Chicken or the egg: Vitamin D deficiency in Chronic Kidney Disease of Uncertain Etiology in Sri Lanka

R Godawita

Center for Research, National Hospital. Kandy, Sri Lanka

MAA Nayanamali (✉ ayesha.medagedara@gmail.com)

Department of Fundamental Nursing, Faculty of Nursing, University of Colombo

KDRR Silva

Department of Applied Nutrition, Faculty of Livestock Fisheries and Nutrition, Wayamba University of Sri Lanka

HTK Abeysundara

Center for Research, National Hospital. Kandy, Sri Lanka

CN Antonypillai

Diabetes and Endocrinology Unit, National Hospital, Kandy

N Nanayakkara

Center for Research, National Hospital. Kandy, Sri Lanka

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Abstract

Background

Vitamin D deficiency is a poorly studied nutritional disorder in CKDu. There are no published studies on vitamin D levels in CKDu; a unique environmental nephropathy in tropical countries. This study was aimed to describe the prevalence of vitamin D, iron and vitamin B₁₂ status in CKDu patients and to determine associations between vitamin D status and socio demographic factors, nutritional status and dietary intake of vitamin D.

Method

This was a cross sectional survey conducted among the CKDu patients in Wilgamuwa area, in Mathale district located in the Central province of Sri Lanka. Data was collected by laboratory evaluation, clinical examination and interviewer administered questionnaire and analyzed using SPSS statistical software.

Results

Out of the 150 of respondents, 74.0% (n = 111) had vitamin D deficiency, 72.0% (n = 108) had anemia, and 3.3% (n = 5) had vitamin B₁₂ deficiency, in both genders. There was no significant difference in the prevalence of anemia, low serum ferritin and vitamin B₁₂ deficiency between males and females. Gender was significantly associated with the vitamin D deficiency (p<0.05). Females were 7.69 times more likely to have vitamin D deficiency compared to males. Vitamin D deficiency was 1.7 times higher among those who received social welfare benefits than those who did not receive it. High intake of fish was protective against vitamin D deficiency.

Conclusion

Isolated Vitamin D deficiency was the most prevalent nutritional deficiency among CKDu patients of Sri Lanka. Correction of these deficiencies may have a favorable effect on CKDu outcome.

Introduction

Chronic kidney disease (CKD) is heralded as a worldwide public health problem due to high prevalence and tremendous burden on death and disability that it causes [1]. Diabetes Mellitus, hypertension and glomerular nephritic diseases are among prominent causations of CKD. However, in recent years, a different form of CKD which has no obvious identified cause has been described in the world [2]. This new disease, the chronic kidney disease of uncertain etiology (CKDu), has different epidemiological characteristics over CKD. Notably, it predominantly affects the young and middle-aged males in rural

discrete pockets of farming areas in tropical countries [3]. Hence, CKDu has become an emerging health problem in developing countries such as El Salvador, Egypt, India, Central America, Nicaragua and Sri Lanka [4]. In Sri Lanka, CKDu was first discovered among young paddy cultivators of North Central province in mid 1990s [3]. A recent population based cross sectional study has reported point prevalence of CKDu in endemic areas of Sri Lanka ranging from 15.1–22.9% [5].

In a healthy individual, ordinary food intake generally provides sufficient nutrients to maintain normal functionality. Increasing bioavailability and decreasing excretion are two body adaptations to dietary nutritional deficiencies. Nevertheless, CKD typically disturbs the intake, absorption, utilization, and/or excretion of nutrients. Further, disease specific dietary and lifestyle modifications lead to nutritional deficiencies [6]. As a result, several nutritional deficiencies have been reported in patients with CKD as well as in CKDu leading to serious implications [7].

Anemia, one of the most common complications in chronic kidney disease, is associated with increased risk of cardiovascular disease, morbidity, and mortality [8]. The prevalence of anemia increases as the kidney function decreases with, an estimated prevalence of 90% in patients with a glomerular filtration rate (GFR) less than 25–30 mL/min² [5, 9]. Undoubtedly, Anemia of CKD is multifactorial. For instance, it could be due to iron, folic acid and B₁₂ deficiency or relative Erythropoietin deficiency. In addition, uremic inhibitors of erythropoiesis, shortened erythrocyte survival, and disordered iron homeostasis or more commonly, a different combination of these factors contribute to the anemia [10].

Derangements of bone mineral metabolism occur early in the course of CKD and worsens along with the decline of renal functions. Further, in CKD, vitamin D deficiency has been reported to be as high as 80% [11]. Vitamin D deficiency is a major risk factor for bone-mineral disorders. Similarly, it has been related to increased risk of non-skeletal health outcomes including mortality, diabetes, and cardiovascular disease [12]. Hence, the Kidney Disease Outcomes Quality Initiative guidelines from the National Kidney Foundation recommend to maintain 25-hydroxyvitamin D level at 30 ng per milliliter or higher in any stage of CKD [13].

Several studies have described the vitamin D, serum iron, vitamin B₁₂ status and associated health implications of these parameters in CKD. However, there is no any published research on the prevalence of vitamin D deficiency among CKDu patients. This cross-sectional study was conducted to describe the prevalence of vitamin D, iron and vitamin B₁₂ status in CKDu patients and to determine associations between vitamin D status and socio demographic factors, nutritional status and dietary intake of vitamin D.

Methodology

This study was conducted in Wilgamuwa Divisional Secretariat Division, a CKDu endemic area in the dry zone of Central Province in Sri Lanka. A total of 150 diagnosed CKDu patients according to Ministry of

Health criteria [14]. including 118 males and 32 females (age less than 65) were randomly selected from the registry of the nephrology clinic conducted in Base Hospital, Hettipola.

A pre-tested interviewer-administered data collection form was used to collect socio-demographic data (age, gender, occupation, education level, number of years living in the area), medication history and the degree of sun exposure. Subjects were categorized into two income levels based on the receipt of social welfare benefits (*Samurdhi*). Anthropometric measurements (height and weight) were taken using standard methods. Patients were categorized into outdoor workers and indoor workers base on their occupational environment. Vitamin D intake was assessed using an interviewer-administered, semi-quantitative food frequency questionnaire consists of vitamin D containing commonly consumed foods. BMI was classified according to the categorization of BMI related to South Asians as underweight (<18.5 kg/m²), normal (18.5-22.9 kg/m²) and above ideal range (> 23 kg/m²) according to the categories of the World Health Organization [15].

A venous blood sample (6 ml) was obtained from the median-cubital vein under aseptic conditions to K-EDTA tubes for hemoglobin measurement and to plain acid washed centrifuge tubes. All blood samples were kept on ice, and were transferred to the laboratory within 6h. Serum was separated immediately by centrifugation at 3000rpm for 10 minutes and serum was kept frozen at -20°C until analysis was completed. Hemoglobin concentration was measured using the standard photometric cyanomethemoglobin method [16]. at the clinical laboratory of the Base Hospital, Hettipola. Serum ferritin, vitamin D and vitamin B₁₂ were measured by chemiluminescent methods at the nephrology laboratory of the National Hospital, Kandy. The stages of CKDu were determined by eGFR values. The patients were categorized based on hemoglobin value, serum ferritin, vitamin D and vitamin B₁₂ values.

Ethical approval for the study was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Peradeniya, Sri Lanka. Informed written consent was obtained from the participants prior to data collection after explaining the purpose of the study.

Statistical Package for Social Sciences (SPSS) version 20 was used to analyze the data. Descriptive statistics were used to summarize the socio-demographic data and prevalence data. Chi-square test was performed to analyze the association between nutritional deficiencies and gender. Independent sample T test was performed to compare BMI, eGFR and Laboratory data between CKDu patients with vitamin D deficiency and CKDu patients without vitamin D deficiency. Level of $p<0.05$ was considered statistically significant. Associations between the presence of vitamin D deficiency and the socio demographic, anthropometric and laboratory variables were examined using binary and multinomial logistic regression. Food group (fish, dairy products, eggs and meat) consumption levels were categorized as satisfactory and unsatisfactory according to the Food-based dietary guidelines for Sri Lankans [17].

Results

A total of 150 patients living in a CKDu endemic area in Sri Lanka were studied. Majority (n=118, 78.7%) of the CKDu patients were males. Mean age (years) was 56.75 ± 7.89 and 54.34 ± 7.87 for females and males, respectively. Table 1 shows the demographic data of the CKDu patients who participated in the study.

Table 1
Demographic characteristics of CKDu patients

Demographic Characteristics	Frequency	Percentage	Mean Value and SD
Gender			
Male	118	78.7	
Female	32	21.3	
Age (years)			55.3 ± 7.9
≤ 30	1	0.7	
31-45	18	12.0	
46-60	84	56.0	
61-65	47	31.3	
Occupation			
Outdoor workers	102	68.0	
Indoor workers	48	32.0	
Education Level			
Not schooled	4	2.7	
Primary	69	46.0	
Secondary	77	51.3	
Number of Years Living in area (years)			43.7 ± 13.2
≤ 15	7	4.7	
16-30	21	14.0	
31-45	45	30.0	
46-60	68	45.3	
≥ 61	9	6.0	

More than half of the patients were middle aged outdoor workers and most of the participants were educated beyond the primary level of education.

Table 2
BMI values of the CKDu patients

BMI (kg/m ²)	Classification	Total %(n)	Male % (n)	Female % (n)
<18.5	Underweight	34.7 (52)	36.4 (43)	28.1 (9)
18.5– 22.9	Normal	43.3 (65)	44.1 (52)	40.6 (13)
>23	Above ideal range	22.0 (33)	19.5 (23)	31.3 (10)

According to the BMI results (Table 2), 43.3% (n= 65) of the CKDu patients were in the healthy weight category. More than one third of the patients were in the underweight category. According to eGFR (ml/min/1.73m²), CKDu was graded in to 6 stages (Table 3). Mean eGFR was 37.56 (SD= 17.19).

Table 3
CKDu stages of the patients

CKDu Stage	eGFR range (ml/min/1.73m ²),	Number of patients % (n)
Stage 1	≥ 90	0.7 (1)
Stage 2	60-89	9.2 (13)
Stage 3a	45-59	17.0 (24)
Stage 3b	30-44	35.5 (50)
Stage 4	15-29	34.8 (49)
Stage 5	<15	2.8 (4)

Table 4
Prevalence of anemia and deficiency of Vitamin D, B₁₂ and Serum ferritin in CKDu patients

Variable	Mean and SD	Male % (n)	Female % (n)	<i>p</i> ¹
Hemoglobin (g/dl)	11.8 ± 1.7			
Anemic (Male:<13 g/dl, Female: <12 g/dl) ²		70.3 (83)	75.0 (24)	0.898
Serum ferritin (ng/ml)	124.2 ± 119.8			
Low Serum Ferritin (<100 ng/ml)		55.9 (66)	40.6 (13)	0.255
Normal (>100ng/ml)		44.1 (52)	59.4 (19)	
Vitamin D (ng/ml)	24.9 ± 7.9			
Deficiency (<20ng/mL)		22.9 (27)	68.8 (22)	0.004
Insufficiency (20-30ng/mL)		45.8 (54)	25 (8)	
Normal (> 30 ng/mL)		31.4 (37)	6.3 (2)	
Vitamin B ₁₂ (pg/mL)	408.7 ± 143.5			
Deficiency (<200 pg/mL)		4.23 (5)	0	0.298
Borderline (200-300 pg/mL)		7.0 (27)	15.6 (5)	
Normal (> 300 pg/mL)		72.9 (86)	84.4 (27)	
¹ Chi-square test; ² WHO cut off values for Anemia				

SD, Standard deviation

Table 4 shows the hemoglobin, Vitamin D, Vitamin B₁₂ and ferritin levels of the patients. Prevalence of vitamin D deficiency was significantly different between males (22.9%) and females (68.8%). There was no significant difference in the prevalence of anemia, low serum ferritin and vitamin B₁₂ deficiency between males and females.

Table 5
Logistic regression analysis for the risk factors associated
with Vitamin D deficiency

Characteristics	Sig.	OR (95% CI)
Gender		
Female		1.00 (ref)
Male	0.01	0.13 (0.03- 0.63)
Age		
≤ 55 years		1.00 (ref)
> 55 years	0.98	1.01 (0.44- 2.34)
Occupation Type		
Indoor		1.00 (ref)
Outdoor	0.29	0.36 (0.06-2.34)
Hours working outside/day		
Low		1.00 (ref)
High	0.26	2.48 (0.51- 12.14)
Area exposed to sun light		
Less area		1.00 (ref)
High area	0.78	1.16 (0.43- 3.12)
BMI		
Normal		1.00 (ref)
Under weight	0.24	1.65 (0.72- 3.77)
Obese/ Overweight	0.04	4.65 (1.05- 20.57)
<i>Samurdhi</i> allowance		
No		1.0 (ref)
Yes	0.155	1.71 (0.82- 3.60)
CKDu Stage		
Early Stage of CKDu (eGFR>45 ml/min/1.73m ²)		1.0 (ref)
*Significant level $P<0.05$		

Characteristics	Sig.	OR (95% CI)
Late Stage of CKDu (eGFR <45 ml/min/1.73m ²)	0.210	1.79 (0.72- 4.49)
*Significant level $P<0.05$		

Table 5 shows the logistic regression analysis for several risk factors associated with vitamin D deficiency. Gender was significantly associated with the vitamin D deficiency ($p<0.05$) Females were 7.69 times more likely to have vitamin D deficiency compared to males.

The most common area exposed to sunlight while working outdoor was, arms and legs (below the knee) (26.7%). Among the patients with vitamin D deficiency, about 27% ($n=20$) of the patients had not exposed any area of the body to sunlight even though they work outdoor. However, there was no association between the area exposed to sunlight and vitamin D deficiency ($P=0.775$). The odds of vitamin D deficiency among Samurdhi allowance receivers was 1.7 times higher than those who did not receive, but it was not statistically significant. There was no significant association between the duration of sun exposure and vitamin D deficiency

Table 6
Prevalence of Vitamin D Deficiency (VDD) in early and late stages of CKDu

	Vitamin D deficiency	Normal Vitamin D
Early Stage of CKDu (eGFR>45 ml/min/1.73m ²)	82% (32)	17.9% (7)
Late Stage of CKDu (eGFR <45 ml/min/1.73m ²)	71.2% (79)	28.8% (32)

Vitamin D deficiency is more common (82%) during the early stages of CKDu while less common during the late stage (Table 6). However, there was no statistically significant association between the stage of CKDu and prevalence of vitamin D deficiency ($p=0.210$).

Table 7

Comparison of BMI, eGFR and Laboratory data between CKDu patients with vitamin D deficiency and CKDu patients without vitamin D deficiency (independent sample t test results)

Variable	Total (n=150)	VDD (n=111)	Non- VDD (n=39)	P value
BMI (kg/m ²)	20.4 ± 3.7	20.3 ± 3.2	20.6 ± 4.7	0.772
Hemoglobin (g/dL)	11.8 ± 1.7	11.8 ± 1.6	11.9 ± 1.7	0.902
eGFR (ml/min/1.73m ²)	37.6± 17.2	39.7 ± 17.9	31.5 ± 13.5	0.479
Serum Creatinine (mg/dl)	2.2 ± 0.9	2.1 ± 0.8	2.7 ± 0.9	0.044*
Vitamin B ₁₂ (pg/ml)	408.6 ± 143.5	392.6 ± 135.6	454.4 ± 156.8	0.112
Serum Ferritin (ng/ml)	124.2 ± 119.8	132.5 ± 130.5	100.6 ± 79.1	0.024*
BMI, Body mass index: eGFR, estimated glomerular filtration rate: SD, standard deviation				

All the values are given as mean +/- Standard deviation

*Significant level $P < 0.05$

Serum creatinine values were significantly high in patients with vitamin D deficiency ($P < 0.044$) (Table 7).

Out of the total of 150 patients, 32 (20.8%) were on 1 alpha medication while 122 (79.2%) were not on vitamin supplementations (1 alpha cholecalciferol). About 68.8% of the patients on 1 alpha medication had vitamin D deficiency (Figure 1). According to two sample proportions test, the proportion of patients with Vitamin D deficiency between 1 alpha treated group and non-treated group shows no significant difference ($p=0.463$)

Table 8
Prevalence of vitamin D deficiency and odd ratio (OR) related to consumption of vitamin D rich food sources

Food Type	Category of intake	N	Prevalence of vitamin D deficiency (%)	OR (95% CI)
Fish	Satisfactory (>3 servings per week)	08	2.7(03)	1.00 (ref)
	Not satisfactory (<3 servings per week)	142	97.3(108)	0.20 (0.04-0.08)
Dairy products	Satisfactory (<1 serving per week)	75	51.3(57)	1.00 (ref)
	Not satisfactory (>1 serving per week)	75	48.6(54)	0.3(0.31-1.38)
Egg	Satisfactory (>3 servings per week)	71	50.5(56)	1.00 (ref)
	Not satisfactory (<3 servings per week)	79	49.5(55)	0.4(0.67-2.95)
Meat	Satisfactory (>3 servings per week)	11	6.3(07)	1.00 (ref)
	Not satisfactory (<3 servings per week)	139	93.7(104)	0.6(0.16-2.13)

According to Table 8, the odds of having Vitamin D deficiency is 5 times higher for patients on non-satisfactory fish consumption compared to the rest. The number of servings of food needed for each day was compared with the Food based dietary guidelines for Sri Lanka.

Discussion

This cross-sectional study was designed to describe the prevalence of vitamin D, iron and vitamin B₁₂ status in CKDu patients and to determine associations between vitamin D status and socio demographic factors, nutritional status and dietary intake of vitamin D in CKDu at Wilgamuwa area, in Matale district.

According to our findings there was a higher prevalence of vitamin D deficiency, iron deficiency anemia and underweight among patients with CKDu. Interestingly, majority of patients in this cross-sectional study had satisfactory BMI and adequate vitamin B₁₂ levels on evaluation. CKDu is known to be endemic among rural farming communities of tropical countries. Hence, nutritional deficiencies are expected due to poor dietary habits as well as dietary and lifestyle modifications due to the disease.

Insufficient Vitamin D has been linked with numerous conditions of the body; these are cancer, heart disease, type 2 diabetes, stress fractures, autoimmune disease, influenza, and depression [18, 19]. Even

more, vitamin D insufficiency is associated with faster progression and mineral bone disease in CKD [11].

According to the results of the present study, vitamin D was significantly lower in women than in men. Traditionally, males more frequently involve in hard work at outdoor. Moreover, culturally they have more liberty to expose their body to sunlight during work. However, there was no significant association between the body areas of sun exposure during work with prevalence of vitamin D deficiency. Even though the majority of CKDu patients were farmers who worked outdoors, vitamin D deficiency seemed to be very common. The possible reasons could be the restricted availability of ultra violet light in the correct range to facilitate skin vitamin D synthesis, or the shaded sunshine due to overcasting of sky, or shadows created by buildings and trees and type of dresses which cover most of the body surface [20]. Melanin pigment in the skin also does not allow the sunlight to penetrate to the deeper layers of the skin [21]. Consumption of vitamin D rich foods were low among the population and frequent consumption of fish was negatively correlated with vitamin D deficiency. Though there were associations between vitamin D deficiency and low dairy products, egg and meat consumption, it was not statistically significant. Poor intake of foods with animal origin seems to be due to multiple reasons, such as cost or religious and cultural believes. Nevertheless, there was a higher prevalence of Vitamin D insufficiency among low-income group (on *samurdhi allowance*/ receipt of social welfare benefits) suggesting financial barriers in access to proper foods with high nutrients.

Along with previous evidence, our findings revealed an inverse relationship between vitamin D status and BMI. This may be due to poor penetration of UV light leading to decreased bioavailability of vitamin D at critical layers of subcutaneous adipose tissue [22]. In previous studies, a significant inverse relationship between vitamin D status and BMI in women has been described, specifically in women born in Turkey and Pakistan. In parallel, a considerably higher proportion of women (20%) than men (11%) were found as obese in a Sri Lankan study [23].

Vitamin D deficiency has been implicated in faster decline of eGFR in CKD and IgA nephropathy [24]. According to the results of an Asian study, vitamin D deficiency/insufficiency is an extremely frequent condition in patients with CKD, especially those with an estimated GFR of less than 15 mL/min/1.73 m² [25]. However, according to our results Vitamin D Deficiency was more common (82%) in early stages of CKDu than the late stage. According to current results, 32 (20.8%) patients were on Vitamin D supplementations (one alpha cholecalciferol), among those 68.8% of the patients had vitamin D deficiency. In vitamin D metabolism one alpha chole calciferol produced after the conversion of 25 (OH) D and not measured in the vitamin D assay. National Kidney Foundation- Kidney disease outcomes Quality Initiative (NKF-KDOQI) guidelines currently recommend Vitamin D supplementation in patients with stage 3to 4 CKD who presents Vitamin D deficiency.

Anemia, one of the common complications of CKD, is associated with poor morbidity and mortality [26]. According to previous studies, the prevalence of Anemia in CKD has been reported higher among the patients with lower eGFR and among the females more than males [27]. A similar trend was observed for serum Ferritin levels, a measure of body iron status. These finding goes parallel with the findings of the

present study. Also, the higher prevalence of anemia in current study population was similar to the previous studies on CKDu in Sri Lanka. Fernando W. et al revealed a significant association of anemia with disease severity among CKDu patients and the study reported 72.3% prevalence of anemia in non-dialysis CKDu [26]. Present study shows more than 70% of the males and about 75% of the females having lower hemoglobin levels than WHO cut offs. Interestingly Folic acid and B₁₂ deficiency was not common among patients with CKDu in Wilgamuwa, Sri Lanka. According to a previous study, there were no patients with vitamin B₁₂ deficiency [26].

The results of the present study identified high prevalence of vitamin D deficiency, which was associated with dietary intakes, income level and gender. Data also revealed the negative association between vitamin D levels and anthropometric measures of nutrition such as BMI. Furthermore, we report a high prevalence of anemia, iron deficiency in addition a very low prevalence of vitamin B₁₂ deficiency. However, the current study results support further studies to identify specific nutritional deficiencies in different communities affected by unique medical problems like CKDu.

Conclusion

Isolated Vitamin D deficiency was the most prevalent nutritional deficiency rather than iron deficiency and B12 deficiency. Correction of these deficiencies may have a favorable effect on CKDu outcome.

Declarations

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest

AUTHORS' CONTRIBUTIONS

MAAN and RG drafted the manuscript under the supervision of KDRRS, HTKA, AVN and NN. All the authors read and approved the final manuscript

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AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request

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Figures

Figure 1

Vitamin D status with the 1 alpha cholecalciferol treatment