Early predictors of cardiac dysfunction in Egyptian children with chronic kidney disease

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ABSTRACT

Background	:	Cardiovascular morbidity (CVM) is the main etiology of mortality in children and adolescents with chronic kidney disease (CKD). CKD associated cardiovascular mortality is more common in children with diastolic cardiac dysfunction which was considered as an early indicator for death, while increased left ventricular mass (LVM) is a strong independent risk factor for these patients. Vitamin D deficiency was previously studied as one of the risk factors for CVM.
Aim	:	The aim of the work was to investigate the relationship between biomarkers of mineral bone disorder including serum 25(OH) Vitamin D3 (25-OH D3), phosphorus and calcium × phosphorus (Ca×Po4) product with diastolic cardiac function and LVM in children and adolescents with CKD.
Subjects and Methods	:	This was a cross-sectional observational study. Participants were classified into two groups: Group I including 86 pediatric patients with CKD (stages 4 or 5) and Group II including 40 healthy controls. Group I was subdivided into IA included children with diastolic dysfunction and IB included cases without diastolic dysfunction. 25-OH D3 level was measured by enhanced chemiluminescence method and intact parathyroid hormone (iPTH) by electrochemiluminescence method. Parameters for diastolic function and LVM were assessed by Doppler echocardiography, tissue Doppler imaging, and M-mode echocardiography.
Results	:	25-OH D3 level was significantly lower in Group I when compared to Group II. Diastolic dysfunction was present in 48.8% of the studied patients and was significantly associated with increased serum phosphorus and calcium-phosphorus product but not with decreased level of 25-OH D3. There was a significant positive correlation between LVM and iPTH.
Conclusions	:	Hyperphosphatemia and high Ca×Po4 product were considered of prognostic value as they predict early diastolic dysfunction and increased LVM in children with CKD.
Keywords	:	Cardiac dysfunction, children, chronic kidney disease, predictors

INTRODUCTION

Early prediction and management of cardiac disease as a cause of morbidity and mortality has become mandatory in management of children and adolescents with chronic kidney disease (CKD).[1-3]

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However, few publications are accessible as regards early recognition of cardiac disease in children and adolescents with CKD.[4-6]

CKD-associated cardiovascular morbidity (CVM) was more commonly reported in the form of diastolic cardiac dysfunction.[7-9]

Diastolic cardiac dysfunction (diastolic heart failure) was defined as clinicopathological phenomenon characterized by clinical manifestations of cardiac failure with a preserved ejection fraction (EF), and abnormal diastolic cardiac function by echocardiographic examination. It has been previously published that diastolic cardiac function was disturbed and left ventricular mass (LVM) was increased early in adult patients with CKD.[10,11]

The high rate of CVM in children with CKD may be attributed to non traditional risk factors which are related to complications of CKD.[9]

Vitamin D status has been previously reported as a non traditional risk factor for CVM due to the commonality of its deficiency in children with CKD.[12]

Vitamin D is a steroid hormone responsible for maintenance of calcium, phosphorus, and parathyroid hormone homeostasis.[13-15] Vitamin D acts also as cell-differentiating and antiproliferative hormone in a variety of systems including the urinary, cardiovascular, and immune systems.[15-17] Insufficiency or deficiency of Vitamin D is very common in the Arabian countries such as Egypt, with a prevalence of 50%–90% in the general pediatric population with a higher incidence in critically ill children in emergency hospitals.[18]

Objectives

The aim of this work was to evaluate 25(OH) Vitamin D3 (25-OH D3), serum phosphorus, and calcium × phosphorus (Ca×Po4) product as biochemical parameters of mineral bone disorder (MBD) and their relation with diastolic cardiac function and LVM, which were considered as early predictors cardiovascular morbidity (CVM) in children and adolescents with CKD patients.

SUBJECTS AND METHODS

Sample size and sampling

The sample size was calculated taking in consideration a significance level of 95%, power 80%, and effect size 30% resulting in 89 children being selected. A sample frame which consists of the files of all unit attendants who fulfill the selection criteria was constructed from which the target population were chosen randomly, where only 86 children participated in our study (3 patients refused to participate).

This study was an observational cross-sectional study which was conducted on 86 children and adolescents

with CKD (Stage 4 or 5) and their ages ranged from 10 to 18 years with a mean value of 13.7 ± 3.9 years. They were 48 (55.8%) males and 38 (44.2%) females who were attending the Pediatric Nephrology Unit of Pediatric Department of Tanta University Hospital (TUH) in the period from January 2017 to January 2018. With forty age- and sex-matched healthy volunteers (controls) as Group II, Group I was further divided as Group IA consisting of cases with diastolic dysfunction and Group IB comprising cases without diastolic dysfunction.

The study was conducted after approval from the Ethical Committee of the Faculty of Medicine, Tanta University and informed written or oral parental consents.

Protocol of management of patients

In addition to specific treatment of the underlying cause of CKD, for example, steroid and immunosuppressive drugs, all patients were receiving supportive therapy in the form of subcutaneous erythropoietin at a dose of 50 IU/kg/session, IV iron dextran 100 mg/kg/week, oral folic acid 1 mg/day, oral calcium 1000 mg/day, oral Vitamin D (one alpha) at a dose of 0.01–0.05 μg/kg/day, and oral antihypertensive medications for hypertensive patients. The goal of pharmacologic treatment of hypertension in children was to reduce blood pressure to below the 95th percentile. Therefore, we used the term "controlled" to indicate blood pressure below the 95th percentile in response to therapy.[19]

Inclusion criteria

All children with CKD and treated by conservative (predialysis) treatment were included in the study.

Our studied patients were subclassified according to serum levels of 25-OH D3 based on the updated version of Kidney Disease Outcomes Quality Initiative guidelines (2003) as normal level (>30 ng/mL), insufficient level (15–30 ng/mL), and deficient level (<15 ng/mL).

Exclusion criteria

Patients with primary cardiac disease (e.g., congenital heart disease, congenital anomalies of coronaries or rheumatic heart disease, and cardiomyopathy), patients with severe anemia (hemoglobin <6.0 g/dL), patients taking erythropoiesis-stimulating agents, patients with known cancer and/or heart failure (EF <40%), patients whose parents were smokers or children on Vitamin D therapy, trauma <6-month duration which may influence collagen metabolism, or presence of arteriovenous fistula for dialysis access.

All patients were subjected to:
1. Full history taking including demographic data; age, sex, child's previous growth and development, history about primary cause of CKD (frequently relapsing nephrotic syndrome, steroid-dependent nephrotic syndrome, steroid-resistant nephrotic

syndrome, lupus nephritis [LN], congenital anomalies of kiney and urinary tract (CAKUT), oxalosis, chronic glomerulonephritis, chronic interstitial nephritis, vasculitis, chronic pyelonephritis, or others) and whether there were referred by a pediatric nephrologist or general pediatrician

2. Thorough clinical examination including:
   - Anthropometric measurements for assessment of nutritional and developmental status which included:
     - Weight – Which was recorded with minimal clothing using an electronic weight scale in kilograms
     - Height – Measuring the distance from the vertex to the base of the heel in centimeters using a stadiometer in standing position
     - Body mass index (BMI) percentile – (<5%, 5%–85%, and ≥85%). Height and body mass index (BMI; kg/m^2 of height) percentiles by age and sex were calculated from tables provided by the Centers for Disease Control and Prevention

   BMI was calculated by the following formula:
   BMI = Weight (kg)/(height [m])[2,20]
     - Mid-arm circumference – Measurement of the circumference of the left upper arm at the midpoint between the tip of the shoulder (olecranon process) and the tip of the elbow (the acromion process) in centimeters
     - Vital signs, especially arterial blood pressure (ABP) which was measured by auscultatory method using a mercury sphygmomanometer, in the semi-sitting position after 10 min of rest, in the nonfistula arm using an appropriate-sized cuff and was taken as the mean value of three successive readings in three different days

   Hypertension was defined as systolic or diastolic blood pressure above the 95th percentile for age, height, and sex or use of antihypertensive medication.[19,21]

3. Routine laboratory investigations including:
   - Complete blood count (CBC) by an automated analyzer
   - Anemia was defined as mean hemoglobin value <11 g/dL[22]
   - Blood urea, blood urea nitrogen, and serum creatinine
   - Serum albumin and serum electrolytes (ionized calcium, potassium, and phosphorus)
   - Urea reduction ratio and single-pool Kt/V values were calculated and used as measures of dialysis adequacy
   - Serum 25-OH D3 levels as per the instruction provided with the kit of LIAISON® DiaSorin, Italy, by enhanced chemiluminescence method[14]
   - Intact parathyroid hormone (iPTH) by electrochemiluminescence method.[14]

Specimen collection and handling

5 millilitres of venous blood was collected using sterile needles through gentle venipuncture under complete aseptic technique. About 2 ml was put on 20 uL EDTA solution as anticoagulant for CBC including differential white blood cell count which was done on Leishman-stained peripheral blood smear with evaluation using ERMA PCE-210 N cell counter from Erma Inc., Japan.

Doppler echocardiography, tissue Doppler imaging, and M-mode echocardiography

They were performed in all patients and controls for the evaluation of diastolic function and LVM.

Diastolic dysfunction was observed in cases with CKD, according to the American Society of Echocardiography and the European Association of Echocardiography guidelines for the assessment of diastolic function by echocardiography.[9]

Echocardiography was performed in Pediatric Nephrology and Cardiology Units of the Pediatric Department of TUH using GE Vivid 7 (GE Medical System, Horten, Norway, with a 3.5-MHz multifrequency transducer). The echocardiography imaging included the two-dimensional (2D) study including E/A ratio which will be based on the average of the six regional values.

Echocardiographic imaging was carried out in the left lateral decubitus position. Besides the standard parasternal (long and short axis) and apical (two- and four-chamber) images, additional apical (Four-chamber) images were obtained that included the interventricular septum, the apex, and the right ventricular (RV)-free wall up to tricuspid annulus. Images were digitally stored in the cine-loop format for offline analysis. Longitudinal strain was assessed offline, on the four-chamber cine loop that included the RV-free wall, using speckle-tracking analysis.

Statistical analysis

The data were organized, tabulated, and statistically analyzed using the Statistical Package for the Social Sciences (SPSS version 17; IBM Corp., Armonk, NY, USA). Data were presented as the mean ± standard deviation. Mean differences between patients and controls were tested using Student's *t*-test. The Bonferroni correction/adjustment procedure was used for *post hoc* analysis to avoid "significance" due to chance only in multiple comparisons with echocardiographic parameters. The correlation between two variables was calculated using Pearson's correlation coefficient (*r*) analysis of variance (F). *P* < 0.05 was considered to be statistically significant. Multiple linear regression

analysis was performed to identify predictors of diastolic dysfunction.[23]

RESULTS

The demographic, clinical, laboratory, and imaging parameters of the studied patients were summarized in Table 1. The mean age of our CKD patients in Group I was 13.7 ± 3.9 years.

Fifty-three (61.6%) studied patients were hypertensive (mean of ABP over 3 months >95th percentile or on antihypertensive medication).

The most common causes of CKD in our study were difficult to treat nephrotic syndrome and LN. Only 12 (13.9%) had chronic glomerulonephritis as a cause of CKD.

Patient characteristics are summarized in Table 1 and no significant difference was noted between the study group and controls ($P > 0.05$).

Mean Vitamin D level was significantly lower in Group I (14.6 ± 6.4 ng/mL) when compared to the control group (16.4 ± 4.7 ng/mL) ($P < 0.001$), and mean iPTH in Group I was 2.3 ± 0.7 pg/mL. Serum protein (7.1 ± 0.45 mg/dL) and serum albumin (4.2 ± 0.61 mg/dL) levels were significantly higher in the controls when compared to the cases ($P < 0.05$).

58% of the cases and 50% of the controls had Vitamin D deficiency. It is to be noted that Vitamin D level was <30 ng/mL in all cases as well as controls. In 42 (48.8%) of 86 studied children, diastolic dysfunction was present. None of the healthy controls had diastolic dysfunction irrespective of Vitamin D level. Vitamin D deficiency (<15 ng/mL) was found in higher proportion in Group IA (28, 66.7%) patients as compared to Group IB (22, 50%) patients. However, this difference was not found to be statistically significant ($P = 0.27$) [Table 2]. Comparison of different demographic and biochemical parameters among the studied patients in Group I was shown in Table 1.

Serum phosphate level was found to be a significant risk factor for the development of diastolic dysfunction ($P < 0.003$) [Table 1]. Furthermore, the calcium-phosphorus product (>55 mg^2/dL^2) was significantly higher in patients with diastolic dysfunction when compared to patients without diastolic dysfunction ($P < 0.05$).

Cases in Group I had a higher mean LVM index (LVMI) than controls (70.3 vs. 23.8, respectively) ($P < 0.001$).

Table 1: Demographic, clinical, and diagnostic data of the studied children with chronic kidney disease

Parameter	Group IA (*n*=42)	Group IB (*n*=44)	*P*
Age (years)			
Mean±SD	13.7±3.9	13.5±3.9	0.46
1ry cause of CKD			
Lupus nephritis	30 (34.9)	13 (30.2)	0.09
FRNS/SDNS/SRNS	44 (51.2)	21 (50)	
chronic glomerulonephritis	12 (13.9)	8 (19.8)	
Sex distribution			
Males	48 (55.8)	24 (57.1)	0.29
Females	38 (44.2)	18 (42.9)	
Clinical signs			
Anemia (Hb<11 gm %)	25 (37.9)	8 (50)	0.0002*
Hypertension: Mean of arterial blood pressure over 3 months>95th percentile, or on antihypertensive medication	53 (61.6)	32 (76.2)	<0.001*
Duration of onset of CKD (months)			
0–6	8 (19)	8 (18.2)	>0.05
6–11	8 (19)	7 (15.9)	
12–36	8 (19)	16 (36.4)	
>36	18 (43.9)	13 (29.5)	
Laboratory investigations (mean±SD)			
Hb (gm/dl)	7.0±1.6	7.8±1.9	>0.05
Serum uric acid (mg/dL)	8.0±2.5	7.6±2.9	>0.05
Serum calcium (mg/dL)	7.7±1.4	8.1±1.6	>0.05
Serum phosphorus (mg/dl)	7.3±2.4	5.5±1.4	0.003*
Serum albumin (mg/dL)	3.6±0.7	3.8±0.6	>0.05
Serum creatinine (mg/dL)	9.7±4.8	8.5±3.7	>0.05
GFR (mL/min/m^2)	10.6±5.7	14.1±24.3	>0.05
Serum iPTH level (pg/ml)	656.5±222.3	453.1±308	>0.05
Serum Vitamin D (ng/mL)	13.58±4.94	15.58±7.62	>0.05
Diagnostic imaging techniques			
LVM (gm)	247.6±114.6	244.8±104.7	0.05
LVMI (gm/m^2)	69.7±28.4	70.8±31.8	>0.05

*Significant. FRNS=Frequently relapsing nephritic syndrome; SDNS=Steroid-dependent nephritic syndrome; SRNS=Steroid-resistant nephrotic syndrome; GFR=Glomerular filtration rate; PTH=parathyroid hormone; LVM=Left ventricular mass; LVMI=Left ventricular mass index; SD=Standard deviation; Hb=Hemoglobin; iPTH=Intact parathyroid hormone

Table 2: A multivariate logistic regression analysis of factors which may affect diastolic function in the studied Group 1A

Characteristic	Adjusted OR	95% Confidence limit	P
Age	0.98	0.93–1.03	0.4
Sex			
Males	0.98	0.7–1.8	0.4
Females	1.21	0.81–1.83	0.36
Duration of onset of CKD (months)			
0–6	1.6	0.79–3.29	0.19
6–11	1.18	0.59–2.37	0.64
12–36	0.73	0.4–1.38	0.34
>36	1.61	0.95–3.46	0.07
Primary cause of CKD			
Lupus nephritis	0.8	0.5–1.3	0.3
FRNS/SDNS/SRNS	0.79	0.49–1.27	0.33
Chronic glomerulonephritis	1.22	0.65–1.27	0.54
BMI (percentage of normal)			
<5 (underweight)	1.23	0.67–2.24	0.51
5–85 (normal reference)	104	0.68–1.9	0.59
85–95 (overweight)	114	0.7–1.85	0.6
Serum 25 (OH) Vitamin D3			
<15 ng/ml (*n*=28, 66.7%)	2	0.8–4.8	0.27
>15 ng/ml (*n*=14, 33.3%)			
Serum calcium (mg/dl)	2.4	1.5–8.5	0.007
Ca×Po4 product (>55 mg^2/dL^2)	2.2	1.1–8.3	0.03*
Serum phosphorus (mg/dl)	2.38	1.7–8.3	0.067
Hypertension	2.53	1.57–4.1	0.001*
Anemia	1.6	1.05–2.43	0.029*

*Significant. BMI=Body mass index; Hypertensive=Mean of arterial blood pressure values over 3 months>95th percentile or on antihypertensive medication; FRNS=Frequently relapsing nephritic syndrome; SDNS=Steroid-dependent nephritic syndrome; SRNS=Steroid-resistant nephrotic syndrome; SD=Standard deviation; BMI=Body mass index; CKD=Chronic kidney disease; OR=Odds ratio

Table 2 summarizes a multivariate logistic regression analysis of factors which may affect diastolic function in the studied Group 1A. They were Ca×Po4 product (*P* = 0.03), hypertension (*P* = 0.001), and anemia (*P* = 0.29).

The LVMI did not significantly correlate with Vitamin D level (*r* = 0.02, *P* > 0.05) by correlation coefficient test (*r*). However, there was statistically significant positive correlation between LVMI and iPTH in our studied patient group (*r* = 0.3, *P* < 0.05) [Table 3].

DISCUSSION

Vitamin D deficiency is known to be associated with CKD in adults, but our study has shown this association in children and adolescents with CKD. Children with CKD were reported to have severe Vitamin D deficiency which may be attributed to the reduced ability of the kidney to convert 25-(OH) Vitamin D into the active form 1, 25 dihydroxyvitamin D.

Recent evidence suggests that the progression of CKD and the associated cardiovascular diseases may be linked to Vitamin D insufficiency or deficiency.[24,25]

Moreover, children with CKD who exhibited marked decrease in glomerular filtration rate also had secondary hyperparathyroidism with resultant hypocalcemia, hyperphosphatemia, and increased Ca×Po4 product. Levin *et al.* previously studied the left ventricular hypertrophy in adult patients with CKD.[25]

Unlike previous studies on adult population, our study the advantage of the absence of the impact of age-related morbidities such as diabetes mellitus and essential or primary hypertension on biochemical or echocardiographic parameters.

In our study, the Vitamin D level was significantly lower in cases as compared to controls. This is similar to that reported by Kari *et al.*[26]

In the current study, there was no statistically significant association between Vitamin D deficiency and diastolic dysfunction in CKD patients (*P* = 0.3), which was in accordance to the report by Pandit *et al.*[27]

Another study also reported that lower Vitamin D levels than normal were not associated with any of the biochemical, conduction (electrocardiographic), or echocardiographic outcomes in individuals who were free of CVD at baseline conditions.[28]

Many authors have reported that blood pressure status is an independent variable for predicting cardiac disease prevalence in pediatric patients with CKD.[29,30] Hypertension and anemia are considered as an indication for annual screening for cardiac diseases in children with CKD, as they are common risk factors for cardiovascular diseases in these children.[31-33]

Chinali *et al.* who studied 132 children with stage 2-4 CKD (aged 3 to 18 years) by 2D echocardiography a reported higher prevalence of systolic dysfunction in their cases than in their controls (25% had lower FS) in the presence of hypertension versus 5% of controls and concluded that systolic dysfunction was associated with anemia.[34]

The North American Pediatric Renal Transplant Cooperative Study revealed the presence of uncontrolled hypertension in 48% of children with early CKD; this increased to 50%–75% in children with end-stage renal disease (ESRD).[35]

Our results regarding correlations between LVMI and the studied biochemical parameters were not in agreement with Patange *et al.*[36] who reported that in their study of 34 pediatric patients with CKD, LVMI correlated with serum 25-OH D3 (*r* = −0.5; *P* < 0.05) and added that serum iPTH levels correlated with diastolic dysfunction of their studied children as evidenced by their echocardiographic data, E/E' ratio (*r* = 0.6; *P* < 0.05) and E' (*r* = −0.6; *P* < 0.05).[36] Hence, multiple previous studies were concerned about

Table 3: Correlations between left ventricular mass index and both serum 25(OH) Vitamin D3 and intact parathyroid hormone in the studied patient group

Parameter	*r*	*P*
25(OH) Vitamin D3	−0.02	>0.05
iPTH	0.3	<0.05

iPTH=Intact parathyroid hormone

the association between serum Vitamin D and cardiac diastolic function.

In the current study, the mean LVMI was significantly higher in cases (70.3 ± 29.8 g/m^2) than in controls (23.8 ± 9.1 g/m^2). This was consistent with other studies,[37-39] which showed increased prevalence of left ventricular hypertrophy in CKD patients. Patange *et al.*[36] in their study of 34 children with CKD showed that LVMI inversely correlated with Vitamin D and it was also statistically significant ($r = -0.5$; $P < 0.05$), whereas in our study, we did not find any significant correlation between them ($r = -0.02$, $P > 0.05$).

Another study showed no clinically significant improvement on administration of Vitamin D in patients with CKD.[40]

We observed a mean level of serum phosphate of 7.3 ± 2.4 mg/dL and 5.5 ± 1.4 mg/dL in cases with and without diastolic dysfunction, respectively. Hence, hyperphosphatemia was found in our work to be a significant risk factor for development of diastolic dysfunction in cases with CKD ($P = 0.003$).

Mahdi *et al.*[41] reported that hyperphosphatemia that promotes loss of mineral from bone can also promote metastatic or vascular calcification.

Galetta *et al.* also reported a statistically significant positive correlation between hyperphosphatemia and increased CVD in their uremic patients on maintenance hemodialysis.[42]

Block *et al.*,[43] Tentori *et al.*,[44] and Gutiérrez *et al.*[45] had reported similar data in their publications. Hence, hyperphosphatemia was considered as a predictable marker of ESRD, especially in patients neglecting dietary phosphate restriction and/or supplemental phosphate binders such as sevelamer.

Increased serum phosphate level has unfavorable outcomes including the development and progression of secondary hyperparathyroidism and a predisposition to extravascular metastatic calcification when Ca×Po4 product becomes elevated. Both conditions may predispose to CVM and mortality in patients with CKD and ESRD.[46]

In this study, there was a significant association between calcium-phosphorus product (>55 mg2/dL^2) and diastolic

dysfunction ($P = 0.03$). This is in accordance with a study reported by Regmi *et al.*[47] Hyperphosphatemia was considered as the main component of CKD-mineral bone disease known to have serious hazardous impact on left ventricular function.

Impaired mineral bone metabolism and increased Ca×Po4 product had been assumed to be main causes of LV systolic and diastolic dysfunction in dialysis patients.[48]

El-Gamasy reported that CKD-MBD in their study on children with ESRD under regular HD was typically of high bone turnover type as serum iPTH and phosphate levels were markedly high and attributed these to low dose of Vitamin D supplementation, inadequate oral calcium intake, phosphate binders, and inadequate compliance.[49]

Mahdi *et al.*[41] also emphasized on maintaining calcium-phosphorous balance for healthy life as its imbalance can lead to irreversible damage to our body system.

In our study, using correlation analysis with LVMI as an outcome of interest, iPTH was found to be an important predictor showing linear relationship, which was statistically significant ($r = 0.47$, $P < 0.05$). Similar results were obtained by Ha *et al.*[50] in their study on 60 predialysis CKD patients. Furthermore, Al-Hilali *et al.*[51] found positive correlation between iPTH and LVMI in their study on their patients on hemodialysis. This may be due to the potential role of iPTH on inter myocyte fibrosis, namely nonreparative interstitial fibrosis with collagen fiber deposition, commonly found in patients with ESRD as reported by Amann *et al.*[52] in their study.

CONCLUSIONS

Vitamin D deficiency is highly prevalent in children with CKD patients as well as in healthy pediatric population.

CKD patients have lower mean Vitamin D levels as compared to healthy age- and sex-matched controls. The healthy controls, despite being Vitamin D deficient, did not have diastolic dysfunction on echocardiography. Vitamin D deficiency was not significantly associated with diastolic dysfunction or LVMI in pediatric CKD patients. However, hyperphosphatemia and calcium-phosphorous product were reported to be better predictors for diastolic dysfunction than other parameters of bone mineral density, and hence, they are considered as early predictors for cardiovascular mortality in predialysis CKD pediatric patients. Secondary hyperparathyroidism may be a bad prognostic marker of cardiovascular disease as it correlates with left ventricular hypertrophy in children with CKD.

Recommendations

Further large-scale studies are needed to determine whether there is a true association between Vitamin D levels and diastolic dysfunction.

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Conflicts of interest

There are no conflicts of interest.

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