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Original Article

Diminished disease progression rate in a chronic kidney disease population following the replacement of dietary water source with quality drinking water: A pilot study

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SUMMARY AT A GLANCE

CKD of unknown cause is a growing problem in many parts of the world. This pilot study from Sri Lanka suggests that in their case, replacement of well water with bottled water for drinking, reduced the rate of renal failure - thus prompting the likelihood of a contaminant in the drinking water as a factor in CKDu.

ABSTRACT:

Aim: **Environmental toxin/s is alleged to be the contributory factor for the chronic kidney disease of unknown aetiology (CKDu) in Sri Lanka. The potential of drinking water as a medium for the nephrotoxic agents in the affected subjects has been comprehensively discoursed in the recent past. The present study was aimed to assess the effect of replacing the habitual drinking water on the kidney function of CKDu patients residing in the North Central Province of Sri Lanka:**

Methods: **An interventional study was carried out to assess the disease progression rate of a CKDu population whose habitual drinking water was replaced by bottled spring water certified by Sri Lanka Standard (SLS) for a period of 18 month along with a population of CKDu patients who continued with their usual drinking water. Kidney function of subjects in both groups were monitored in terms of blood pressure, serum creatinine, serum calcium, serum phosphorus, hemoglobin, estimated glomerular filtration rate and urinary protein at 6 months intervals during the intervention and follow up periods.**

Results: **Diminished disease progression rate was observed in CKDu patients in the intervention group when compared with the non- intervention group based on serum creatinine, Hb, estimated glomerular filtration rate and urinary protein levels. Extensive interventional studies are required to generalize effect of drinking water on CKDu population.**

Conclusion: **The habitual drinking water is likely to be a contributory factor towards the progression of the disease.**

Chronic kidney disease of unknown aetiology is reported primarily among rural populations in confined geographical areas of Sri Lanka. The disease is not attributable for any known causes of chronic kidney disease and is assumed to be due to an environmental nephrotoxin.[1] High fluoride levels in the ground water of endemic areas and its potential of being toxic to kidneys in the presence of Na^+ or Ca^{2+} in water, heavy metal contaminated water and food chains are such attributed environmental factors.[1–6] Studies highlight the possibility of drinking water source of the affected being contaminated with nephrotoxic agents. As the endemic areas are agricultural, leaching of fertilizers into water system is believed to increase iconicity in drinking water leading to CKDu.[7] Consuming water from abandon wells and spraying glyphosate and other pesticides to the paddy fields are reported to be surplus factors towards the origin of this disease.[8] Studies highlight the synergistic effect of high fluoride, cadmium and hardness in drinking water of high CKDu prevalent areas as the cause.[9] Conversely low levels of nephrotoxic elements in drinking water of endemic areas are reported and recommendations are been made to study the potential interactions among low doses of these elements and other risk factors leading to CKDu.[10] Attempts have been made to demonstrate the effect of drinking water from endemic areas on the kidney function

of animal models. Mice fed with water contaminated with cyanobacterial strains from the endemic areas have shown histopathological changes in kidneys (Dissanayaka DM, 2011, unpubl. data).

Diminished kidney function and histopathological changes have been shown in Wistar rats fed with water from these high endemic areas (Thammitiyagodage MG 2010a, unpubl. data). All of these studies exceedingly indicate that water in the CKDu endemic areas might be acting as a source or medium for environmental nephrotoxin/s. The effect of drinking water from the concerned areas on the human kidney function has not been tested to date. The objective of the current study was to monitor and compare the kidney function of CKDu patients, when their dietary water source was replaced with a bottled SLS certified spring water source from a non-endemic area.

METHODS

An interventional study was carried out on CKDu patients whose habitual drinking water was replaced with bottled water [intervention group (IG), $n = 15$] while another group of CKDu patients continued with their usual drinking water [non-intervention group (NIG), $n = 15$].The study was carried out in Medawachchiya, a major CKDu endemic area in Sri Lanka. The patients of both groups were in stage III of CKDu and residing in Medawachchiya Divisional Secretariat of Anuradhapura district, Sri Lanka. They were randomly selected from stage III CKDu confirmed patients attending the renal care unit of Medawachchiya base hospital using random number tables. All the subjects were diagnosed and confirmed to be having CKDu by biochemical tests, abdominal ultrasound scan and histo-pathological reports of renal biopsies. Further, all known causes of chronic kidney disease including diabetes mellitus, long standing hypertension, glomerular nephritis, urolithaisis, congenital kidney diseases, past history of snake bite and leptospirosis were used as the exclusion criteria in selecting the subjects. The subjects of the IG were given adequate amounts of quality bottled water for drinking and cooking purposes for the entire family, assuming that the other family members would take part in the use of quality water. Thus, bottled water provided replaced their previous dietary water source. For washing of rice and vegetables, water from their habitual sources was used. Bottled water was used for cooking, having drained habitual water used for washing. Consumption and distribution of bottled water was monitored, to maintain adequate supplies at all times to these patients. Quality bottled water given to these subjects bore SLS and ISO 22000 certification and the water supplying company was registered with the Ministry of Health, Sri Lanka. Water source for this bottled water was from a non CKDu endemic area. The water used for drinking and cooking by the NIG was not changed and they continued using their habitual water supply. Ethical clearance for this study was obtained from the committee on Research and Ethical Review, Faculty of Medicine, University of Peradeniya, Sri Lanka (2008/EC/34). Written informed consent was obtained from all the participants and they were requested to continue with their normal medication and clinic visits, while participating in the research programme.

The entire study period was divided into two sections of an 18-month period and a 6-month period. During the 18-month intervention period, bottled water was supplied to the IG for consumption of their entire family and bottled water was discontinued during the subsequent 6-month monitoring period. Both groups were monitored for disease progression at the commencement of the study and after 6, 12, 18 and 24 months of the study. Body mass index (BMI), blood pressure (sphygmomanometer, Fazzini 20096, Vimodrone, Italy), serum creatinine (Jaffe's method, Human INF 109 101 GB, Germany kit), serum calcium (O-cresolphtalein complexone method, BIOLABO REAGENTS, AT 80004, France kit), serum phosphorus (Ammonium molybdate method, BIOLABO REAGENTS CNQ: TB, FT 80015, France kit), hemoglobin (Sahli's method) and estimated Glomerular Filtration rate – eGFR [Modification of Diet in Renal Disease (MDRD) equation] and urinary protein (semi-quantitative URISTIK A_{10} reagent strips and sulphosalicylic acid test) were used as the parameters for assessing disease progression at each of these time points. All the assays were standardized prior to the commencement of the study. Since MDRD equation has not been validated for Sri Lankan populations, the original MDRD study equation was used excluding the constant for African American subjects to assess eGFR as recommended by National Kidney Disease Education Program.[11,12]

For analyzing markers in blood, 6 mL of blood was drawn by an experienced medical officer by venepuncturing the forearm without the use of a tourniquet. Blood was dispensed into acid washed sterilized polypropylene tubes, for the preparation of serum. This prevented binding of calcium and phosphorous to the surface of the tube. Serum aliquots (100 μL) were stored at −40°C in polypropylene eppendorf tubes until analysis. Frozen serum samples were allowed to thaw at room temperature and analyzed in triplicate for selected parameters. Data entered were double checked, concentrations were calculated and normality of the values was tested using Anderson–Darling, Ryan–Joiner and Kolmogorov–Smirnov tests for normality. Data were analyzed using parametric tests (paired t-test and 2-sample t-test) in Minitab version 16.0 (2010, State College, PA: Minitab Inc., www.minitab.com, 2010).

RESULTS

The study experienced participant drop outs reducing the sample number to 12 and 14 in IG and NIG groups, respectively, (Flow chart 1). Farmers ($n = 9$), constructors ($n = 1$) and housewives ($n = 2$) were found in the employment composition of the IG group, while farmers ($n = 8$), merchants

($n = 2$), teachers ($n = 2$) and housewives ($n = 2$) were found in that of the other. No significant changes were obtained between the two groups for age or for any of the tested parameters prior to the intervention (Table 1).

The BMI of the IG (22.65–23.6 kg/m^2) and NIG (21.55 to 22.61 kg/m^2) were almost within normal limits during the study (Table 2, Fig. 1(g)). Statistically significant difference ($P > 0.05$) in BMI values were not observed between the two groups or when compared with the initial value of each group at each time point (Table 2).

The mean blood pressures of the subjects in both groups were below 140/90 Hg mm at the commencement, and at most of the time intervals. Significant difference in the systolic blood pressure was seen with the NIG only at 24 months compared to the 0 time value. Significant increases in the diastolic blood pressure compared to initial value were seen at 12, 24 months and 18, 24 months in the IG and NIG respectively (Table 2, Fig. 1f). An Increase in diastolic blood pressure was seen with the IG only at 12 months when compared with the NIG (Table 2).The mean serum creatinine concentration gradually increased in both groups with time. The increase became significant than the initial value from 6 months onwards with the NIG but from 12 months onwards with the IG. Between the two groups, significantly higher serum creatinine values were observed at 6, 12 and 18 months in the NIG compared to the other. Six months after the discontinuation of bottled water to the IG, a significant difference in the mean serum creatinine value was not observed between the two groups (Table 3, Fig. 1(a)).

Significant decrease in eGFR compared to the initial value was not observed during the intervention, but only after the discontinuation of the bottled water in IG. Significant decrease in eGFR compared to the initial value was observed in NIG from 6 months onward. Though no significant difference was found between the two groups in eGFR at the commencement, significantly high eGFR values ($P < 0.05$) were observed in IG compared to NIG throughout the intervention period (Table 3 , Fig. 1 (b)).

In the IG, a significant decrease ($P < 0.05$) in Hb level compared to the initial value was noted only at 12 months during the intervention and 6 months after the discontinuation of bottled water. When the same comparison was made in the NIG, significantly low mean Hb ($P < 0.05$) values were noted from 6 months onward. Although not significant, the mean Hb levels of the IG were relatively higher than those of NIG from 6 months onwards during the entire experimental period (Table 3, Fig. 1(c)).

The mean serum calcium concentrations gradually decreased with time in both groups and, conversely, an increasing trend was noted in serum phosphorous concentrations. Throughout the study, serum calcium and phosphorus did not significantly vary compared to the initial value in the IG. Significantly low ($P < 0.05$) serum calcium concentrations compared to the initial value were observed at 6, 12 and 24 months in the NIG, while serum phosphorous was not significantly altered during the entire study. Significant differences ($P > 0.05$) in mean serum calcium concentrations were not detected between the two groups throughout the study, while significantly higher ($P < 0.05$) mean phosphorous concentration than the IG was noted in the NIG at 18 months (Table 4, Fig. 1 (d) and (e)).

At the commencement of the study majority of the IG (66.6%) and NIG (64.3%) were negative for dipstick

Table 1 Basic Demographic data of CKDu patients participated in the interventional study

Parameter	Intervention group ($n = 12$)	Non-intervention group ($n = 14$)	*P*-value
Age (years)	44.0	44.5	($P > 0.05$)
Male: Female	2:1	2.5:1	–
Farmers	75%	57.1%	–
Non-farmers	25%	42.9%	–

Table 2 Variation in BMI and blood pressure amongst CKDu patients of the two groups during the study

Time point (months)	BMI (kg/m^2) Mean ± SD		*P*-value	Systolic blood pressure (mmHg) Mean ± SD		*P*-value	Diastolic blood pressure (mmHg) Mean ± SD		*P*-value
	IG ($n = 12$)	NIG ($n = 14$)		IG ($n = 12$)	NIG ($n = 14$)		IG ($n = 12$)	NIG ($n = 14$)	
0	23.60 ± 3.77	21.70 ± 2.22	0.143	124 ± 17.5	116 ± 11.8	0.205	78 ± 10.7	75 ± 9.3	0.479
6	22.65 ± 4.61 (0.585)	21.81 ± 2.26 (0.900)	0.573	121 ± 15.5 (0.331)	110 ± 11.7 (0.158)	0.081	73 ± 10.8 (0.122)	74 ± 8.6 (0.609)	0.769
12	23.56 ± 4.22 (0.979)	21.89 ± 2.20 (0.826)	0.234	139 ± 24.7 (0.127)	123 ± 9.0 (0.064)	0.059	92 ± 13.7 (0.003)*	78 ± 8.2 (0.385)	0.006*
18	23.23 ± 4.28 (0.826)	22.48 ± 2.02 (0.343)	0.582	130 ± 9.1 (0.342)	123 ± 9.9 (0.117)	0.095	84 ± 7.3 (0.080)	84 ± 6.2 (0.014)*	0.869
IG-Bottled water supply discontinued and replaced with original water source NIG-Continued with original water source									
24	23.23 ± 4.25 (0.822)	22.61 ± 2.17 (0.282)	0.658	132 ± 11.4 (0.312)	127 ± 9.2 (0.002)*	0.303	87 ± 5.9 (0.002)*	83 ± 7.0 (0.035)*	0.096

IG, intervention group; NIG, non-intervention group. *Statistically significant ($P < 0.05$) *P*-value within the parenthesis: value at each time point was compared with the 0 time value (Paired *t*-test) *P*-value in separate columns: means of the intervention and non-intervention groups were compared at each time point (2 sample *t*-test)

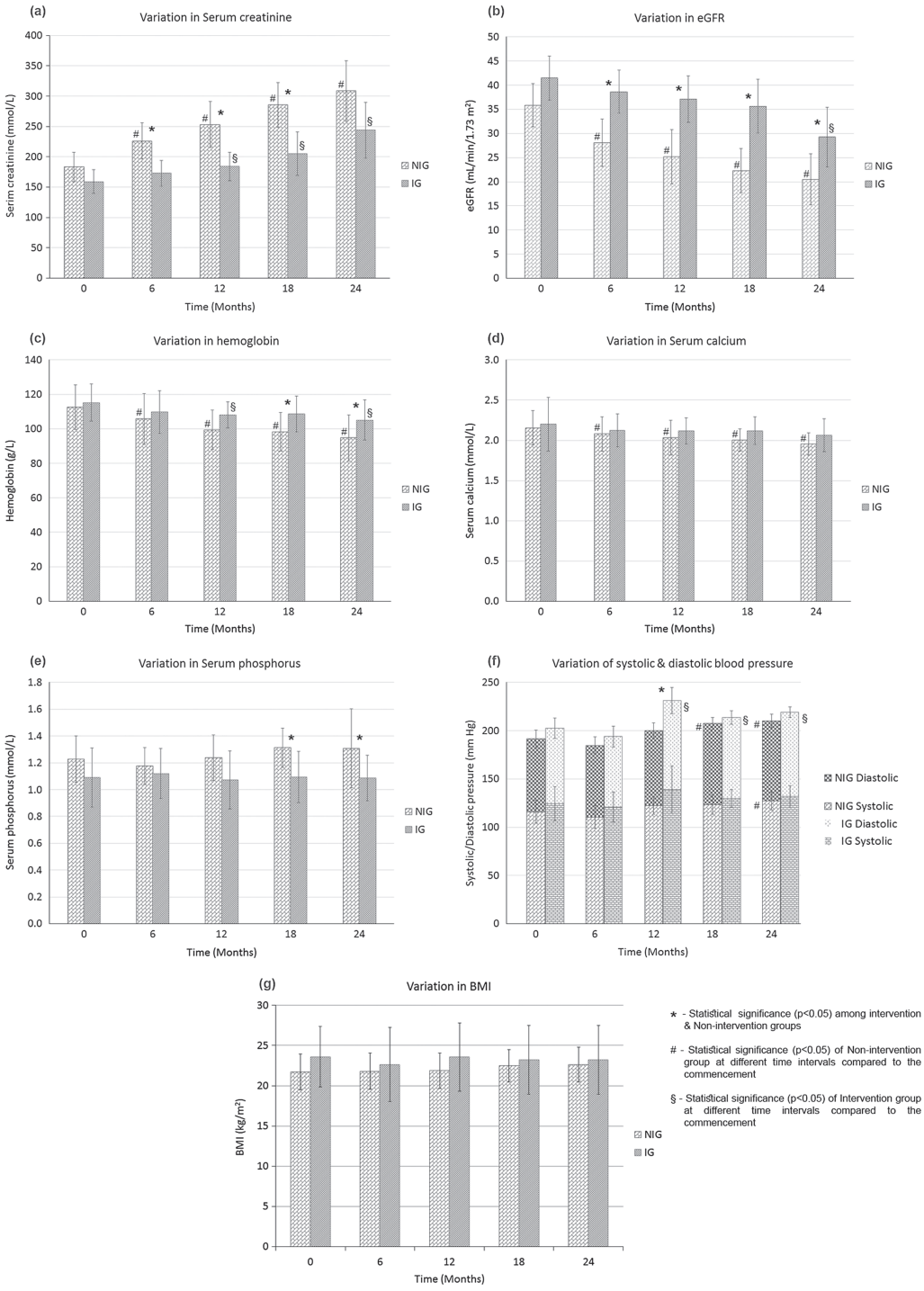

Fig. 1 Variation of tested parameters among intervention (IG) and non-intervention (NIG) groups.

proteinuria test. Gradually, the percentage of subjects negative for proteinuria, decreased and the percentage positive including trace increased in both groups. Fifty percent of the IG was negative for proteinuria up to 12 months, while 50% or more in NIG were positive for proteinuria from 6 months onward (Fig. 2).

DISCUSSION

The present study intended to assess the disease progression rate in CKDu patients whose habitual dietary water was replaced with quality drinking water.

The mean BMI of the CKDu patients of both study groups were almost within the cutoff limit for Asians (18.5–23.0 kg/

Table 3 Variation in serum creatinine, eGFR and hemoglobin levels amongst CKDu patients of the two groups during the study

Time (months)	Serum creatinine (mmol/L) Mean ± SD		*P*-value	eGFR (mL/min per 1.73m^2) Mean ± SD		*P*-value	Haemoglobin (g/L) Mean ± SD		*P*-value
	IG (*n* = 12)	NIG (*n* = 14)		IG (*n* = 12)	NIG (*n* = 14)		IG (*n* = 12)	NIG (*n* = 14)	
0	158.91 ± 19.4	183.19 ± 24.3	0.208	41.49 ± 4.6	35.82 ± 4.5	0.247	11.5 ± 1.8	11.3 ± 1.3	0.582
6	172.91 ± 21.1 (0.160)	226.11 ± 29.8 (< 0.001)*	0.014	38.62 ± 4.4 (0.274)	28.11 ± 4.9 (< 0.001)*	0.026*	11.0 ± 1.2 (0.188)	10.6 ± 1.5 (0.008)*	0.464
12	184.19 ± 23.6 (0.047)*	253.23 ± 38.1 (< 0.001)*	0.19	37.06 ± 4.8 (0.114)	25.15 ± 5.7 (< 0.001)*	0.026*	10.8 ± 0.8 (0.025)*	10.0 ± 2.5 (0.010)*	0.186
18	205.25 ± 35.9 (0.045)*	286.04 ± 36.7 (< 0.001)*	0.038	35.64 ± 5.6 (0.170)	22.28 ± 4.6 (< 0.001)*	0.027*	10.9 ± 1.0 (0.127)	9.8 ± 1.1 (<0.001)*	0.022*
IG, Bottled water supply discontinued and replaced with original water source; NIG, Continued with original water source.									
24	243.9 ± 40.0 (0.004)*	308.41 ± 50.0 (< 0.001)*	0.131	29.26 ± 6.2 (0.004)*	20.47 ± 5.3 (< 0.001)*	0.076	10.5 ± 1.2 (0.022)*	9.5 ± 1.3 (<0.001)*	0.045*

IG –intervention group, NIG-non-intervention group *Statistically significant ($P < 0.05$) *P*-value within the parenthesis: value at each time point was compared with the 0 time value (Paired *t*-test) *P*-value in separate columns: means of the intervention and non-intervention groups were compared at each time point (2 sample *t*-test)

Table 4 Variation in serum calcium and phosphorous levels amongst CKDu patients of the two groups during the study

Time points (months)	Serum calcium (mmol/L) Mean ± SD		*P*-value	Serum phosphorous (mg/dL) Mean ± SD		*P*-value
	IG (*n* = 12)	NIG (*n* = 14)		IG (*n* = 12)	NIG (*n* = 14)	
0	2.2 ± 0.34	2.16 ± 0.21	0.690	1.09 ± 0.22	1.23 ± 0.17	0.268
6	2.12 ± 0.21 (0.487)	2.08 ± 0.21 (0.044)*	0.595	1.12 ± 0.19 (0.736)	1.18 ± 0.14 (0.426)	0.582
12	2.12 ± 0.16 (0.432)	2.03 ± 0.22 (0.024)*	0.249	1.07 ± 0.22 (0.394)	1.24 ± 0.17 (0.861)	0.069
18	2.12 ± 0.17 (0.477)	2.01 ± 0.14 (0.056)	0.081	1.09 ± 0.19 (0.691)	1.31 ± 0.15 (0.230)	0.006*
IG-Bottled water supply discontinued and replaced with original water source NIG-Continued with original water source						
24	2.06 ± 0.20 (0.278)	1.96 ± 0.14 (0.010)*	0.128	1.09 ± 0.17 (0.539)	1.31 ± 0.29 (0.418)	0.055

IG, intervention group; NIG, non-intervention group. *Statistically significant ($P < 0.05$) *P*-value within the parenthesis: value at each time point was compared with the 0 time value (Paired *t*-test) *P*-value in separate columns: means of the intervention and non-intervention groups were compared at each time point (2 sample *t*-test)

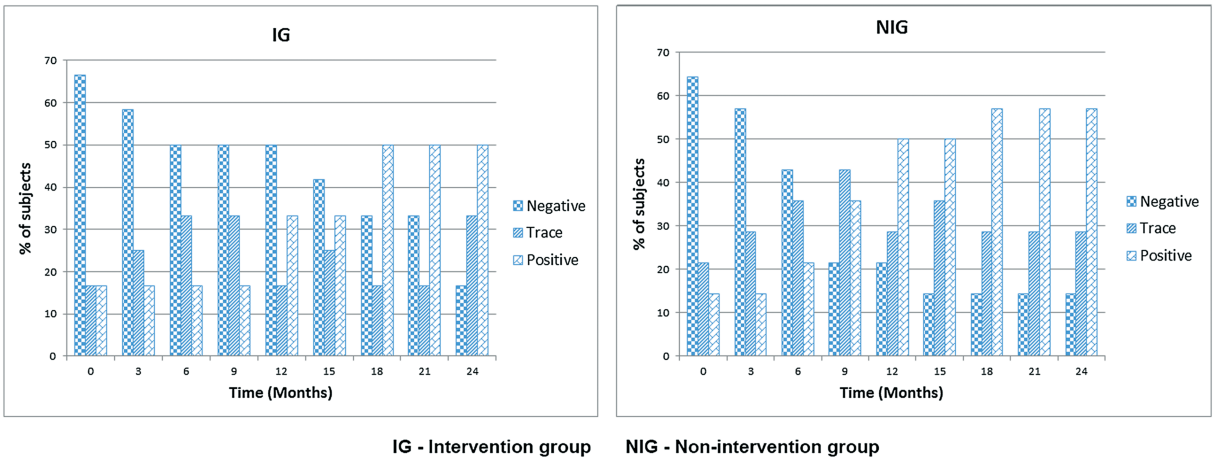

Fig. 2 Variation in excretion of urinary protein among subjects of intervention (IG) and non-intervention (NIG) groups.

m^2) [13]and devoid of significant changes throughout the study indicating no gross difference in the nutritional status of the two groups. Therefore BMI is unlikely to be associated with disease progression rate of the current study populations as revealed by prior studies.[14–17] At the commencement of the study, none of the subjects in each group were taking antihypertensive drugs as medications. At the latter part of the study, two subjects in each IG and NIG groups were found to be having high blood pressure recordings and were started with angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) to maintain their blood pressure. ACE inhibitors included enalapril and captopril while ARBs included losartan potassium. This clinical status might have accounted for the significant changes in diastolic BP noted during the study. This limited effectively commenting on the diseases progression based on blood pressure values.

The gradual progression of disease in both CKDu groups of the study was indicated by the successive increase in mean serum creatinine and decreases in eGFR, haemoglobin and calcium levels. However, higher disease progression rate in NIG compared to IG was signposted with the tested parameters. Though no significant variations (in tested parameters) were found between the two groups at the commencement, early appearance of significant variations in serum creatinine, eGFR, haemoglobin and increased rate of urinary protein excretion in NIG, indicated higher disease progression rate among them.

The effect of water on the disease progression was noted from another aspect. An accelerated disease progression was seen in IG with the withdrawal of bottled water at 18 months. This could be exemplified with the loss of significant variations in serum creatinine and eGFR between the two groups at 24 months. Significantly high ($P < 0.05$) Hb values seen in the IG at 24 months after the withdrawal compared to NIG, could be attributed to red blood cell physiology. The lifespan of the red blood cells is 120 days. Hence the red blood cells synthesized at around 18 months, might have remained in the circulation for about 4 months and contributed to the maintenance of Hb levels in the IG at significantly higher levels even after the discontinuation of bottled water. Throughout the study, the mean serum phosphorous levels of CKDu patients of both the groups were within the normal range. The tested populations were in the stage III of the disease and therefore serum levels might not have got affected yet.

In the present study, the maximum deviation in biochemical/anthropometric parameters between the two groups in the order of disease progression from the lowest to the highest is BMI < systolic blood pressure < diastolic blood pressure < serum phosphorous < serum calcium <Hb < eGFR < serum creatinine, the lowest being BMI and highest being serum creatinine. Based on the results of the study, it could be inferred that water replacement is likely to have contributed towards betterment of the IG subjects.

Previous studies have suggested the likelihood of multiple factors acting synergistically in the pathogenesis of CKDu and heavy metals and fluoride are few environmental factors considered to be contributing towards this.[5,6] The possibility of water as a source for the environmental nephrotoxins has been tested using animal models. Significantly low ($P < 0.001$) GFR values have been obtained in Wistar rats fed with water from sources of CKDu patients when compared to a control group of rats fed with tap water from Colombo, Sri Lanka (Thammitiyagodage, MG 2010b, unpubl. data), in which distinct tubular nephrosis, multifocal periglomerular and peritubular non-suppurative, interstitial nephritis were found during histopathoilogical examination of samples obtained from rats in the test group. The current study was the first attempt to distinguish the effect of drinking water source on the CKDu progression. In the international context, studies have shown the possibility to reverse the Cadmium-induced kidney damage in humans living in cadmium-polluted areas subsequent to reduction of cadmium contaminated rice for 3 years.[18] However, the absence of reversibility, but diminution in the diseases progression rate during intervention explicates the possibility of many factors contributing towards the development and the deterioration of CKDu. Accelerated

disease progression rate observed with the withdrawal of bottled water supply and returning to the habitual drinking water source indicates the possibility of water been contaminated with nephrotoxic agents.

Subjects under investigation could not be rigorously controlled for ethical reasons and were continuously medicated and monitored. Therefore, an authentic effect of bottled water alone on the kidneys of CKDu patients could not be ascertained as in an animal experiment. However, it is worthwhile to note that these changes are taking place in spite of medical treatment to slow down and improve the renal status. CKDu patients are given comprehensive clinical care and complications including blood pressure, bone mineral metabolism and anaemia are managed to international standards at the main and satellite renal care centres established in CKDu endemic area. Stage III patients are seen, investigated and managed at clinics once a month.

The subjects selected were diagnosed and confirmed as not having any other comorbidities but only CKDu. However, their lifestyle including smoking, dehydration could affect the origin and the progression of the disease.[19] None of the study participants were in the habit of smoking during the study. But one subject in the NIG and two from the IG had had the habit of smoking more than 5 years prior to the diagnosis. Smoking might not have affected the disease progression of the two considered study populations of the present study. The study did not have approaches to measure the average daily water consumption of the individual subjects involved. But the consumption of bottled water by 12 subjects in IG was tightly monitored. Adequate bottled water was supplied to the whole family and they were advised strictly to use bottled water for both cooking and drinking. They were asked to carry a bottle of water supplied to the field, working places or whenever they went out of their homes. Unannounced visits were made to their homes and working places to check the consumption of the supplied bottled water. When the average amount of bottled water consumed by each subject plus the family was compared against that of the non-affected residents of NCP, Sri Lanka, who consumes the same type of bottled water, a general agreement was found in the amounts consumed. This was effective in ensuring that the supply is adequate for the whole family including the affected individual.

The number of subjects included in the study could not be increased due to financial constraints, transportation problems, poor compliance and difficulty in monitoring. The effect of small sample size on the quality of study results was minimized by considering variations of each parameter as a difference of the initial value and value at each time point of a particular group and as a comparison between the two groups. Therefore, the subjects of a particular group were made to act as their own controls, while being compared to another control group. The current study unties new avenues for future research. A mass scale multi-centered interventional study of the same design would be more pertinent to access the effect of drinking water sources on the disease progression and generalizing data to the entire CKDu population. Studying the effect of other environmental factors or tangible sources on disease progression rate would be beneficial in managing the disease with less complications and ensuring the quality of life of those affected.

In conclusion, kidney function of CKDu patients, whose dietary water was not replaced with bottled water, seems to deteriorate faster than the CKDu patients whose dietary water was replaced with bottled water. The study thus revealed that the habitual dietary and drinking water is likely to be a contributory factor towards progression of the disease. Extensive studies in the same arena are recommended to assess the effect of drinking water on CKDu disease progression.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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