratory study.

Calculation of sample size for village-B: The sample size was calculated based on the prevalence of CKD (80%) in village-A , with a confidence interval of 95% and 20 % relative precision, further, considering the design effect of 2 and 5% non-response, the required sample size was arrived at 50 individuals per group. Thus, a total of 50 adult subjects (34 men and 16 women) were randomly selected from Village-B. The study and procedures were approved by Institutional Review Board (IRB) of National Institute of Nutrition (ICMR), Hyderabad, India. Written informed consent was obtained from all the participants.

Anthropometry and Clinical Examination: The anthropometric parameters such as height and weight were recorded. The clinical examination was done for detection of signs and symptoms related renal failure, musculo-skeletal disorders and skeletal fluorosis. History of hypertension, diabetes and consumption of NSAIDs was collected. Blood pressure was measured using mercury sphygmomanometer.

Sample Collection and Laboratory Investigations: Blood and spot urine samples were collected from all the subjects and transported to laboratory, following the necessary precautions, for further analysis. About 5.0 ml of intra venous blood was collected in two vaccutainer tubes for whole blood and serum. Haemoglobin and lead (Pb) levels in blood were determined by Cyanmethaemoglobin method and Lead Care Blood Lead Testing System (ESA, USA), respectively. Serum total Alkaline Phosphate (ALP), creatinine and urea levels were determined on ACETM clinical auto-analyzer. The serum 25-OH-vitamin D3 and intact Parathyroid Hormone (iPTH) levels were estimated by Immuno Radiometric Assay (IRMA) and Chemiluminescence kit methods, respectively. Serum Ca, Mg, Cu and Zn levels were estimated by flame atomic absorption spectrophotometer (Avanta, Australia), whereas serum Sr was estimated by Inductively Coupled Plasma Mass Spectrometry (ICPMS, Perkin Elmer, USA.). The serum phosphorus levels were estimated by routine 'Fiske and Subbarow' method.

Urinary sugar, albumin and hematuria were determined by semi-quantitative dip stick method (Bayer Pharmaceuticals). Urinary fluoride content was estimated with 'Orion ion specific electrode' (EA–940, Boston, MA, USA). The kidney function of all the participants was assessed and classified into stages by GFR-MDRD formula for adult subjects (19). Drinking water samples from all the tube wells were collected in clean poly-propylene bottles. A total of three water samples in duplicate were collected at initial, mid-stream & end of continuous flow for 8–10 minutes from each tube well. The fluoride content and a set of 22 toxic, trace element levels were estimated as explained above using Orion-electrode and ICPMS, respectively.

Statistical Analysis: Mean and standard deviation (SD) were calculated for all the variables. Between two groups, statistical analysis was done using student t-test to assess the differences. Wherever 'heterogeneity' in the data of a particular variable was observed, non-parametric, Mann-Whitney U test was performed. For the categorical variables, the association between cases (village- A) and controls (village- B) was assessed using Chi-square test. The results were considered significant at $p<0.05$. The data were analyzed using SPSS 15.0 Window's version.

Results

Demographic Information: An un-operational mica mine was noted in the vicinity of Village-A, but not in Village-B. In both the villages, tube wells were the only sources of drinking water. The depth of the wells was about 150–200 feet. Ten such tube wells have been under operation as source of drinking water for both the villages. The rest of the activities such as type of crop cultivation, irrigation methods, agriculture and farming were comparable between the two villages.

Anthropometry and Clinical Examination: The mean age, height, weight and body mass index (BMI) of the two groups are presented in Table 1. The economic status, demographic profile and access to staple foods were comparable between villages. Thirty two percent of participants from Village-A and 28% from village-B had hypertension. The mean systolic and diastolic blood pressures were comparable among the two groups (Table 1). Puffiness of face (4%) and pallor (39%) were observed among the subjects from Village-A alone. No signs and symptoms of fluorosis such as dental mottling, genu varum and genu valgum were reported among the subjects of both the villages. Majority of the participants from Village-A have complained of severe body pains (81%) with low back pain (42.6%) and swelling of feet (6%), while only 7% of subjects from Village-B had reported body pains. All the subjects from Village-A had given the history of consumption of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as Diclofenac sodium, Ibuprofen, Nimusulide, Sulindac, Naproxyphen etc., since past 6-8 years. While the subjects from Village-B did not give history of consumption of NSAIDs.

About 92% of subjects from Village-A were at different stages of CKD as assessed by GFR-MDRD equation, while only 10% of subjects from Village-B had abnormal GFR. Severe stages of CKD (IV and V) was reported among 46% of the subjects from Village-A only.

Biochemical, trace and toxic elemental levels: The mean Hb levels were comparable among the two

groups. However, a higher prevalence of anemia was reported among the subjects in Village-A as compared to Village-B. The blood Pb levels ranged from 2.0 – 17.5 µg/dl in Village-A and 4.2 – 15.6 µg/dl in Village-B. The mean blood Pb levels were comparable between the groups and within the cut-off limits (< 20µg/dl in adults) specified by the Centre for Disease Control and prevention (CDC), Atlanta, USA (Table 2).

The mean serum creatinine levels were significantly ($p<0.001$) higher among the subjects in Village-A as compared to Village-B. The elevated serum creatinine (≥1.5mg/dl) was reported to be higher among the subjects in Village-A (Men: 74% and Women: 43%) as against only 6% each in Village-B. Serum urea levels of subjects in Village-A ranged from 12.0 to135.0 mg/dl, while it was ranged from 12.0 – 60.0 mg/dl in Village-B. The mean serum urea levels were significantly ($p < 0.001$) higher among the subjects in Village-A as compared to the subjects in Village-B. The prevalence of proteinuria and haematuria was significantly ($p< 0.001$) high among the subjects in Village-A as compared to Village-B, while the mean urinary fluoride was significantly higher ($p<0.05$) among the subjects in village-B as compared to village-A (Table 2). However, the urine samples of both the groups were found negative for the presence of sugar.

The mean ALP levels of subjects in Village-A was significantly ($p < 0.05$) higher than Village-B (Fig. 1). The serum 25-(OH) Vitamin D3 levels ranged from 42.1 – 112.6 ng/ml in Village-A and it was 73.5 – 169.5 ng/ml in Village-B. The mean Vitamin D3 levels were certainly lower among the participants in Village-A as compared to Village-B, but the difference was statistically not significant ($p>0.05$). The serum iPTH levels ranged from 189.2 – 361.7 pg/ml in Village-A and 21.9 – 42.5 pg/ml in Village-B. Similar to that of ALP levels, mean serum iPTH levels were also significantly ($p < 0.01$) higher in Village-A as compared to Village-B (Figure 1).

The serum elemental levels of subjects from Village-A and Village-B are presented in Figure 2. The mean calcium levels were significantly ($p<0.05$) lower in Village-A than Village-B subjects. However, mean serum Zn levels were significantly ($p<0.05$) higher in Village-A than Village-B subjects. The serum Sr levels among the participants in Village-A was ranged from 0.0020 – 0.0380 mg/dl, whereas in Village-B they ranged between 0.0005 and 0.0015 mg/dl. Significantly ($p<0.05$) higher levels of serum Sr were noted among subjects in Village-A as compared to Village-B (Figure 2). However, no significant differences were observed in the mean values of serum Cu, Mg and P levels among the subjects in two villages.

Drinking Water Elemental Levels: The mean levels of 22 trace and toxic metals (Li, B, Al, Si, V, Cr, Mn, Fe, Ni, Co, Cu, Zn, As, Se, Rb, Sr, Mo, Ag, Cd, Sb, Ba and Pb) in drinking water samples from village-A and Village-B were given in Tables 3 & 4. The mean levels of set of 15 elements were within the permissible limits specified by WHO criteria for drinking water (Table 3). In view of the unavailability of WHO cut-off limits for Li, B, Si, Rb and Sr, the potable drinking water (Manjeera river) supplied by Municipal Corporation of Hyderabad (MCH) was used as reference. Mean levels of Li, Si, Rb and Sr were significantly ($p <0.05$) higher in drinking water of Village-A as compared to Village-B and potable water supplied by MCH (Table 4). The mean Sr and Si levels of Village-A tube-well drinking water were about 4 – 6 folds higher than the Village-B tube-well and Manjeera potable water levels.

Discussion

The etiology of chronic kidney disease (CKD) is multi-factorial, among which exposure to certain heavy metals, organic solvents and trace elements such as Si and Sr are well known factors (14, 20). In the present study, a majority of subjects from Village-A were at various stages of CKD and 46% of them had severe CKD (stage IV and V), where the drinking water samples contain higher levels of silica and strontium. Whereas, the prevalence of severe forms CKD was nil and the corresponding silica and strontium levels of drinking water samples in Village-B was lower as compared to Village-A. Similarly, it is well known that renal function can be assessed by biomarkers in blood (creatinine, urea etc.), urine (presence of proteins / albumin, heam etc.) and renal imaging by ultrasonography (19, 21, 22). In the present study, subjects from Village-A had significantly elevated levels of serum creatinine, urea, proteinuria and haematuria as compared to Village-B suggesting the renal injury.

The inter-relationship between CKD and bone mineral metabolism has been well documented. In CKD, kidney loses the ability to remove phosphorus from blood and also unable to activate adequate amounts of Vit.-D to maintain normal levels of Ca. This in turn leads to elevated levels of PTH

production and release, to compensate Ca levels. Ultimately all these metabolic changes result in bone deformation, bone pain, and altered risks of fractures (14,18). In the present study, our observations are in line with the above mentioned mechanism where a significant ($p<0.01$) elevated serum iPTH and reduceed 25-(OH) Vitamin D3 levels (Statistically insignificant) was observed in Village-A subjects, but not in Village-B. Similarly, the serum Ca levels were significantly ($p<0.05$) lower in Village-A participants as compared to Village-B, whereas no significant difference was observed in serum phosphorous levels among the two groups. These observations are in line with the recent studies who have demonstrated normal levels of Ca and phosphate until GFR fell below 40 ml/min in patients with CKD stage III to V; however, the elevated PTH levels were noted even as high as GFR < 60 ml/min (23, 24). The serum ALP is considered as a marker of bone resorption, and its rise in CKD patients is associated with worsening of bone mineral density (18). In the present study, a significant ($p<0.05$) elevated levels of serum ALP along with abnormalities of other bone related biomarkers among Village-A participants suggests CKD–associated bone and mineral disorders. In addition, a number of trace minerals particularly Cu, Mn, Zn etc. are essential in bone metabolism as cofactors for specific enzymes (25). The lower levels of serum Cu, Zn and Mg levels (Cu < 0.08, Zn < 0.07 and Mg <1.8 mg/dL) were observed among the subjects in both the villages.

In the present study, we have observed that significantly elevated levels of serum Sr among the subjects in Village-A as compared to Village-B. It is well known fact that Sr, to a great extent resembles Ca, and more than 99% of total body burden of Sr is present in bone (14). The possible reasons for such high levels of serum Sr among the subjects in Village-A might be due to consumption of contaminated tube-well drinking water, since the drinking water Sr levels of Village-A were significantly ($p < 0.05$) higher than Village-B (about 2 folds) and Manjeera river potable water (about 4 folds). We speculate that elevated levels of serum Sr might have dual role with a direct nephrotoxic action and an indirect toxicity exerted by interfering with Ca homeostasis and Vitamin D metabolisms among the subjects in Village-A (14, 17).

National Nutrition Monitoring Bureau (NNMB) has reported that the median dietary intake of calcium was 370 and 328 mg/day, among adult rural men and women respectively, as against the recommended intake of 600 (26). The recent reports suggest that consumption of high Sr coupled with invariably low dietary Ca intake may lead to osteomalacia, characterized by increased bone/body pains (14). Such situation was prevalent in Village-A, where the people were chronically exposed to Sr through drinking water. In addition, consumption of low dietary Ca might be one of the reasons for various forms of severe body/bone pains reported by the subjects in Village-A. In addition, the studies conducted in rat models have demonstrated that higher doses of oral Sr administration led to defective bone formation by decreased bone mineral density and decreased size of bone apatite (15,16).

Similarly, Silica levels in drinking water samples of Village-A were significantly higher as compared to the water samples of Village-B. The mica (Potassium Aluminum Silicate) is the predominant mineral in Village-A earth crusts, which was evident by the presence of an un-operational mica mine in the vicinity of this village. It is clear that climatic changes such as less rainfall, unavailability of surface water have led to exploitation of ground water for irrigation and domestic use through tube wells.

Epidemiological and animal studies have suggested that silica is known to cause kidney damage when it was consumed in excess for long duration (10-13). In the present study, Village-A had no alternate source of drinking water other than tube wells, which had elevated levels of Silica. In contrary to oral SiO_2 exposure in the present study, nephrotoxic effect of silica dust inhalation during the mining process was also reported over decades (11, 12).

In the present study, it appears that the synergistic effect of elevated levels of serum Sr and low dietary Ca might have led to ‘osteomalacia” in Village-A. To alleviate the diffused bone/body pains, the subjects from Village-A would have habituated to use various NSAIDs such as Diclofenac sodium, Ibuprofen, Nimusulide, Sulindac, Naproxyphen etc. It was well documented that long-term usage of various NSAIDs could cause the nephrotoxicity (27). While, the presence of heavy metals in the drinking water samples of both villages were within WHO limits. Similarly, the drinking water and spot urine fluoride content was also within the specified limits and no signs and symptoms related to fluorosis were observed among the subjects in both the villages.

Conclusion

Thus, the high prevalence of endemic kidney disease among the subjects in Village-A could be attributed to the synergistic effects of chronic exposure to high Si and Sr in drinking water along with frequent use of NSAID's. Therefore, it is emphasized that there is a need for a comprehensive study in order to confirm the role of geogenic contaminants in general and silica and strontium in particular in ground water in causation of CKD among the population residing in the mica belt.

Recommendation

It is recommended that the state government should provide surface water for the drinking purpose in the region of mica belt. Further, over the counter sale of painkillers should be banned and indiscriminate use of NSAIDs should be discouraged among the community.

Limitation of the study

We have not estimated the serum levels of Silica and Strontium and other trace elements. Similarly, the presence of pesticides in food and blood was not estimated. The dietary pattern/practices of the subjects were not obtained in the present study.

Relevance of the study

This study may provide the clue to the possible adverse health effects of geogenic contaminants.

Authors Contribution

KAL, AN & GT conceived and designed the study. All authors involved in data collection. BK analyzed the data. RYS estimated bio-chemical parameters. AN & RYS prepared the manuscript.

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Tables

TABLE 1 ANTHROPOMETRY AND BLOOD PRESSURE PROFILE OF THE PARTICIPANTS

S. No.	Variables	Village A (n=52)	Village B (n=50)
1	Age (years)	44.5±11.10	48.1±16.11
2	Height (cm)	162.5±8.40	157.0±7.43
3	Weight (kg)	56.3±12.57	50.9±11.34
4	BMI (kg/m2)	21.3±4.08	20.6±3.78
5	Systolic Blood Pressure (mm of Hg)	127.7±19.47	128.3±18.84
6	Diastolic Blood Pressure (mm of Hg)	83.5±7.68	80.4±9.16

Values represent mean±SD of variables. No significant difference was noted between Village-A and Village-B participant's anthropometry and blood pressure values.

TABLE 2 BIOCHEMICAL AND URINE PROFILE OF THE PARTICIPANTS

S. No.	Parameter	Village-A (n=52)	Village-B (n=50)
1	Blood Hb (g/dL)	11.4±2.02	11.8±2.10
2	Blood Lead (µg /dL)	9.0±5.82	8.3±5.02
3	Serum Creatinine (mg/dL)	2.25±1.154**	0.85±0.284
4	Serum urea (mg/dL)	61.8±33.67**	23.8±8.69
5	Urinary Fluoride (mg/L)	1.1±0.92**	2.2± 1.32
6	Proteinuria (%)	63.5**	20.0
7	Haematuria (%)	26.9**	2.0

*Values are mean±SD of variables. ** Indicates significantly different at P<0.001 Proteinuria and haematuria were given as 'percent of positive individuals' for presence of protein and blood in urine respectively.*

TABLE 3 MINERAL CONTENT (PPB) OF DRINKING WATER SAMPLES WITH REFERENCE TO WHO CUT OFF

S. No.	Mineral	Village A	Village B	WHO Cut-off Values
1	Al	14.43±19.192	28.42±11.300	30
2	V	53.69±30.852	29.40±12.700	100
3	Cr	2.4±0.22	6.8±3.10	50
4	Mn	1.38±1.314	5.2±3.250	50
5	Fe	58.31±16.957	68.15±19.300	100
6	Ni	2.88±0.682	4.80±3.900	50
7	Co	0.20±0.064	0.50±0.200	50
8	Cu	5.00±1.582*	10.20±2.800	50
9	Zn	10.40±16.109	15.80±9.200	5000
10	As	2.84±0.418	2.50±0.500	10
11	Se	5.57±2.430	6.20±2.100	10
12	Mo	1.87±1.516	2.6±1.100	250
13	Ag	0.01±0.010	0.01±.010	0.01
14	Sb	0.39±0.120	0.90±0.200	10
15	Ba	38.88±13.500	51.20±10.600	1000
16	Pb	2.22±3.119*	10.8±6.900	50

*Values represent mean±SD of variables. * Significantly different at p<0.05*

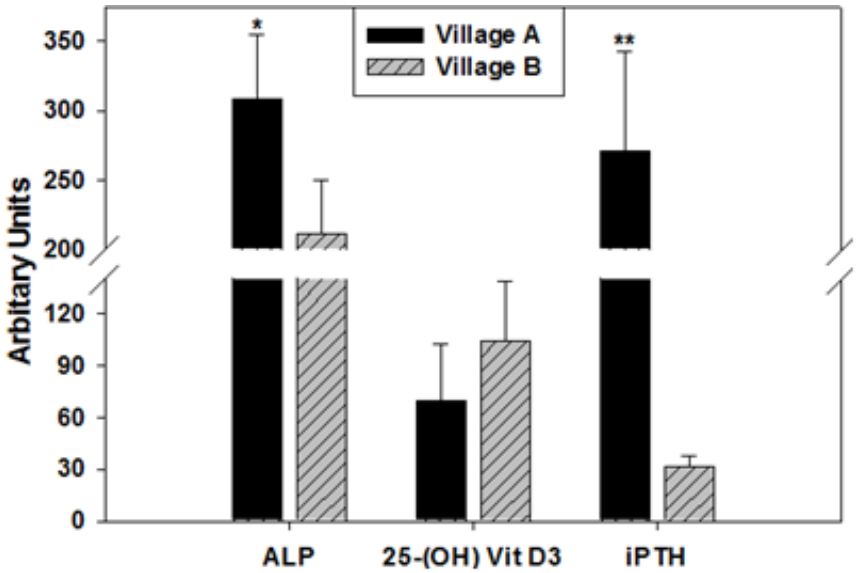
TABLE 4 MINERAL CONTENT (PPB) OF DRINKING WATER SAMPLES WITH REFERENCE TO MANJEERA RIVER POTABLE WATER

S. No.	Mineral	Village A	Village B	Manjeera river Potable water
1	Li	5.91±2.868*	3.25±1.600	2.27
2	B	199.31±75.667	102.4±88.500	55
3	Si	44.76±2.512*	11.4±6.300	7.19
4	Rb	5.50±6.380*	1.50±1.800	1.05
5	Sr	2306.50±936.204*	1150.00±701.000	574

*Values represent mean±SD of variables. * Indicates values are significantly different at p < 0.05*

Figures

FIGURE 1 SERUM BONE MARKER LEVELS



*ALP: Alkaline Phosphatase (IU/L); 25-(OH) Vit D3: Serum 25 – (OH) Vitamin D3 (ng/ml); iPTH : Serum intact Parathyroid hormone (pg/ml); Bars represent mean±SD of variables; * Indicates levels significantly different at p<0.05; ** Indicates Levels significantly different at p<0.01*

FIGURE 2 SERUM ELEMENT LEVELS