The link between bone disease and cardiovascular complications in hemodialysis patients

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Abstract

Introduction: The burden on the cardiovascular system is the main cause of mortality in chronic renal patients, and bone disease, which also may cause disability, is one of the most important complications in those patients. The aim of this study was to determine the link between cardiovascular and bone disease, which frequently occur together.

Methods: In this matched case-control study, 70 subjects were subjected for full laboratory assessment as well as estimation of parathyroid hormone (PTH) level, vitamin D level, complete echocardiography, and dual energy absorptiometry. Of the 70 patients, 50 were on regular hemodialysis, and there were 20 normal controls matched with the patients with respect to age and gender.

Results: There was a significant decrease in the mean value of serum vitamin D in the hemodialysis patients, i.e., their mean value was 20.47 ± 9.60 whereas the controls had a mean value of 37.15 ± 7.67. Thus, there was a highly-significant, negative correlation between vitamin D and left ventricular mass (LVM) in the patients. We found that there was a highly-significant increase in the mean PTH levels of the patients (820.22 ± 393.51), whereas it was 57.60 ± 13.72 for the controls. The statistical significance was less than 0.001, a highly-significant increase in the mean of the T score levels in the patients (-2.15 ± 2.56), whereas it was -0.47 ± 0.71 for the controls with a statistical significance of less than 0.001. There also was a highly-significant correlation between the T score and LVM.

Conclusion: A significant correlation was found between bone disease and the occurrence of a left ventricular mass. We recommend early strict correction of the serum levels of vitamin D, PTH, calcium, and phosphorus.

Keywords: cardiovascular complication, hemodialysis, echocardiography

1. Introduction

1.1. Background and study logic

The cardiovascular burden is considered to be the main cause of mortality in chronic kidney disease (CKD). Three pathological forms of cardiovascular disease have been defined, i.e., alterations in cardiac geometry, atherosclerosis, and arteriosclerosis. Although patients with CKD have many of the risk factors that occur in the general population, there also are non-traditional, uremia-related risk factors (1). Disordered mineral metabolism may have an important role in the pathophysiology of end-stage renal disease. The parathyroid hormone level is elevated in CKD patients due to several factors that result from vitamin D deficiency, i.e., altered renal function, decreased intestinal absorption of vitamin D, and resistance to its calcemic action (2). Also, a high parathyroid level was found to contribute to increased occurrences of left ventricular masses independent of other traditional factors, and chronic elevation of this level has been associated with increased vascular calcifications and increased morbidity and mortality (2). In addition, the prevalence of osteoporosis in the population with CKD exceeds that of the general population as bone turnover is high in secondary hyperparathyroidism with osteitis fibrosa; bone resorption rates exceed bone formation rates, and osteopenia progresses to osteoporosis; in low bone turnover states, as is the case for adynamic bone disease, both bone formation and resorption rates are reduced and the loss of bone mass occurs

(3). Some researchers have stated that, paradoxically, CKD mineralization co-exists with skeletal demineralization, and this is the reason that half of the patients will have some form of cardiovascular calcification even before dialysis (4).

1.2. Objective
The objectives of this clinical trial were to evaluate the relationships between PTH, vitamin D levels, T score, and left ventricular mass in order to clarify the link between bone disease and cardiovascular complications in end-stage renal disease.

2. Material and methods
There were 70 subjects in the study, and they represented different age groups and both Genders. The 70 subjects were divided into two groups, i.e., a group of 50 patients who were on regular hemodialysis and a group of 20 healthy controls. Full medical histories were obtained for all of the subjects, and all of them underwent clinical examinations and laboratory investigations (serum urea, creatinine, serum calcium, serum phosphorus, total cholesterol, triglycerides, HDL, LDL, complete blood count, CRP, and parathyroid hormone estimation. In addition to standard M mode echocardiography, two-dimensional and pulsed wave Doppler echocardiograms were obtained soon after a session of routine hemodialysis using. Bone density was measured by Dual energy X-ray absortiometry (DXA) scan of the femoral neck, and the results were expressed as mean ± standard deviation or number (%). Comparisons between categorical data were performed using the chi-squared test. According to test of normality, comparisons of normally-distributed variables were performed using the unpaired t-test. Comparisons between the variables that were not normally distributed were performed using the Mann-Whitney test. The correlations between variables were determined using the Spearman Rank test. The SPSS computer program (version 16 for Windows) was used to analyze the data. P-values ≤ 0.05 were considered significant.

3. Results
The ages of the participants were in the range of 31-37 and 34-76 in the control and study groups, respectively. Table 1 shows a comparison of the demographic data for the case and control groups. There were significant differences between the two groups regarding age, body mass index (BMI), and smoking, but there was no significant difference in the gender of the two groups. Also, there were significant differences between the control and study groups regarding their systolic blood pressures (119.25 ± 8.17 vs. 134.33 ± 21.78), diastolic blood pressures (79.80 ± 4.26 vs. 84.33 ± 12.69), serum creatinine levels (1.21 ± 0.16 vs. 8.02 ± 2.12 mg/dl), serum urea (30.3 ± 4.32 vs. 140.27 ±28.04 mg/dl), serum calcium (9.7 ± 0.7 vs. 9.12 ± 1.2 mg/dl), serum PO_4 (3.32 ± 0.83 vs. 5.2 ± 1.78 mg/dl), serum triglyceride (152.15 ± 12.81 vs. 237.0 ± 107.5 mg/dl), serum HDL (51.1 ± 15.95 vs. 34.1 ± 20.2 mg/dl), serum albumin (3.99 ± 0.45 vs. 3.62 ± 0.48 mg/dl), serum hemoglobin (13.15 ± 1.3 vs. 10.05 ± 2.24 gm/dl), platelet count, and serum CRP (Table 1). In addition, our findings showed that there were significant differences in the T scores (-0.47 ± 0.71 vs. -2.15 ± 2.56), PTH (57.60 ± 13.72 vs. 820.22 ± 393.51), and Vitamin D (37.15 ± 7.67 vs. 20.47 ± 9.60) between two groups (p = 0.001). According to Spearman's Rho correlation analysis, there were correlations between Left ventricular mass (LVM) and T. score, PTH, and vitamin D (p = 0.001).

4. Discussion
There was a high prevalence, i.e., about 80%, of cardiovascular disease in hemodialysis patients related to age, prevalence of diabetes, and dialytic age (1). There were lower degrees of cardiovascular involvement in Stage I-IV CKD patients than in hemodialysis and peritoneal dialysis patients (2, 3). It was definitively apparent that patients with stage IIIb-IV renal disease, based on the K/DOQI CKD classification, had cardiovascular risk, as also was the case for those who underwent renal replacement therapy, i.e., hemodialysis, peritoneal dialysis, and transplants (4). Alterations in mineral bone metabolism is associated with CKD and referred to as CKD-MBD (5). These alterations can include (a) changes in the morphology of bones, such as their volume, turnover, and mineralization; (b) abnormalities in calcium, phosphorus, PTH, vitamin D and fibroblast growth factor-23 (FGF-23); and (c) calcification of blood vessels and soft tissue (5). The current understanding of CKD–MBD indicates that phosphorus, PTH, calcium, FGF-23 (a phosphatonin hormone that is elevated in CKD to promote the renal excretion of phosphate), and vitamin D are the main regulators of mineral and bone metabolism (6). These factors are interrelated, and the parathyroid gland, kidneys, bones, and intestinal tract are the major organs that they target. Hypocalcemia, hyperphosphatemia, hyperparathyroidism, hypovitaminosis D, and elevated FGF-23 are the biochemical abnormalities that occur in CKD–MBD; even so, it is not uncommon to see significant variations, especially in serum calcium (7). Bone abnormalities in CKD include high bone turnover disease related to secondary hyperparathyroidism, i.e., osteitis fibrosa cystica; low turnover disease, i.e., adynamic bone disease; osteomalacia,

i.e., low turnover disease accompanied by undermineralized bone tissue; and mixed disease, in which features of both high and low bone turnover disease are present (8).

Table 1. Comparison between the two groups regarding their demographic characteristics, clinical examinations, and laboratory and echocardiography findings

Variables		p-value
Demographic characteristics	Age	0.021
	Gender	0.441
	BMI	0.026
	Smoking	0.001
Clinical examinations	Systolic blood pressure	0.004
	Diastolic blood pressure	0.037
	Pulse	0.126
Serum findings	Creatinine	0.001
	Urea	0.001
	Calcium	0.018
	Po_4	0.001
	Cholesterol	0.163
	Triglyceride	0.001
	HDL	0.010
	LDL	0.103
	Albumin	0.005
	Hemoglobin	0.001
	WBC	0.684
	Platelet count	0.001
	CRP	0.001
Echocardiography data	EDD (cm)	0.359
	ESD (cm)	0.002
	FS (%)	0.037
	PWT (cm)	0.001
	IVST (cm)	0.001
	EF (%)	0.003
	LVM	0.010
	Wall motion abnormality	0.007
	Diastolic Dysfunction	0.001
	Pericardial effusion.	0.169
	Pulmonary hypertension	0.022
	Calcification	0.001

The evidence that has been generated to date suggests that vitamin D deficiency might contribute to the extraordinarily high mortality risk among dialysis patients (9). The data from patients who have and who do not have chronic kidney disease (CKD) indicate vitamin D might protect against cardiovascular diseases, immune disorders, or cancer in addition to its classic effects on bone and mineral metabolism (10). A strong association between vitamin D deficiency and cardiovascular disease has been found in the general population (11). Lack of vitamin D influences the cardiovascular system, causing atherosclerosis, enabling vascular inflammation, endothelial dysfunction, formation of foam cells, and proliferation of smooth muscle cells, vascular calcification, fibrosis, and cardiac hypertrophy (12). It also leads to myocardial and arterial thickening and left ventricular hypertrophy (13, 14). The 25 (OH) Vitamin D was measured to find the relationship between heart and kidney disease, and, in some studies, the crosstalk between the kidney and heart. Low vitamin D levels have been associated with increased arterial stiffness and left ventricular hypertrophy (LVH) in the general population and in children with chronic kidney disease (15-17). In our study, we measured vitamin D in hemodialysis patients and controls and found a significant decrease in mean serum vitamin D in hemodialysis patients compared to controls with a mean of 20.47 ± 9.60 for HD patients vs. a mean of 37.15 ± 7.67 for controls. This is in agreement with many studies that have indicated low vitamin D levels in hemodialysis patients (9, 18, 19). Vitamin D is the substrate that

the 1α-hydroxylase enzyme in the kidney converts into 1,25(OH)$_2$ vitamin D, the active form of vitamin D. Declining renal function is associated with reduction of renal production of 1,25(OH)$_2$ vitamin D. However, it was discovered later that, apart from the kidney, many other organs are also able to produce 1,25(OH)$_2$ vitamin D locally, which clearly depends on availability of the substrate vitamin D (20). So, deficiency of this substrate might be a rate limiting step in production of the active form of vitamin D in hemodialysis patients. Factors that have been suggested as a cause of vitamin D include decreased ultraviolet-B induced vitamin D production in the skin with diminished sun exposure (21). We also found a highly significant negative correlation between vitamin D and LVM in the studied patients. This is in agreement with Chang et al., who found that lower vitamin D levels were correlated with higher left ventricular mass and increased arterial stiffness in older patients (22). Earlier studies that investigated patients with CKD also showed an association between vitamin D deficiency and adverse cardiac changes, especially left ventricular hypertrophy (23, 24). Research in the molecular and cell biology areas have elucidated the role of vitamin D receptor (VDR) activation and regulation of the renin-angiotensin system (RAAS) as pathophysiologic mechanisms responsible for these changes (25-27). LV hypertrophy is an independent risk factor for mortality in adult patients with CKD, and, in these patients, regression of LV mass has been associated with survival (28). It has even been reported that nutritional supplementation with vitamin D can reverse left ventricular hypertrophy in adult CKD patients who are receiving hemodialysis (24). Parathyroid hormone abnormalities have long been recognized in CKD and hemodialysis patients. First, secondary hyperparathyroidism occurs caused by hyperphosphatemia, decreased active form of vitamin D, hypocalcemia. Prolonged hyperplasia of the parathyroid gland can cause autonomous or tertiary hyperparathyroidism. Then again, there are the treatments used that affect mineral homeostasis. Vitamin D analogues are used to treat hypocalcemia, vitamin D deficiency, and hyperparathyroidism with the possible adverse effects of producing hypercalcemia, hyperphosphatemia, and over suppression of the parathyroid gland. Parathyroid hormone levels less than 200% of the upper limit of normal out the patient at high risk of low bone turnover or adynamic bone disease. Calcimimetics are used to treat hyperparathyroidism with high or normal calcium levels, but, again, there is a risk of over suppression of the parathyroid gland (29).

In our study, we found a highly-significant increase in the mean PTH levels in our patients (820.22 ± 393.51) when compared to controls (57.60 ± 13.72) with a statistical significance of less than 0.001. There also was a highly significant positive correlation between PTH and LVM. Many studies also have demonstrated that chronically elevated PTH levels are associated with elevated cardiovascular mortality. Also, PTH levels have been associated with LVH irrespective of blood pressure effects. Secondary parathyroidism has been associated with LVH, especially if chronic uremia is present. While the exact mechanisms are unclear, PTH can stimulate the secretion of aldosterone, which is a mediator of cardiac hypertrophy. Also, PTH activates kinase C protein in cardiomyocytes, causing an increase in cellular mass. It has been noted that parathyroidectomy can cause a decrease in LV mass, and this finding supports the role of elevated PTH levels in the development of LVH (30). Patients with chronic kidney disease are exposed to another bone disease before or after developing kidney disease, i.e., osteoporosis, which is a common disease that is characterized by low bone mass and skeletal fragility resulting in an increased risk of fracture (31). However, it is difficult to diagnose osteoporosis in the setting of CKD. DXA, quantitative computed tomography, and high resolution peripheral computed tomography are imaging methods that quantify bone mass. DXA is widely available, but screening by DXA in CKD has been controversial because it cannot discriminate between cortical and trabecular bone or determine turnover or mineralization. However, recent trials have suggested that DXA of the total hip and femoral neck can predict future fractures (32). The results of this study showed a highly significant increase in mean levels of the T scores in our patients (-2.15 ± 2.56) when compared to controls (-0.47 ± 0.71) with a statistical significance of less than 0.001. There also was a highly significant positive correlation between T score and LVM. Several researchers have provided evidence of a possible correlation between cardiovascular disease and osteoporosis; in a study conducted on 180 post-menopausal women, the researchers explored the relationship between low bone mineral density and T score and coronary artery disease risk (33). Another study found increased arteriosclerosis in 558 patients, carotid and femoral pulsed wave velocity, and it seemed to be correlated with bone mineral density of the femoral neck (34). In addition, in a study conducted by Debby et al., it was reported that six of the highest ranked studies showed that there is moderate evidence that individuals with low bone mass had higher cardiovascular mortality rates than subjects with normal bone mass, and the shared common path physiology was estrogen deficiency and inflammation (35).

Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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