Comparison of Metabolic Bone Markers in Diabetic and Non-Diabetic Chronic Kidney Diseases in Government Medical College, Thrissur, Kerala, India

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ABSTRACT

BACKGROUND

The term 'Chronic Kidney Disease-Mineral and Bone Disorder' (CKD-MBD) has been used to describe clinically, the abnormalities in the bone and mineral metabolism associated with CKD. In CKD, serum levels of metabolic bone disease markers generally reflect a high bone turnover state (hyperphosphatemia, hypocalcaemia, hypersecretion of PTH, increased ALP). However, it has been noted that in diabetic CKD patients on regular haemodialysis, there is an impaired secretion of PTH when compared to the non-diabetics on haemodialysis. In this study we intend to evaluate the serum bone markers in both diabetic and non-diabetic CHD patients. If a significant association can be demonstrated between diabetes mellitus and a low bone turnover state, then treatment guidelines can be tailored accordingly in the diabetic CHD patients.

METHODS

A hospital based cross-sectional study was done on 150 patients attending the Dialysis Unit of Govt. Medical College, Thrissur district, Kerala, India, from March 2014 to March 2015. Estimation of serum FBS, creatinine, calcium, phosphorus, ALP and PTH was done.

RESULTS

The mean levels of serum phosphorus and PTH are significantly lower in the diabetic CHD population than in the non-diabetics, but mean serum ALP is significantly higher in the diabetic CHD patients. Statistical significance is seen in the serum metabolic bone disease markers except calcium among diabetic and non-diabetic chronic kidney disease.

CONCLUSIONS

The serum levels of PTH and phosphorus were found to be significantly lower in diabetic CHD patients than in their non-diabetic counterparts. Serum ALP levels were significantly higher in the diabetics. This demonstrates that a relative hypoparathyroidism is prevalent among the diabetic CHD patients and hence, prevention of deterioration of the already existing low turnover bone disease in such patients should be the treatment motto. Avoidance of oral calcium supplements, vitamin D supplements and increased calcium in the dialysate would be ideal, since these can lead to hypercalcemia and further suppress the PTH secretion.

KEYWORDS

Diabetes Mellitus, Chronic Kidney Disease, Bone Markers

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BACKGROUND

Chronic kidney disease (CKD) comprises of a broad spectrum of different pathophysiological processes, which are associated with abnormalities in the various functions of the kidney and a resultant progressive decline in the glomerular filtration rate (GFR). CKD stage 5 or end-stage renal disease (ESRD) represents a stage of CKD where due to the decreasing kidney function there is an accumulation of fluid, electrolytes and various toxins that are normally removed by the renal system. Those CKD patients who have been undergoing maintenance haemodialysis (MHD) for a period of not less than three months are termed chronic haemodialysis (CHD) patients.

A wide range of complications can be seen associated with CKD, of which the most common include anemia, malnutrition, and hypertension and bone disease. The term 'Chronic Kidney Disease-Mineral and Bone Disorder' (CKD-MBD) has been used to describe clinically a broad syndrome associated with CKD which manifests as abnormalities in the bone and mineral metabolism and / or extra-skeletal calcification.[1] The kidney plays an important role in the normal metabolism of the minerals calcium and phosphorus. Any disturbances which might affect the functioning of this organ can result in an imbalance in the calcium and phosphorus metabolism which can in turn cause disorders of the bone.

The effects of the CKD complications that arise from disturbances in the metabolism of calcium and phosphorus are most evident in the skeleton and the vascular bed. Secondary hyperparathyroidism (SHPTH) is a commonly observed complication among the CKD patients. It is characterized by an excessive level of parathyroid hormone (PTH) in the serum, parathyroid hyperplasia, hypocalcaemia and hyperphosphatemia.[2] This disorder can eventually lead to clinically significant long term consequences[3] and increase the risk for cardiovascular morbidity and mortality in the CKD population.[4,5]

Diabetes mellitus (DM), one of the most common chronic metabolic diseases, has been on the increase worldwide and in India. This can be attributed to the increasing obesity and sedentary lifestyle which have now become the most important risk factors associated with DM.[6] It has been noted in studies that DM is one of the two leading causes of CKD in India.[7] In CKD, hyperphosphatemia is encountered with due to the decreased excretion of phosphorus by the kidneys. Also, inadequate production of the active form of vitamin D by the kidney results in decreased levels of serum calcium. Both these factors together cause hyper secretion of PTH in an attempt to normalize the levels of serum calcium and serum phosphorus. Alkaline phosphatase (ALP) levels are also found to be increased in CKD due to the high bone turnover state induced by PTH over activity.[8] However, it has been demonstrated in various studies that diabetic CKD patients on regular haemodialysis have an impaired secretion of PTH when compared to the non-diabetics on haemodialysis.[9]

Chronic kidney disease is a common disease seen in our country. Since Kerala is the unofficial 'diabetic capital of India', the subject of whether DM has any effect on the levels of metabolic bone disease markers in serum is one of medical importance. This can help in altering treatment plans accordingly and thereby decreasing morbidity and mortality associated with mineral and bone disorders seen in CKD. There have been very few studies conducted concerning this subject in India. Hence, this study is being done to prove a relation between DM with serum PTH, calcium, phosphorus and ALP in CHD patients attending the Dialysis Unit of Govt. Medical College, Thrissur.

Objectives

1. To study the prevalence of DM in CHD patients.
2. To evaluate the effect of DM on serum levels of metabolic bone disease markers (PTH, calcium, phosphorus, ALP) in CHD patients.

METHODS

The study was a hospital based cross-sectional study done among patients attending the Dialysis Unit of Govt. Medical College, Thrissur district, Kerala, India, from March 2014 to March 2015. Sample size was calculated using the formula,

$$Sample\ size = (z\alpha)^2 pq/d^2$$

zα = 1.96
p = 41 % [7]
q = 59 % (1 - p)
d = 8.2 (20 % p)

Substituting the values in the above formula we get 138.2039 which is the minimum sample size required. A total of 150 patients were included in the study to increase the sensitivity of the study.

Inclusion Criteria

CKD patients irrespective of cause, aged between 18-80 yrs, undergoing haemodialysis > 3 months

Exclusion Criteria

Subjects diagnosed with primary hyperparathyroidism and those with liver disease.

Written informed consent from the patients satisfying the inclusion criteria were obtained. On admission, data regarding the baseline characteristics of each patient - Age, Sex, history of DM, duration of haemodialysis was collected. The patients were grouped according to diabetic status (diabetic or non-diabetic). Venous blood samples were drawn from the patient before the start of haemodialysis for the estimation of the various biochemical parameters in metabolic bone disease. Estimation of serum FBS, creatinine, calcium, phosphorus and ALP was done using Fully Automated Clinical Chemistry Analyzer Erba-Mannheim 360 and estimation of PTH in the serum sample was done by Enzyme linked immunosorbent assay (ELISA) using Rayto RT-2100C Micro plate reader and BioRad PW40 Washer.

All the data collected was coded and analysed using SPSS 18.0 statistical software. The frequency distribution and descriptive statistics of the study population was done. The quantitative variables were presented as mean ±standard deviation (SD). The qualitative variables were expressed in percentage. Comparison of the means of serum PTH, calcium, phosphorus, ALP and magnesium among diabetic and non-diabetic CHD patients was done using Student's t-test. Comparison of the means of serum PTH, calcium, phosphorus, and ALP among the different age categories was done using one-way analysis of variance (ANOVA). All the tests were 2-tailed and taken to be statistically significant if p value < 0.05.

Statistical Analysis

All the data collected was coded and analyzed using SPSS 18.0 statistical software. Comparison of the means of serum PTH, calcium, phosphorus and ALP among diabetic and non-diabetic CHD patients was done using Student's t-test.

RESULTS

The mean age of the study population was found to be 50.27 ± 12.85 years. The mean age of the male study subjects was 52.45 ± 11.73 years, and that of the female study subjects was 45.65 ± 13.97 years. The number of male and females were found to be 102 (68 %) and 48 (32 %) respectively. The characteristics of the study population are described in Table 1.

Parameter	Mean ± SD	Minimum	Maximum
Age (years)	50.27 ±12.85	22	78
Duration of haemodialysis (years)	3.57 ± 1.77	1	8
Creatinine (mg / dL)	8.74 ± 2.72	3	16.8
Fasting blood sugar (mg / dL)	98.74 ± 28.76	64	173
Parathyroid hormone (pg / mL)	357.27 ± 222.58	47	831
Calcium (mg / dL)	7.92 ± 0.81	5	10
Phosphorus (mg / dL)	5.04 ± 1.48	1.8	8.3
Alkaline phosphatase (U / L)	281.33 ± 202.45	46	1048

Table 1. Characteristics of the Study Population

Among the 150 CHD study subjects, there were 67 diabetics and 83 non-diabetic patients. The prevalence of DM among CHD patients was found to be 44.70 %.

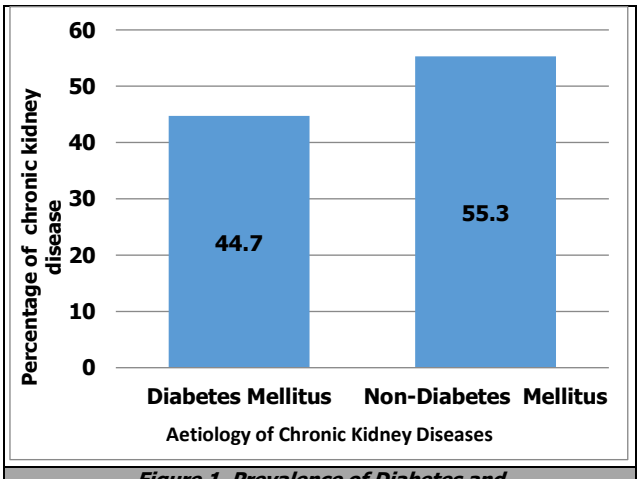

Figure 1. Prevalence of Diabetes and Non-Diabetes in Chronic Kidney Disease

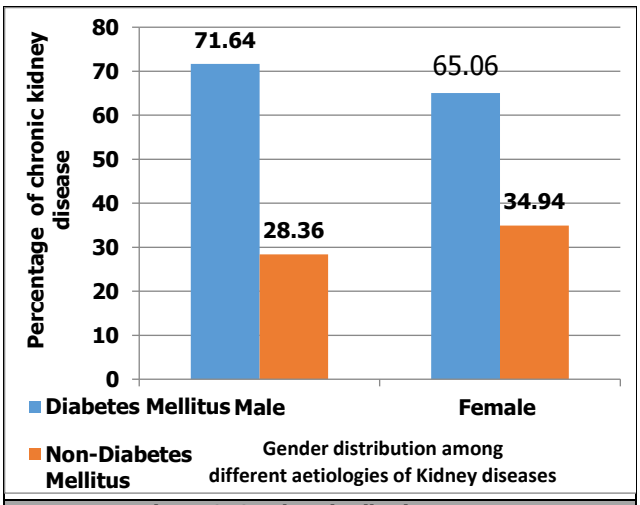

Figure 2. Gender Distribution among Diabetics and Non-Diabetics

Parameter	Diabetics (n = 67) Mean ± SD	Non-Diabetics (n = 83) Mean ± SD	t	Mean Difference	p
Parathyroid hormone (pg / mL)	146.58 ± 51.04	527.35 ± 149.59	19.09	380.77	0.001
Calcium (mg / dL)	7.84 ± 0.84	7.99 ± 0.78	1.14	0.15	0.256
Phosphorus (mg / dL)	4.53 ±1.56	5.45 ± 1.28	3.95	0.91	0.001
Alkaline phosphatase (U / L)	344.93 ± 224.14	230 ± 167.54	-3.59	-114.92	0.001

Table 2. Serum Metabolic Bone Disease Markers in Diabetic and Non-Diabetic CHD Patients (Student's t-Test)

The mean levels of serum phosphorus and PTH are significantly lower in the diabetic CHD population than in the non-diabetics, but mean serum ALP is significantly higher in the diabetic CHD patients. Statistical significance is seen in the serum metabolic bone disease markers except calcium among diabetic and non-diabetic chronic kidney disease.

DISCUSSION

Chronic kidney disease is a chronic non-communicable condition which is commonly encountered in the present day scenario. An increasing prevalence of CKD is being observed in the developed Western countries through the last couple of decades. This could be attributed to the increasing life expectancy and the rise in the prevalence of lifestyle diseases like DM and hypertension (HTN).[10] The developing nations are not far behind in this aspect with the easy availability of better medical facilities, lack of exercise and the increasingly sedentary lifestyle.

It has been estimated that there are around 55,000 patients who are on dialysis in India. This population is growing at an alarming trend of 10 - 20 % annually.[11] DM, HTN, autoimmune disease, old age, previous episode of acute kidney injury and family history of renal disease are some of the risk factors predisposing to CKD. Data collected from around the world, between 1990 and 2002, showed that DM and HTN alone accounted for the majority of kidney failure cases (44.6 % due to DM and 26.9 % due to HTN).[12] It has been seen in studies that the aetiological spectrum of primary disease among CKD patients in India comprise of

DM (41 %), HTN (22 %), chronic glomerulonephritis (16 %), chronic interstitial disease (5.4 %), ischaemic nephropathy (5.4 %), obstructive uropathy (2.7%), miscellaneous (2.7 %) and other unknown causes (5.4 %).[13] Variations have been observed from region-to-region in this distribution pattern.[14] Nevertheless, it has now been reported that DM and HTN account for about 40-60% of CKD cases in India, with diabetic nephropathy emerging as the major cause.[15]

Improving Global Outcomes (KDIGO) Controversies Conference on 'Definition, Evaluation and Classification of Renal Osteodystrophy' held in 2005 recommended that the term renal Osteodystrophy (ROD) be used solely for defining the bone pathology associated with CKD. It was also proposed that the many clinical, biochemical and imaging abnormalities that have been identified as correlates of ROD, be defined more broadly as a clinical entity or syndrome called 'Chronic Kidney Disease-Mineral and Bone Disorder.[16]

The PTH levels in circulation have been used as an indicator of the bone turnover. It is used together with measurements of serum calcium, serum phosphorus and serum ALP, to help evaluate, diagnose and guide the treatment in CKD-MBD. According to the KDIGO workgroup which evaluated the clinical utility of biomarkers in the assessment of CKD-MBD, serum PTH levels used along with serum total ALP levels were established to be helpful in predicting the bone turnover. bALP may have a distinct advantage over the total ALP,[17] but to overcome the high cost of measurement of bALP it was suggested that the total ALP may be used. In CKD-MBD, the laboratory parameters most strongly associated with morbidity and mortality is the serum PTH, serum calcium and serum phosphorus levels.[18] Even though bone biopsy is considered the gold standard for the diagnosis of ROD, biochemical markers like PTH, calcium, phosphorus and ALP may be used as alternative diagnostic tools. Studies have shown that when liver disease has been excluded, intact PTH (iPTH) and ALP can be used for the diagnosis of CKD-MBD.[19]

Many hypotheses have been put forward to explain the relative hypoparathyroidism seen in diabetic CHD patients when compared to their non-diabetic counterparts. It has been noted that DM is accompanied by an increased risk of bone disease.[20] Studies have shown that the poor metabolic control associated with DM can result in alterations of calcium homeostasis.[21] Diabetic patients present a lower level of serum PTH and calcium values than the non-diabetic population. Paula FJ t al, have documented the inhibitory effect that poor metabolic control has on low calcium-mediated PTH secretion.[22] Low PTH concentrations can result in decreased bone formation and weak bones which lead to a higher risk of vertebral fractures in diabetic patients.[23] It has been observed in studies that the low calcium levels are associated with a decreased bone mass.[24] Diabetes mellitus being one of the leading causes of CKD has been constantly evaluated for its role in the development of CKD-MBD. The increasing prevalence of DM in Kerala imparts a great deal of medical significance to this disease and its effects.

In the present cross-sectional study among CHD patients, the prevalence and effects of DM on serum levels of PTH, calcium, phosphorus and ALP was evaluated. It was seen that among the total 150 subjects who took part in this study, 68% was male and 32% was female. The average age of the study subjects was 50.27 ± 12.85 years. Rajapurkar MM et al, conducted a study on 'what do we know about chronic kidney disease in India: first report of the Indian CKD registry' and it was seen that the mean age of CKD was 50.1 ± 14.6 years, and the male female ratio was 70:30.[15] The mean age in studies conducted outside India was found to be 46 ± 18 years.[25]

The prevalence of DM among the study subjects was found to be 44.7 %. Dash SC et al, conducted a study on 'Incidence of chronic kidney disease in India' and found that DM had a prevalence of 41 % among the CKD population. [13] However, in a study conducted by Joy MS et al, in the United States of America, it was seen that DM accounted for about 44.6 % cases of CKD.[12] The increased prevalence in our study population which approximates that seen in the developed countries could be explained by the fact that diabetes is gaining a stronger foothold in our population with the increasing consumption of junk food and sedentary lifestyle. These factors can lead to obesity which is a major risk factor for DM.

Among the diabetic CHD patients, 71.64 % were males and 28.36% were females. The mean age of the diabetic CHD population was found to be 52.81 ± 11.92 years. It was also noted that the majority of diabetics (32.84 %) in the study population were in the age category of 41 - 50 years.

The mean levels of PTH and phosphorus were seen to be significantly lower among the diabetics than the non-diabetics in the study population. However, the mean level of ALP was found to be significantly higher in the diabetics. In this study, the mean PTH value among the diabetic CHD patients was found to be below 300 pg / mL, which is the target cut-off for CKD stage 5 patients on MHD as per the NKF K/DOQI guidelines.[26] On the other hand, the mean serum PTH values among the non-diabetics were found to be higher than the target value. A statistical significance was demonstrated in the serum levels of PTH among diabetic and non-diabetic CHD patients ($p = 0.001$). This is similar to the findings by Dan S et al, among the South Indian population.[14] It has been postulated that there are two mechanisms behind the relative hypoparathyroidism caused by DM. The suppression of PTH secretion can be considered to be due to hyperinsulinemia or hyperglycaemia seen in DM, or the presence of advanced glycation end products (AGEs).[14] Sugimoto T et al, in their study demonstrated that increasing the concentration of glucose in the medium of cultured bovine parathyroid cells caused an inhibition of the secretion of PTH by the cells.[27] Likewise, in another study conducted by Clowes JA et al, it was seen that induction of hyperinsulinemia resulted in a decrease in the PTH values.[28] Makita Z et al, in their studies noted that the level of AGEs was higher in diabetics ESRD patients than both the non-diabetic ESRD patients and the diabetic non-ESRD patients.[29] The excessive accumulation of AGEs in the tissues is seen to suppress the secretion of PTH in response to hypocalcaemia and also the osteoblastic activity resulting in adynamic bone disease.[30]

The mean serum calcium level of the whole study population was found to be below the target range of 8.4-9.5 mg/dL recommended in the NKF K/DOQI guidelines.[26] Both the diabetics and non-diabetics had a mean serum calcium value in the hypocalcaemic range and no statistical significance could be demonstrated in the serum calcium levels among diabetic and non-diabetic CHD patients. This is similar to findings in other studies done both in India and abroad in countries like Egypt.[14,25]

A statistically significant difference was seen in the serum phosphorus levels among diabetic and non-diabetic CHD patients in this study. The mean phosphorus level of the study population was found to be within the target range recommended by NKF K/DOQI (3.5 - 5.5 mg / dL).[26] It was noted that in the diabetics the mean phosphorus level was within the target range but in the non-diabetics it was near the upper limit of the target range. A study by Aubia J et al, has shown that there can be a relative hyperphosphaturia in DM which may affect the hyperphosphatemia normally seen with CKD.[31] The resultant lower levels of serum phosphorus could in turn have a protective effect against secondary hyperparathyroidism. But even small increases in the high normal ranges of serum levels of phosphorus in CKD patients with DM can increase their risk for cardiovascular mortality and morbidity.[32]

The mean serum total ALP level among the study subjects was found to be above the cut-off of the target range (> 128 U / L). Both the diabetic and non-diabetics had mean ALP values above the target range. It was noted that there was a statistical significance in the serum ALP levels among diabetic and non-diabetic CHD patients. This could be explained by the increased bone turnover seen in CKD-MBD. This is similar to the findings seen in a study done by Nasri H et al.[25]

From the above observations, it can be inferred that statistical significance was noted in the serum levels of PTH, Phosphorus and ALP among diabetic and non-diabetic CHD patients. Thus it can be said that a relative hypoparathyroidism is more prevalent among diabetic CHD patients that could manifest as adynamic bone disease. Care should be taken while treating diabetic CHD patients with bone disease. Oral calcium supplements, vitamin D supplements and increased calcium in the dialysate should be avoided since they can lead to hypercalcemia. This can further suppress the PTH secretion and result in aggravation of the already existing low turnover bone disease in such patients.

Limitations

The present study was a hospital based study. A larger community-based study could give a better idea of the CKD population in the Thrissur district of Kerala. Even though KDIGO have suggested that total ALP along with the other biochemical parameters is sufficient to make a diagnosis of CKD-MBD, the use of high sensitivity bone specific ALP would make the study more specific.

CONCLUSIONS

The prevalence of DM among CHD patients was found to be 44.70%. 71.64 % of the male CHD subjects were found to be diabetic whereas, among the female CHD subjects, the prevalence was about 65.06 %.

A statistically significant association was demonstrated in the serum PTH ($p = 0.001$), phosphorus ($p = 0.001$) and ALP ($p = 0.001$) levels among diabetic and non-diabetic CHD patient. No statistical significance could be demonstrated between DM and serum calcium ($p=0.256$).

The serum levels of PTH and phosphorus were found to be significantly lower in diabetic CHD patients than in their non-diabetic counterparts. Serum ALP levels were significantly higher in the diabetics. This demonstrates that a relative hypoparathyroidism is prevalent among the diabetic CHD patients and so care should be taken while treating such patients. Prevention of deterioration of the already existing low turnover bone disease in such patients should be the treatment motto. Avoidance of oral calcium supplements, vitamin D supplements and increased calcium in the dialysate would be ideal, since these can lead to hypercalcemia and further suppress the PTH secretion.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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