Role of High PTH in Developing Cardiac Diastolic Dysfunction in Pre-dialysis & MHD Patients

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ABSTRACT:
Background: End-stage kidney disease (ESKD) poses a significant global health challenge. Approximately 70% of ESKD patients undergo hemodialysis (HD) or peritoneal dialysis (PD), and cardiovascular disease (CVD) is their leading cause of death, with a 9% annual mortality rate. Cardiac issues such as left ventricular hypertrophy (LVH) and dysfunction are prevalent in these patients, often worsening with dialysis. Secondary hyperparathyroidism (SHPT) due to impaired kidney function contributes to vascular calcifications, affecting cardiovascular health. ***Aim of the study:*** This study aims to elucidate the role of high PTH in developing cardiac diastolic dysfunction in both pre-dialysis and hemodialysis. ***Methods:*** The study conducted at the Department of Nephrology in BSMMU, Dhaka, Bangladesh, observed 80 CKD patients on hemodialysis over a year (from November 2022 to September 2023). Participants met specific criteria and provided informed consent. Data collection involved medical and socioeconomic history, physical examinations, anthropometric measurements, and blood tests. Tests included hematological, biochemical, and hormonal analyses, with serum iPTH measured by chemiluminescent assay. Echocardiograms assessed cardiac function and morphology. Inclusion criteria involved age (18-65), CKD stage 4 or 5, and > six months on hemodialysis, while exclusion criteria included certain cardiac, renal, and systemic conditions. ***Result:*** The study included 80 participants, primarily male (63.7%), with an average age of 43.1±12.9 years. Elevated iPTH levels were strongly linked to higher serum phosphate ($p=0.026$), Ca × PO4 product ($p=0.010$), and LVMI ($p=0.001$), as well as increased LA diameter ($p<0.001$). Multivariate analysis identified elevated iPTH as a significant predictor of diastolic dysfunction ($p=0.002$, OR 1.01). High iPTH levels correlated with worsening diastolic dysfunction and higher serum phosphate levels. ***Conclusion:*** Parathyroid hormone (PTH) levels contribute to cardiac diastolic dysfunction in pre-dialysis and maintenance hemodialysis patients. High PTH is linked to increased serum phosphate, calcium-phosphate product, and left atrial diameter, emphasizing the need to monitor PTH levels to prevent cardiovascular complications in chronic kidney disease.

INTRODUCTION

End-stage kidney disease (ESKD) represents a growing global health and healthcare challenge. In the United States, the occurrence of ESRD was 390.2 cases per million population in 2018, with a prevalence rate of 242 cases per million [1]. Approximately 759 out of every million people receive treatment for ESRD [2]. About 70.7% of patients with ESRD undergo treatment with either hemodialysis (HD) or peritoneal dialysis (PD) [1]. Individuals with end-stage renal disease (ESRD) experience a significantly elevated mortality rate [3]. Cardiovascular diseases constitute the primary cause of mortality among dialysis patients. The annual mortality rate from cardiovascular disease (CVD) in this population is 9% [4]. Additionally, cardiac issues such as left ventricular hypertrophy (LVH) and left ventricular (LV) dysfunction are highly prevalent among these patients. These

conditions frequently worsen during dialysis therapy. Studies indicate that over 70% of dialysis patients exhibit LVH, LV dilation, or reduced fractional shortening at the start of dialysis treatment, and LVH has been observed in more than 50% of individuals with chronic kidney disease before they initiate dialysis [5]. While coronary artery disease and valvular disease are commonly attributed as major causes of these abnormalities, many dialysis patients with cardiac issues do not present with these conditions. Numerous studies suggest that cardiac abnormalities in these patients may instead be linked to hypertension, volume overload, anemia, hypoalbuminemia, or various uremic factors. Among these factors, the role of parathyroid hormone (PTH) has been highlighted in the development of several cardiovascular abnormalities associated with ESRD [6]. As kidney function declines, the kidneys lose their ability to efficiently excrete phosphate, leading to hypocalcemia. This drop in calcium levels stimulates the parathyroid glands to produce and release increased amounts of PTH, a process known as secondary hyperparathyroidism (SHPT) [7,8]. SHPT plays a significant role in the development of vascular and valvular calcifications, which are associated with various cardiovascular complications. Arterial calcification can affect both the intima (inner layer) and media (middle layer) of blood vessel walls, contributing to increased calcium deposition in atherosclerotic plaques and arterial stiffness. These changes are linked to the development of conditions such as ischemic heart disease and concentric LVH [9]. Elevated phosphate levels contribute to arterial calcification and are associated with increased left ventricular mass index (LVMi), increasing the risk of sudden cardiac death in dialysis patients. [10,11,12]. These vascular and structural cardiac changes often lead to diastolic dysfunction (DD), characterized by impaired ventricular relaxation and elevated atrial pressure [13]. DD is a common but under-recognized issue in CKD and dialysis populations, frequently linked to myocardial fibrosis, vascular calcification, and left ventricular hypertrophy. Parathyroid hormone (PTH) may influence these changes through its effects on fibrosis and calcium handling [14,15]. This study aimed to assess the association between high PTH levels and diastolic dysfunction in pre-dialysis and maintenance hemodialysis patients.

METHODOLOGY & MATERIALS

This cross-sectional observational study was conducted in the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The study duration was one year, from November 2022 to September 2023. Purposively, 80 patients with CKD Stages 4 and 5 and on maintenance hemodialysis were included as per the selection (inclusion & exclusion) criteria. Before collecting data, informed consent was taken from every participant, and ethical approval was obtained from the institution's ethics committee.

Inclusion criteria:

- Age: 18 to 65 years.
- All predialysis CKD (stage 4, 5) patients.
- All patients on maintenance hemodialysis for >6 months.
- S. iPTH > 2 times the upper normal limit.

Exclusion criteria:

- All patients with primary cardiac diseases, such as evidence of congenital heart disease or rheumatic heart disease and decompensated cardiac disease (DCM/ICM).
- Renal allograft recipients.
- Severe anemia
- Advanced COPD patients
- Malignancy
- Advanced liver disease.

After these exclusions, the remaining 80 subjects were divided into two groups based on plasma PTH level. Patients with Predialysis were classified in group A (n=40), while those with MHD Patients in group B (n=40). All patients agreed to participate in this protocol and signed an informed consent document.

Data collection:
Upon enrollment, comprehensive medical and socioeconomic histories were documented using a structured data sheet. A thorough physical examination was conducted, with all findings recorded. Anthropometric measurements, including height and weight, were taken, and BMI was calculated based on these measurements.

Data analysis:
All statistical analysis was performed using Windows-based computer software with Statistical Packages for Social Sciences (SPSS-27.0). Quantitative data were expressed as mean and standard deviation, and qualitative data as frequency distribution and percentage. The association between parametric data by Unpaired t-test, one-way ANOVA test, and nonparametric data was analyzed using the chi-square test. Multiple logistics regression analysis/ Multivariate regression analysis was done to see the effect of Serum iPTH on cardiac structural and functional abnormality. Pearson's correlation coefficient test will be used to find out the correlation. For all statistical tests, a p-value of <0.05 will be considered statistically significant at a 95% confidence interval (CI).

RESULT
Table 1 presented demographic data of 80 patients. The mean age was 43.1±12.9 years, with 20% under 30, 26.2% aged 31–40, 22.5% aged 41–50, and 31.3% over 50. Males comprised 63.7%, females 36.3%. Most (91.3%) had normal BMI (18.1–25.0 kg/m²), 7.5% were underweight (<18.1 kg/m²), and 1.3% overweight (25–29.9 kg/m²). Both groups had comparable mean ages (63±12 vs. 60±15 years, p=0.588) and BMI (21.1±3.1 vs. 20.9±2.8 kg/m², p=0.752). Hemodialysis duration was significantly longer in Group B (114.6±58.3 vs. 58.9±56.1 months, p<0.0001). No significant differences were observed in blood pressure, hypertension, diabetes, smoking, or ACE-I/ARB use. Vitamin D use (90% vs. 53%, p=0.004). Group B also had higher intact PTH levels (555.2±229.0 vs. 125.1±90.3 pg/ml, p<0.0001), while other biochemical markers showed no significant differences (Table 2). Table 3 compared clinical and echocardiographic findings across No DD (n=18), Grade I (n=48), and Grade II DD (n=14). Serum phosphate, Ca×P product, and iPTH rose significantly with DD severity (p=0.002, p=0.002, p=0.000). Echocardiographic markers—left atrial diameter (p=0.000), septal thickness (p=0.016), LVM (p=0.000), LVMI (p=0.000), LVEDD (p=0.002), and LVESD (p=0.009)—also increased significantly with worsening DD. Serum phosphate (5.49±1.06 vs. 6.34±1.94 mg/dl, p=0.026), Ca×P product (45.49±8.32 vs. 53.33±15.37 mg²/dl², p=0.010), and LA diameter (35.11±3.20 vs. 38.00±3.06 mm, p<0.001) were significantly higher in the >300 group (Table 4). E/A ratio showed a significant positive correlation with serum phosphate (r=0.300, p=0.007), Ca×P product (r=0.320, p=0.004), and iPTH (r=0.358, p=0.001). LA diameter correlated significantly with serum phosphate (r=0.346, p=0.002), Ca×P product (r=0.348, p=0.002), and iPTH (r=0.276, p=0.013) (Table 5). Among the variables analyzed, only iPTH (p=0.002, OR=1.01, 95% CI: 1.004–1.016) was found to be a statistically significant independent predictor of diastolic dysfunction (Table 6). Figure 1 illustrated the link between elevated iPTH (>300 pg/ml) and diastolic dysfunction severity. In the normal function group, 88.9% had iPTH <300, while 11.1% had iPTH >300. In Grade 1 dysfunction, 68.8% had high iPTH and 31.1% low. This trend intensified in Grade 2, where 92.9% had high iPTH and only 7.1% had low iPTH. Patients with normal diastolic function had the lowest mean S. PO4 level at 4.93 mg/dl. This value rises in patients with Grade 1 diastolic dysfunction, where the mean S. PO4 is 6.13 mg/dl, and further escalates in those with Grade 2 diastolic dysfunction, reaching 6.93 mg/dl (Figure 2).

Table 1: Demographic characteristics of the study patients (N=80).

Variables	Frequency (n)	Percentage (%)
Age group (years)		
<30	16	20
31-40	21	26.2
41-50	18	22.5
>50	25	31.3
Mean±SD	43.1±12.9	
Sex		

Male	51	63.7
Female	29	36.3
BMI (kg/m^2)		
Underweight (<18.1)	6	7.5
Normal weight (18.1-25.0)	73	91.3
Overweight (25-29.9)	1	1.3

Table 2: Distribution of the study patients according to underlying cause of CKD (N=80).

Clinical characteristics	Group A (n=40)	Group B (n=40)	p-value
Age (years)	63±12	60±15	0.588
Male	29(47)	12(60)	0.28
Body mass index (kg/m^2)	21.1±3.1	20.9±2.8	0.752
HD duration (months)	58.9±56.1	114.6±58.3	<0.0001
Systolic BP (mmHg)	140.9±20.0	141.2±18.4	0.96
Diastolic (mmHg)	75.1±13.4	77.7±9.0	0.489
Hypertension (%)	42(69)	16(80)	0.319
Diabetes mellitus (%)	19(31)	7(35)	0.701
Smoking (%)	29(48)	10(50)	0.858
ACE-I/ARB (%)	23(34)	10(50)	0.338
$CaCO_3$ (%)	58(95)	19(95)	-
Vitamin D (%)	32(53)	18(90)	0.004
Albumin (g/dI)	3.6±0.5	3.9±0.5	0.315
HbAIc (%)	6.0±1.1	6.0±0.8	0.944
Hematocrit (%)	32.0±3.4	32.6±5.5	0.693
Ca (mg/dI)	9.3±0.5	9.4±0.7	0.615
P (mg/dI)	5.3±0.9	5.6±0.9	0.323
Ca×p (mg2/dI2)	50.1±10.9	52.8±9.0	0.238
Intact PTH (pg/mI)	125.1±90.3	555.2±229.0	<0.0001

Table-3: Comparison of all parameters among the different grade of diastolic dysfunction (N=80)

Variables	Diastolic dysfunction grading			p-value
	No DD (n=18)	G-I DD (n=48)	G-II DD (n=14)	
Age (years)	44.33±12.03	42.23±13.25	44.57±13.75	.760
BMI (kg/m^2)	19.54±1.95	20.14±1.80	19.57±1.21	.343
SBP	125.00±16.00	128.33±16.16	126.79±16.13	.750
Corrected Ca (mg/dl)	8.37±0.66	8.38±1.07	8.42±0.36	.984
S. PO_4 (mg/dl)	4.93±0.80	6.13±1.28	6.93±2.82	.002*
Ca × PO_4 product (mg2/dl2)	41.29±6.63	51.42±10.58	57.46±21.82	.002*
iPTH (pg/ml)	216.8±123.2	409.4±202.3	557.3±188.2	.000*
Vitamin D (ng/ml)	21.71±5.52	20.64±6.89	21.62±6.07	.784
E/A ratio	2.06±2.60	1.20±0.28	1.90±1.78	.058
LA diameter (mm)	33.39±2.52	37.05±1.96	40.57±4.09	.000*
Average E/e	9.91±1.52	10.04±1.74	11.18±1.45	.058
TR max velocity (m/sec)	3.33±3.93	2.69±0.37	2.95±0.18	.472
Septal wall thickness (mm)	8.08±2.44	9.76±1.95	10.16±3.08	.016*
LVM (gm)	149.44±44.07	192.61±41.94	234.76±44.70	.000*
LVMI (gm/m^2)	99.42±26.12	128.23±24.95	154.24±27.19	.000*
LVEDD (mm)	48.78±5.66	50.10±4.39	54.29±2.30	.002*
LVESD (mm)	31.39±4.49	32.07±3.57	35.50±4.59	.009*

SBP= Systolic Blood Pressure, S. PO_4 = Serum Phosphate, Ca×PO_4 =Calcium Phosphate product, iPTH= Intact Parathormone.

Table 4: Comparison of all parameters between iPTH<300(pg/ml) and iPTH>300(pg/ml) patients' groups (N=80)

Variables	iPTH <300	iPTH >300	p-value
	Mean±SD		
Age (years)	42.78±12.87	43.33±13.14	.853
BMI (kg/m^2)	19.76±1.47	20.01±1.93	.538
SBP	124.69±15.65	129.06±16.10	.232
Corrected Ca (mg/dl)	8.36±0.64	8.41±1.04	.810
S. PO_4 (mg/dl)	5.49±1.06	6.34±1.94	<.026*
Ca × PO_4 product (mg2/dl2)	45.49±8.32	53.33±15.37	<.010*
iPTH (pg/ml)	192.31±46.94	525.08±172.42	<.001*
Vitamin D (ng/ml)	20.27±5.24	21.57±7.09	.379
LVMI (gm/m2)	106.66±24.10	139.39±27.68	.001*
E/A Ratio	1.01±0.24	1.25±0.28	<0.001*
Average E/e	10.12±1.04	10.27±2.01	.683
LA diameter (mm)	35.11±3.20	38.00±3.06	<.001*

S. PO_4 =Serum Phosphate, Ca × PO_4 =Calcium Phosphate product, iPTH= Intact Parathormone, LVMI= Left Ventricular Mass Index, LA= Left Atrium.

Table 5: Correlation of LVDD parameters with biochemical predictors (N=80)

Outcome variables	Predictors	r- value	p-value
E/A Ratio	Corrected Ca (mg/dl)	0.075	0.509
	S. PO_4 (mg/dl)	0.300*	0.007
	Ca × PO_4 product (mg2/dl2)	0.320*	0.004
	iPTH (pg/ml)	0.358*	0.001
	Vitamin D (ng/ml)	-0.058	0.607
LA diameter (mm)	Corrected Ca (mg/dl)	-0.019	0.864
	S. PO_4 (mg/dl)	.346*	0.002
	Ca × PO_4 product (mg2/dl2)	.348*	0.002
	iPTH (pg/ml)	.276*	0.013
	Vitamin D (ng/ml)	-0.033	0.775

Table 6: Multivariate logistic regression performed to predict risk factors of diastolic dysfunction (N=80)

Variables	p-value	OR	95% CI	
			Lower	Upper
HTN	0.464	1.799	0.374	8.656
DM	0.68	1.373	0.305	6.171
Ca × PO_4 product (mg2/dl2)	0.184	1.132	0.943	1.359
iPTH (pg/ml)	0.002	1.01	1.004	1.016
S. PO_4	0.718	1.311	0.301	5.714

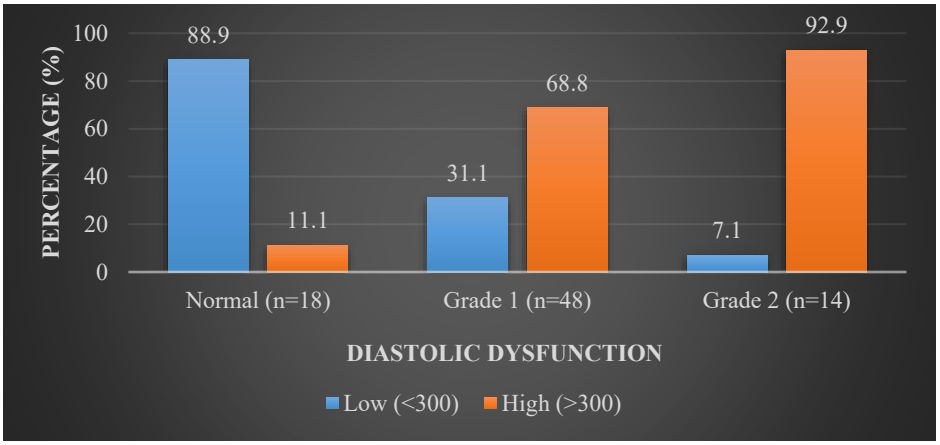

Figure 1: Association of high iPTH with severity of diastolic dysfunction (N=80)

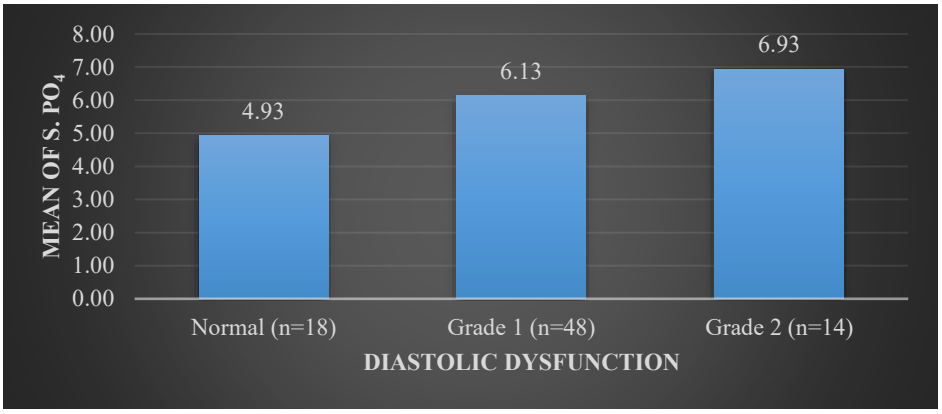

Figure 2: Bar diagram showing the comparison S. PO_4 among the severity of diastolic dysfunction

DISCUSSION

Cardiac diastolic dysfunction is a common and severe complication in patients with chronic kidney disease (CKD), encompassing both those in pre-dialysis stages and those undergoing maintenance hemodialysis (MHD). This discussion delves into the influence of elevated parathyroid hormone (PTH) levels on the progression of cardiac diastolic dysfunction in pre-dialysis and MHD patients. In terms of demographic characteristics, it was observed that 31.3% of the patients were aged between 50 and 65 years. The mean age was 43.1±12.9 years, with a range from 18 to 65 years. Among the patients, 51 (63.7%) were male and 29 (36.3%) were female. Most patients (91.3%) had a normal BMI (18.1-25.0 kg/m²), with a mean BMI of 22.1±2.3 kg/m². Similarly, Al-Hilali et al. (2009) reported a median age of 57 in their study population, which is higher than in our study because patients over 65 years old were excluded [16]. A similar male predominance was noted by Hamid Nasri et al. (2004) and Randon et al. (2015) [17,18]. The BMI range observed in this study was consistent with findings by Al-Hilali et al. (2009) [16]. In this study, both groups were similar in terms of age, gender distribution, body mass index (BMI), blood pressure, and prevalence of common comorbidities such as hypertension and diabetes mellitus. However, significant differences emerged in dialysis duration, serum vitamin D levels and intact parathyroid hormone (iPTH) levels. Notably, the dialysis duration was significantly longer in Group B (114.6±58.3 months) than in Group A (58.9±56.1 months, $p<0.0001$), suggesting a possible association between prolonged hemodialysis and increased mineral bone disorder or cardiovascular complications. This aligns with findings from Cao et al., who reported that the cumulative dialysis exposure contributes to vascular calcification and cardiac structural abnormalities in CKD patients [19]. Serum iPTH levels were also significantly elevated in Group B (555.2±229.0 pg/ml) compared to Group A (125.1±90.3 pg/ml, $p<0.0001$), indicating a more advanced secondary hyperparathyroidism. High PTH levels are known to promote left ventricular hypertrophy and myocardial fibrosis, as supported by Naves-Díaz et al., who found elevated PTH to be independently associated with cardiovascular mortality in dialysis patients [20]. Vitamin D deficiency was also more prevalent in Group A (only 53%

receiving supplementation) compared to 90% in Group B (p=0.004). Vitamin D has been shown to exert cardioprotective and anti-inflammatory effects in CKD, and inadequate replacement may contribute to worsening diastolic function. Similar observations were made by Moorthi et al., who highlighted the importance of correcting vitamin D deficiency in managing CKD-mineral and bone disorder (CKD-MBD) [21]. We also analyzed echocardiographic parameters across increasing grades of diastolic dysfunction (DD)—from no DD to Grade I and Grade II. While demographic parameters such as age, BMI, and blood pressure remained comparable across groups, significant differences were found in biochemical and echocardiographic markers of mineral bone disorder and cardiac remodeling. Serum phosphate (S. PO4), Ca × PO4 product, and iPTH levels progressively increased from no DD to Grade II DD (p=0.002, 0.002, and <0.001, respectively), indicating a close association between worsening mineral metabolism and declining diastolic function. These findings are consistent with the work of Qunibi et al., who showed that hyperphosphatemia and elevated calcium-phosphate product were strong predictors of cardiovascular calcification and mortality in ESRD patients [22]. Significant left atrial (LA) enlargement and increasing left ventricular mass index (LVMI) were also noted across the worsening grades of DD (p<0.001 for both), consistent with structural cardiac changes accompanying diastolic impairment. Increased septal wall thickness, LVEDD, and LVESD values across the DD groups further reinforce the impact of volume overload and myocardial hypertrophy. These findings mirror those of Rroji et al., who observed that elevated PTH and phosphate levels were directly linked with concentric hypertrophy and impaired ventricular compliance [23]. Furthermore, the E/A ratio and average E/e values trended toward abnormality with advancing DD, although not statistically significant in this sample. This showed similarity with the study by Otsuka et al. [24]. In our study, we can see that the proportion of patients with iPTH >300 pg/ml dramatically increased with the severity of diastolic dysfunction—from just 11.1% in the normal function group to 68.8% in Grade 1, and a striking 92.9% in Grade 2 dysfunction. This suggests a graded relationship between secondary hyperparathyroidism and diastolic impairment, reinforcing iPTH as a potential biomarker for early cardiac remodeling in CKD. These findings are consistent with studies by Mondal et al., which demonstrated that excess PTH promotes myocardial fibrosis, ventricular stiffness, and impaired relaxation [25]. Our study showed that serum phosphate levels rose proportionally with the severity of diastolic dysfunction, increasing from a mean of 4.93 mg/dl in patients with normal function to 6.13 mg/dl in Grade 1 and 6.93 mg/dl in Grade 2. This reinforces the role of hyperphosphatemia in vascular and valvular calcification, both of which contribute to impaired diastolic filling. The observed trend parallels data from Nitta et al., who linked elevated phosphate to left ventricular hypertrophy and arterial stiffness in ESRD patients [26].

Limitations of the study:

In this study, there was potential selection bias as participants were chosen purposively. Additionally, confounding factors such as medication use and varying degrees of underlying cardiovascular conditions were not fully controlled. Longitudinal studies with larger, more diverse populations are needed to confirm these findings and elucidate the mechanisms involved.

CONCLUSION

The study concludes that elevated parathyroid hormone (PTH) levels significantly contribute to the development of cardiac diastolic dysfunction in both pre-dialysis and maintenance hemodialysis (MHD) patients. High PTH is associated with increased serum phosphate, calcium-phosphate product, and left atrial diameter, all of which are predictors of cardiac structural and functional abnormalities. The findings underscore the importance of monitoring and managing PTH levels to mitigate cardiovascular complications in chronic kidney disease patients.

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