Original Article

Renal Bone Disease : Biochemical Marker in CKD

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Abstract

Objectives : The Renal bone disease is one of the important complication of chronic kidney disease. This study was undertaken to identify some biochemical markers like parathyroid hormone (PTH) and alkaline phosphatase (ALP) which can help to predict the renal bone disease before doing bone biopsy.

Methods : To understand the parameters 120 subjects were studied, ages ranging from 20 to 60 years. Among them 100 (male = 70, and female = 30) were chronic kidney disease patients stage III, IV & V as experimental group and 20 were healthy control group - A (male = 12, female = 08). The study subjects both in control and the experimental group were well matched by age and body weight. The chronic kidney disease patients were divided into three groups on the basis of creatinine clearence: group-B1 (CKD- III, n=34), group-B2 (CKD –IV, n=36) and group-B3 (CKD - stage V, n= 30). The study parameters were serum alkaline phosphatase & serum PTH.

Results : The Mean (±SD) of serum alkaline phosphatase were 49.40± 58.48, 97.54± 58.48, 173.44± 122.11 and 341.83 ± 159.08 in group A, B1, B2 and B3 respectively. The mean values of alkaline phosphatase in experimental group were compared with control group and the differences were found statistically highly significant. The mean values of serum alkaline phosphatase also showed highly significant differences in group B2 than B1 ($p < 0.001$) and group B3 than B1 ($p < 0.000$). The Mean (±SD) values of serum PTH were 40.60±10.44, 78.10±19.99, 105.89±37.22l, and 220.10±127.18 in group A, B1, B2 and B3 respectively. The mean serum PTH were lower in group A than group B1 ($p<0.004$), B2 ($p< 0.0001$) and B3 ($P<0.0001$) which were statistically highly significant. Serum PTH was compared within the groups of the experimental subjects, in group B2 was higher than group B1 ($p< 0.002$), group B3 was higher than B1 ($p < 0.000$) and group B3 also higher than group B2 ($p < 0.0001$). The differences were statistically highly significant. Serum PTH level was higher in all experimental groups than the control group ($p< 0.0001$***).

Conclusion : The Renal bone disease is one of the important complication of chronic kidney disease and the gold standard of diagnosing renal bone disease is bone biopsy. But assessment of these biochemical markers parathyroid hormone (PTH) and alkaline phosphatase (ALP) which can help to predict the renal bone disease before doing bone biopsy.

Key Word : Renal Bone Disease, Biochemical Marker, CKD (chronic kidney disease)

Introduction

The management of chronic kidney disease & mineral bone disorder (CKD-MBD) is central to the care of patients with kidney disease. Key to these efforts is the availability of clinically accessible biomarkers that can help distinguish between a wide variety of bone and mineral disturbances related to kidney failure.

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Two such markers, parathyroid hormone (PTH) and alkaline phosphatase, are well-established in current guidelines[7] for managing CKD-MBD are familiar to most clinical practitioners.

PTH has been a mainstay in the evaluation of bone and mineral metabolism in CKD patients for more than three decades. The long-term consequences associated with persistently elevated PTH levels in CKD have been well-described and include high-turnover bone disease, anemia, cardiovascular disease (CVD) and mortality.[1]

As a result, both the Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that PTH levels should be regularly monitored beginning in stage 3 CKD (i.e., estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m^2), and that elevated levels should be treated with a combination of dietary phosphorus restriction and supplement of vitamin D and/or calcimimetics.[1,2]

Alkaline phosphatase is an enzyme that removes phosphate from proteins and nucleotides and can be detected in a variety of tissues throughout the body.[3] Because the highest concentrations of the enzyme are found in the liver and bone, an elevated total alkaline phosphatase level is most often indicative of bone pathology such as high-turnover bone disease.

The measurement of alkaline phosphatase has been advocated as an adjunct test for non-invasively assessing bone turnover in CKD patients, particularly in clinical scenarios in which elevated PTH levels may be challenging to interpret.[2] These recommendations were based upon studies that showed that elevated alkaline phosphatase levels have predictive value in diagnosing high-turnover bone disease in both pre-dialysis and end-stage kidney disease population[2]. The more recent KDIGO guidelines recommend that the measurement of alkaline phosphatase levels should commence in stage 3 CKD, and that in patients with stage 4-5 CKD, alkaline phosphatase should be measured at least every 12 months, and more frequently when monitoring response to therapy.[2,4,5]

In addition to its potential utility in assessing bone health, recent evidence suggests that alkaline phosphatase level have value for predicting CVD outcomes.[4] Large prospective studies showed that elevated alkaline phosphatase levels were independently associated with increased risks of renal bone disease and CVD- related hospitalization and mortality in patients across the spectrum of kidney function.[6-7]

Materials & Methods

A total number of one hundred twenty (120) subjects of age ranging from 20 – 60 years, consisted of hundred (100) chronic renal failure patients (Group B) and twenty (20) apparently healthy subjects as a control (Group A). All the experimental subjects (Group B) was again subdivided into three groups on the basis of creatinine clearance rate :

Group B1 = Stage -III (30 – 59 ml / min / 1.73 m2 bsa),

Group B2 = Stage – IV (15 – 29 ml /min / 1.73 m2 bsa),

Group B3 = Stage - V (<15 ml / min / 1.73m2 bsa).

PTH was measured by chemi luminescent immuno assay, phosphate by colorimetric method in both control and experimental group.

Data were expressed as Mean ± SD. Comparison between two groups were done by using unpaired student's "t" test using SPSS version -10.

Results

Serum alkaline phosphatase:

The results are shown in table I.

The Mean (±SD) of serum alkaline phosphatase were 49.40± 58.48, 97.54± 58.48, 173.44± 122.11 and 341.83 ± 159.08 in group A, B1, B2 and B3 respectively.

The mean values of alkaline phosphatase in experimental group were compared with that of control group: A vs. B1 ($p < 0.007$), A vs. B2 ($p < 0.0001$) and A vs. B3 ($p < 0.0001$) and found statistically highly significant difference.

The mean values of serum alkaline phosphatase also showed highly significant differences in group B2 than B1 ($p < 0.001$) and group B3 than B1 ($p< 0.0001$), but there were no significant difference between B2 and B3 ($p < 0.157$).

Table – I

Mean (± SD) Serum alkaline phosphatase in different study groups (n =120)

Groups	n	Mean ± SD
A	20	49.54 ± 58.48
B1	34	97.46± 38.48
B2	36	173.44± 120.11
B3	30	341.83± 159.08

Statistical analysis

Groups	t	df	p value
A vs B1	3.632	52	0.007***
A vs B2	4.515	54	0.0001***
A vs B3	8.181	48	0.0001***
B1 vs B2	3.285	68	0.001***
B1 vs B3	8.345	62	0.0001***
B2 vs B3	4.863	64	0.157ns

The Results were expressed as Mean ± SD . Unpaired student 't' test was performed to compare between groups. The test of significance was done and p values <0.05 was accepted as significance level.

A = Apparently healthy control group
B1 = Stage III CKD
B2 = Stage IV CKD
B3 = Stage V CKD
CKD = Chronic kidney Disease
n = Number of subjects
ns = Not significant
df = degree of freedom
p*** = highly significant

Table –II

Mean (± SD) Parathyroid hormone in different study groups (n =120)

Groups	n	Mean ± SD
A	20	40.60 ±10.44
B1	34	79.11± 19.99
B2	36	105.89± 37.22
B3	30	220.10± 127.18

Statistical analysis

Groups	t	df	p value
A vs B1	7.974	52	0.004***
A vs B2	7.651	54	0.001***
A vs B3	6.276	48	0.0001***
B1 vs B2	3.719	68	0.002***
B1 vs B3	9.382	62	0.0001***
B2 vs B3	5.137	64	0.0001***

The Results were expressed as Mean ± SD. Unpaired student 't' test was performed to compare between groups. The test of significance was done and p values <0.05 was accepted as significance level.

A = Apparently healthy control group
B1 = Stage III CKD
B2 = Stage IV CKD
B3 = Stage V CKD
n = Number of subjects
ns = Not significant
df = degree of freedom
p*** = Highly significant

Serum PTH

The results are shown in table II

The Mean (±SD) values of serum PTH were 40.60±10.44, 78.10±19.99, 105.89±37.22 and 220.10±127.18 in group A, B1, B2 and B3 respectively.

The mean serum PTH were lower in group A than group B1 (p<0.004), B2 (p< 0.0001) and B3 (P<0.0001) which were statistically highly significant.

Serum PTH was compared between the groups of the experimental subjects. The values in group B2 was higher than group B1 (p< 0.002), group B3 was higher than B1 (p < 0.0001) and group B3 also higher than group B2 (p < 0.000). The differences were statistically highly significant. Serum PTH were negatively correlated with, serum inorganic phosphate (r = 0.362, P<0.000) (Fig: XIII) and serum alkaline phosphatase (r = 0.558, P <0.0001) (Fig. XIV). All these findings were statistically significant.

Discussion

Abnormal skeletal structure and function are relatively common findings in patients with CKD. This is especially in patients requiring dialysis.[8] Extraskeletal "soft tissue" calcification is often a feature of CKD-MBD with some evidence of reciprocity between skeletal and soft tissue calcium content.[9,10] This important interplay between skeleton, vessels, and outcome was recognized by the Kidney Disease Improving Global Outcomes (KDIGO) initiative in its CKD-MBD position paper of 2006.[10] The diagnosis of the skeletal component of the CKD-MBD triad is biopsy-based histomorphometric analysis of bone biopsy specimens which is a painful and invasive procedure, is now much less commonly performed in clinical practice.

The objective of this study was to estimate the early marker of renal bone disease as parathyroid hormone and alakaline phosphatase. It was found that in all the experimental group mean serum PTH was significantly higher than the control group A than group B1 (p<0.004), B2 (p< 0.0001) and B3 (P<0.0001) which were statistically highly significant. Kovesdy et. al studied and find that hyperparathyroidism, due to progressive phosphate retention and lack of vitamin D activity, is the major promotor of the development of osteitis fibrosa.[11]

This study also simulate with the findings that near universally sustained elevation of PTH concentrations is seen by the time of dialysis therapy begins that at the time of CKD stage -V and PTH is much more reflective of bone remodeling.[3] Although it has high sensitivity for detecting hyper-parathyroid renal bone disease.[11] The Serum PTH among the three stages of the experimental subjects.

The values in group B2 was higher than group B1 (p< 0.002), group B3 was higher than B1 (p < 0.0001) and group B3 also higher than group B2 (p < 0.0001). It was found that in advance stages of CKD the serum PTH level progressively and significantly increases. It is believed that the disease and treatment paradigm shift from the "high turnover"/high PTH osteitis fibrosa lesions predominating in the 1960s to 1980s has great significance for the bone abnormalities and must be able to detect using current biomarkers.

Tonelli et. al studied and find out that ALP is an important marker of high-turnover bone disease and, as such, it is associated with serum PTH, which itself has been linked to increased mortality.[2,11] This study also shows the same elevated level of ALP which supports our findings. Rogidor et al showed that even the lower ALP could also be indicative of low-turnover bone disease.[7–9] Eknoyan et al suggest to measure this readily available and inexpensive biomarker to singled out as an individual therapeutic target of CKD-MBD.[12]

Conclusion

From this study it can be concluded that parathyroid hormone and alkaline phosphatase are the important biochemical markers of renal bone disease and they started rising at the early stages of chronic kidney disease. It also be concluded that as the chronic kidney disease progresses the biochemical markers also gradually increases. There are so many complications of chronic kidney disease and important one is the renal bone disease.

So our findings suggest that these markers should be taken in consideration in making diagnosis and management of the patients of chronic kidney disease.

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