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EFFECTS OF SHORT TERM ALENDRONATE ADMINISTRATION ON BONE MINERAL DENSITY IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: Osteoporosis is highly prevalent in CKD patients and is characterized by low bone mass leading to decreased bone strength. It is associated with an increased risk of fracture, thus increasing morbidity and mortality. Bisphosphonate administration decreases fracture risk in postmenopausal females with osteoporosis. There are limited studies showing effects of short term alendronate administration on BMD in predialysis osteoporotic patients with CKD.

Methods: This study was conducted on fifty adult patients with chronic kidney disease. Patients were divided into two groups. Group A consisted of seventeen patients with CKD stage 3 (eGFR 45-30 ml/min/1.73m^2) and Group B comprised thirty three patients with CKD stage 4 (eGFR 30-15 ml/min/1.73m^2). The study included male patients between age 18-75 years and premenopausal non pregnant females older than 18 years of age. All the patients were osteoporotic having T score < -2.5 on DEXA scan. The patients were administered 70 mg alendronate tablet once a week for 6 weeks. Renal parameters, parathyroid hormone, calcium, phosphorous and alkaline phosphatase levels were assayed at baseline for 6 months. Serum (iPTH) level (pg/ml) was measured by chemiluminescent immune assay (CLIA) method and serum 25 Hydroxy Vitamin D level (ng/ml) was measured by enzyme linked immunosorbent assay (ELISA) method. Bone Mineral Density (BMD) was measured at baseline for 6 months, by dual energy x-ray absorptiometry at lumbar spine and neck of femur and lowest values were included. The results were obtained for T score, Z score and bone mineral density (g/cm^2).

Results: The BMD, T score and Z score increased in both groups after 6 months with a statistically significant difference in the treatment group. In Group A, T score, Z score and BMD (g/cm^2) increased from -2.60±0.086, -2.13±0.28, and 0.80±0.008 at baseline to -2.57±0.097, -2.11±0.26 and 0.81±0.008 after six months. In Group B, the T score, Z score and BMD (g/cm^2) increased from -3.17±0.24, -2.82±0.33 and 0.738±0.03 to -3.16±0.25, -2.66±0.95 and 0.743±0.03 after six months with a statistically significant difference. eGFR decreased in both groups but the difference was statistically non-significant (P>0.05). The serum iPTH levels increased after 6 months in both groups with a statistically insignificant difference. There was an increase in serum calcium and decrease in serum phosphate levels after six months, however the difference was statistically insignificant (p>0.05). The SAP values decreased in both groups after six months with a statistically insignificant difference. The main side-effect in the alendronate group was the occurrence of gastroesophageal reflux symptoms in two subjects.

Conclusion: Low-dose alendronate, administered for a limited duration, appears to be well tolerated in CKD patients. The BMD increased in both groups suggesting a bone-preserving effect of alendronate.

Keywords: Alendronate, Osteoporosis, Chronic kidney disease, Bisphosphonate.

INTRODUCTION

Chronic kidney disease (CKD) is an emerging public health issue affecting around 5% to 10% of the population globally. [1] In patients with CKD, there is a progressive loss in mineral homeostasis with deterioration of the kidney function leading to disturbances in bone and mineral metabolism and thus is an important cause of morbidity and mortality. [2] Advanced stages of CKD are further complicated by impaired production of 1.25 Hydroxy vitamin D and secondary hyperparathyroidism and parathyroid hormone resistance. Bone and mineral metabolism disorders in patients with CKD represent a spectrum of skeletal disorders ranging from high turnover lesions of secondary hyperparathyroidism to low turnover lesions of osteomalacia and adynamic bone disease. The term chronic kidney disease - mineral and bone disorder (CKD-MBD) is used for systemic disorders of mineral and bone metabolism as a result of CKD. Osteoporosis is highly prevalent in CKD patients and is characterized by low bone mass leading to decreased bone strength. Osteoporosis adversely affects the already compromised quality of life of CKD patients. It is associated with an increased risk of fracture, thus increasing morbidity and mortality. [3, 4] Dual energy X-ray absorptiometry (DEXA) is the most widely used method for bone mineral density (BMD) assessment due to its lower cost, accuracy, short scan time and low radiation dose.

Calcium, vitamin D, calcitonin and estrogen/androgen therapy were used for the management of low BMD, until the introduction of bisphosphonates in the 1990s. Bisphosphonates, derivatives of inorganic pyrophosphate are a group of antiresorptive drugs widely used in the treatment of osteoporosis, osteogenesis imperfecta, and several other bone diseases. [5] They are powerful inhibitors of bone resorption, and act by decreasing osteoclast mediated bone resorption. [5, 6] Randomized controlled trials have shown that bisphosphonate administration decreases fracture risk in postmenopausal females with osteoporosis. [7] Alendronic acid or Alendronate sodium is a nitrogen containing bisphosphonate and is a widely used drug for the treatment of osteoporosis. It is orally administered and weekly administration is as effective as daily dosing. Various studies have shown that alendronate administration has a beneficial effect on BMD even in patients with CKD and manifested no renal adverse effects. [8] This drug has also shown beneficial effects on BMD in renal transplant patients. [9] Recent studies have shown that it also has an added benefit to reducing the progression of vascular and soft tissue calcification. [10]

The modern era has seen important advances in the understanding and management of osteoporosis, but in patients with CKD it remains a complex issue that has yet to be clearly defined. There are very few studies carried out in the past regarding underlying mechanisms and management of osteoporosis in pre dialysis patients with chronic kidney disease and hence the present study was undertaken. Although studies have demonstrated a beneficial effect of alendronate on BMD in CKD patients, most of the studies were either in early CKD or in patients on haemodialysis. The present prospective study was therefore carried out to assess the effect of short term alendronate therapy in predialysis patients with advanced CKD including stages 3 and 4.

MATERIAL AND METHODS

The present study was conducted on fifty adult patients with chronic kidney disease either of stage 3 or 4 on regular follow up of kidney and dialysis clinic at Pt. B.D. Sharma PGIMS, Rohtak. The study included male patients between age 18-75 years and premenopausal non pregnant females older than 18 years of age. All the patients were osteoporotic having T score < -2.5 on DEXA scan. Only patients who had intact PTH levels between 100 and 300 pg/ml and 25(OH) Vitamin D levels greater than 20 ng/ml were included in the study. In patients with 25(OH) Vit D levels less than 20 ng/ml, 25(OH) Vit D were repleted to 20 ng/ml or greater than this before inclusion in the study. The intention was to treat patients with elevated PTH levels who nonetheless were under generally acceptable control: individuals with intact PTH < 32 pmol/L (300 pg/mL) and calcium x phosphorous product < 5.65 (equivalent to 70 in imperial units) who were independently functional and ambulatory.

Patients with CKD stage 5 & 5D, on maintainace haemodialysis, and post renal transplants were not included in the study. Patients with markedly depressed PTH levels (which may indicate low bone turnover disease) or markedly elevated

PTH (which may indicate hyperparathyroid bone disease), having history of parathyroidectomy and with history of hormone replacement therapy within the previous 2 years were excluded from the study. Patients with history of bone tumors, multiple myeloma, any esophageal abnormality, osteonecrosis of jaw, other causes of metabolic bone disease, having preexisting psychiatric illness and post-menopausal women were also not included in the study.

After taking written informed consent and a thorough history, each participant went under detailed clinical, biochemical and radiological examination. The study was approved by the ethical committee of Pt. B.D. Sharma University of Health Sciences. Patients were divided into two groups. Group A consisted of seventeen patients with CKD stage 3 (eGFR 45-30 ml/min/1.73 m^2) and Group B comprised thirty three patients with CKD stage 4 (eGFR 30-15 ml/min/1.73 m^2).

Patients were administered alendronate dose of 70 mg orally once per week, for a total of six weeks (i.e. six doses in total). Alendronate was selected as it is an oral medication and is therefore easy to administer to outpatients. They were directed to take the medication after an overnight fast with a full glass of water only and were instructed not to lie down for at least 30 min after ingestion. Patients were detailed about the side effects and were followed up fortnightly till 24 weeks of therapy for any untoward side effects like gastroesophageal irritation, osteonecrosis of jaw, nephrotoxicity, muscle and joint pain and skin rashes. The patients were contacted telephonically periodically for any side effects. Osteonecrosis of jaw was screened in patients complaining of jaw pain by X-ray of jaw.

Routine biochemical investigations were carried out at baseline and repeated at 6 months. Serum Calcium, phosphorous, total alkaline phosphatase and iPTH levels were obtained at baseline and at 6 months. Serum (iPTH) level (pg/ml) was measured by chemiluminescent immune assay (CLIA) method at baseline and after 6 months. Serum 25 Hydroxy Vitamin D level (ng/ml) was measured by enzyme linked immunosorbent assay (ELISA) method at baseline and after 6 months.

Bone Mineral Density (BMD) was measured at baseline and after 6 months, by dual energy x-ray absorptiometry at lumbar spine and neck of femur and lowest values were included (DEXA, Hologic Explorer QDR series 90797). The results were obtained in T score, Z score and bone mineral density (g/cm^2). Z score is the number of standard deviations from the mean of a healthy age and gender matched normal population, which allows the comparison of BMD between patients of different age and gender. T score is the number of standard deviations from the mean of a healthy young adult population (20-40 years old); it is used for the definition of osteopenia (between -1.0 and -2.5 T score) and osteoporosis (less than -2.5 T score).

Statistical analysis

At the end of the study, the data was expressed as mean ±1SD or range. Probability values of <0.05 were considered to be significant in all the analysis. The Statistical analyses were performed using independent t-test, paired t-test and chi square test. The correlations were tested using the Pearson correlation coefficient analysis. All statistical calculations were carried out using SPSS 20.0 software.

RESULTS

In our study, the majority of patients were above 40 years of age. The mean age of the patients in Group A was 52.47±12.42 with a range of 30-70 years. Group B had a mean age of 46.54±8.98 with a range of 30-65 years. Out of all 50 patients, 37 were male and 13 were female. The most common cause of CKD in Group A and Group B was diabetes mellitus followed by chronic glomerulonephritis and hypertension. Less frequent etiology included adult polycystic kidney disease, obstructive uropathy and renal amyloidosis. The baseline biochemical parameters of patients of both the groups are depicted in Table 1.

Renal parameters including blood urea, serum creatinine and eGFR deteriorated in both the groups after six months but the difference was statistically insignificant. The corrected serum calcium, phosphate, serum alkaline phosphatase (SAP) and intact Parathyroid Hormone (iPTH) values also changed after six months in both groups but with an insignificant difference (Table 2 & 3). The mean corrected serum calcium & iPTH increased after 6 months in both groups with a statistically insignificant difference. The mean serum phosphate and SAP decreased after six months, but with a statistically insignificant difference. In Group A, T score, Z score and BMD (g/cm^2) increased from -2.60±0.086, -2.13±0.28,

Table 1. *Baseline Biochemical Parameters*

Baseline Biochemical Parameter	Group A (n=17)	Group B (n=33)	P-value
Haemoglobin (g/dl)	8.15±0.85	7.76±0.67	>0.05
Blood Urea (mg/dl)	84.52±18.55	101.72±25.87	<0.05
Serum Creatinine (mg/dl)	2.08±0.16	2.83±0.32	<0.001
estimated Glomerular Filtration Rate (ml/min/1.73 m^2)	35.60±3.68	23.47±3.64	<0.001
Corrected Serum Calcium (mg/dl)	8.15±0.27	7.50±0.16	<0.001
Serum Phosphate (mg/dl)	6.32±0.32	7.11±0.34	<0.001
Serum Alkaline Phosphatase (IU/L)	124.11±13.02	145.15±18.25	<0.001
25 Hydroxy Vitamin D (ng/ml)	26.79±0.86	23.64±1.56	<0.001
Intact Parathyroid Hormone (pg/ml)	226.47±3.24	245.66±13.61	<0.001

Table 2. *Comparison of baseline and at six months parameters in Group A*

Parameters	Baseline	At 6 months	P-value
Blood Urea (mg/dl)	84.52±18.55	85.17±18.70	>0.05
Serum Creatinine (mg/dl)	2.08±0.16	2.09±0.17	>0.05
eGFR	35.60±3.68	35.37±3.77	>0.05
Corrected Serum Calcium (mg/dl)	8.15±0.27	8.17±0.30	>0.05
Serum Phosphate (mg/dl)	6.32±0.32	6.31±0.33	>0.05
Serum Alkaline Phosphatase (IU/L)	124.11±13.02	123.05±12.23	>0.05
Intact Parathyroid Hormone (pg/ml)	226.47±3.24	226.55±2.89	>0.05
T score	-2.60±0.086	-2.57±0.097,	<0.05
Z score	-2.13±0.28	-2.11±0.26	<0.05
Bone Mineral Density (g/cm^2)	0.80±0.008	0.81±0.008	<0.05

Table 3. *Comparison of baseline and at six months parameters in Group B*

Parameters	Baseline	At 6 months	P-value
Blood Urea (mg/dl)	101.72±25.87	102.54±26.01	>0.05
Serum Creatinine (mg/dl)	2.83±0.32	2.85±0.33	>0.05
eGFR	23.47±3.64	23.33±3.75	>0.05
Corrected Serum Calcium (mg/dl)	7.50±0.16	7.51±0.18	>0.05
Serum Phosphate (mg/dl)	7.11±0.34	7.10±0.34	>0.05
Serum Alkaline Phosphatase (IU/L)	145.15±18.25	144.27±16.27	>0.05
Intact Parathyroid Hormone (pg/ml)	245.66±13.61	246.27±13.48	>0.05
T score	-3.17±0.24	-3.16±0.25	<0.05
Z score	-2.82±0.33	-2.66±0.95	<0.05
Bone Mineral Density (g/cm^2)	0.738±0.03	0.743±0.03	<0.05

and 0.80±0.008 at baseline to -2.57±0.097, -2.11±0.26 and 0.81±0.008 after six months (Table 2 & Figure 1). The increase was statistically significant (paired t-test, $p<0.05$). In Group B, also results were similar to Group A. In Group B, the T score, Z score and BMD (g/cm2) increased from -3.17±0.24, -2.82±0.33 and 0.738±0.03 to -3.16±0.25, -2.66±0.95 and 0.743±0.03 after six months with a statistically significant difference (paired t-test, $p<0.05$) (Table 3 & Figure 2).

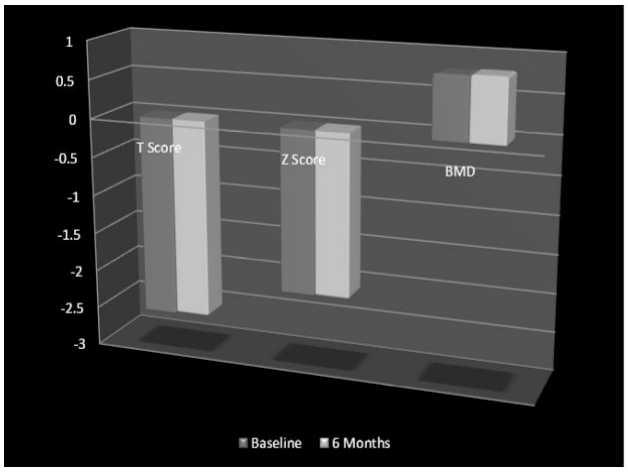

Figure 1. *Comparison of baseline and at six months bone densitometric data in Group*

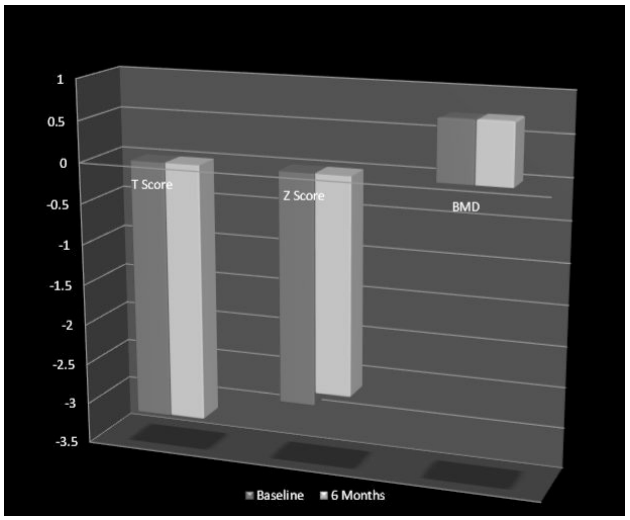

Figure 2. *Comparison of baseline and at six months bone densitometric data in Group B*

Out of 50 patients, 2 patients experienced gastroesophageal irritation and one patient experienced muscle and joint pain as an adverse effect. However, they were statistically insignificant (chi square test, $p>0.05$). Nephrotoxicity was defined as rapid increase in serum creatinine i.e. absolute increase of 0.5 mg/dl from baseline after 24 hrs of drug intake. None of the patient had such an increase in serum creatinine. Although blood urea and serum creatinine increased and eGFR decreased in both groups after six months, the difference was statistically insignificant. Any of the above mentioned side effects did not lead to withdrawal of drug in any patient.

DISCUSSION

Chronic kidney disease mineral and bone disorder (CKD-MBD) is a systemic disorder that is associated with increased incidence of fracture, cardiovascular disease and high mortality. It is associated with derangements in bone and mineral metabolism that lead to abnormal regulation of calcium, phosphorous, vitamin D, and parathyroid hormone (PTH). [11] Because the early initiation of appropriate therapy may prevent or ameliorate the mineral and bone disorder that develops in late CKD, the ability to define the pathophysiologic process underlying abnormality and the efficacy and safety of drugs required needs to be established. Osteoporosis is a condition characterised by low bone mass leading to reduced bone strength and increased incidence of fractures. Data from the National Health and Nutrition Examination Survey (NHANES) reported that the incidence of osteoporosis together with mild impairments in renal function (defined as an eGFR of <35 ml/min) is 0% among women aged 50-59 years old, 7.3% among those 60-69 years old, 21.3% among those 70 to 79 years old, and 53.9% among those eighty years or older. [12] Osteoporosis in CKD is a major part of the of metabolic bone disease and therefore, its diagnosis and management may differ from general population. Bisphosphonates are a class of antiresorptive drugs and are most widely prescribed drugs to treat osteoporosis. They work by the mechanism of osteoclast inhibition and therefore prevent the loss of bone mass. Bisphosphonates use has been associated with decreased incidence of fracture in the general population and even in patients with CKD. [13] Over the past few years, bisphosphonate use in patients with kidney disease has become widespread. In the current scenario, these drugs

are being increasingly used by nephrologists and this may be because of safety data available with bisphosphonate use in patients with kidney disease and the effect on BMD achieved in general osteoporotic patients have also been demonstrated in patients with kidney disease. Keeping in view these facts, this study was planned to evaluate effects of short term alendronate therapy on BMD in fifty osteoporotic predialysis patients, with CKD stage 3 and 4 respectively.

In the present study, we investigated the effects of a short course of alendronate on BMD in stable chronic kidney disease predialysis patients to evaluate whether use of this drug could preserve or increase bone mineral density. Alendronic acid or Alendronate sodium is a nitrogen containing bisphosphonate drug extensively used in the treatment of osteoporosis. It has an oral route of administration and can be administered either daily or weekly. Alendronate was selected as it is an oral medication and is therefore easy to administer to outpatients. The short period of six weeks was selected because of two reasons. Even 6 weeks of alendronate use has shown to increase BMD after six months in women at risk for osteoporosis. [14] Secondly, because of the concerns that drug accumulation of bisphosphonates has renal mode of excretion and therefore has not been very much used in patients with CKD. In the present study, the T score, Z score and BMD (g/cm^2) in lumbar spine increased after the short term alendronate therapy in group A and group B. The increase in T score, Z score and BMD in both groups was statistically significant. In the present study, renal functions deteriorated in both groups after six months, but with a statistically insignificant difference. None of the patients experienced nephrotoxicity due to the alendronate therapy. The serum iPTH levels increased after 6 months in both groups. The serum iPTH levels were expected to rise after six months because the anti osteolytic effect of alendronate decreases bone turnover and acutely causes hypocalcaemia, thereby exacerbating secondary hyperparathyroidism. However, the increase in iPTH levels in both groups was statistically insignificant. There was an increase in serum calcium and decrease in serum phosphate levels after six months, however the difference was statistically insignificant ($p>0.05$). This difference may be due to the increased PTH levels. The SAP values decreased in both groups after six months with a statistically insignificant difference. The decrease in bone turnover due to bisphosphonates led to decrease in SAP after six months. Two patients experienced mild gastroesophageal reflux symptoms and one patient complained of mild muscle and joint pain. However, none of the patients had to discontinue drug therapy and adverse effects were statistically insignificant ($p>0.05$). In the present study, we were able to demonstrate that a short course of alendronate increases BMD, T score and Z score in patients with CKD stage 3 and CKD 4 with a statistically significant difference. The significant difference may be due to better control of biochemical parameters, adequate Vitamin D levels and better control of hyperphosphatemia in patients with CKD not on haemodialysis.

Our results were in concordance with a randomized placebo controlled study conducted by Wetmore et al. [15] They studied the effects of short term alendronate on bone mineral density in haemodialysis patients. 31 healthy HD patients were randomized to placebo versus 40 mg alendronate, taken once a week for 6 weeks. The BMD and T-scores in specific regions of the hip were stable in the treatment group and decreased in the placebo group. The lumbar spine density increased minimally in both groups. The main side-effect in the alendronate group was the occurrence of gastroesophageal reflux symptoms in three subjects. They concluded that low dose alendronate, administered for a limited duration, has a beneficial effect on BMD in dialysis patients. Shahbazian et al. conducted a controlled double blind randomized clinical trial studying the effect and safety of alendronate on bone density in patients with chronic kidney disease. [16] Forty four CKD patients between 18 and 45 years old with CKD stage 1 & 2 with BMD at least one SD lower than the normal level for the same age and gender were enrolled in the study. Participants were assigned randomly to either intervention or control group with 22 patients in each group. The intervention group received 10 mg alendronate daily for one year. After the completion of the trial, bone density decreased in all patients in the control group, but increased in the experimental group, in lumbar spine and femoral neck, 6.4% and 4.5% respectively. They concluded that Alendronate is safe in these patients and increases the bone density in CKD stage 1 and 2. Another study by Shahbazian et al. evaluated the efficacy and safety of alendronate in the prevention of bone loss in renal transplant recipients and found that the BMD in patients treated with alendronate increased significantly

both at the lumbar vertebrae and femoral neck while it decreased in the placebo group. [17]

Jamal et al. carried out a secondary analysis of the fracture intervention trial to determine if alendronate had differential effects on BMD and fracture by renal function. [18] They concluded that alendronate is safe and effective among this group of women with reduced renal function.

Alteration in the bone metabolism in CKD not only affects bone health but it has systemic effects also. When bone resorption exceeds bone formation rates in CKD, phosphorus and calcium release leads to heterotopic mineralization especially in the vasculature. The failure of the skeleton to absorb positive phosphate balance in CKD is an important stimulus to heterotopic mineralization, and links the skeleton and osteoporosis in CKD to cardiovascular events and mortality. This link between osteoporosis and vascular calcification is now well defined in CKD and calls for urgent attention in order to prevent not only morbidities like fracture but also the mortality risk associated with increased cardiovascular events. [19]

Our results with respect to BMD were consistent with a pilot randomized controlled trial by Toussaint et al. in which they studied the effect of Alendronate on BMD and vascular calcification in CKD Stages 4 and 5. [20] Patients were randomly assigned to either alendronate, 70 mg (n=25), or matching placebo (n=25), administered weekly. There was an increase in lumbar spine BMD and a trend toward better pulse wave velocity with alendronate. Femoral BMD was similar between the groups. At 18 months, there was no difference in vascular calcification progression withwhen alendronate was compared to the placebo. In our study, the effect of alendronate on vascular calcification was not evaluated due to technical constraints and therefore needs to be planned in future. This is important because bisphosphonates have been reported to affect the vasculature and decrease atherosclerosis. Bisphosphonates may accumulate in atherosclerotic arteries probably due to high affinity for calcium and hydroxyapatite in calcified athermanous lesions. Bisphosphonates have also been found to accumulate in healthy aortas due to the inhibition of atherosclerosis or the anti-cytotoxic effect. [21]

The present study was associated with certain limitations. The small sample size and limited duration of the study were the major limitations. Another limitation to our study was that apart from PTH and ALP levels, no other markers of bone turnover were measured and bone biopsies were not performed. The role of bisphosphonates in decreasing vascular calcification and arterial stiffness which are highly prevalent in patients with CKD, also need to be evaluated in future. Therefore, further long interventional and case controlled randomized studies are required to determine the effective role of bisphosphonates in the treatment of BMD and the reduction of vascular calcification in predialysis CKD patients.

CONCLUSION

In conclusion, a state of reduced bone density is seen early in the course of CKD as estimated from reduced BMD levels, increased prevalence of osteoporosis and increased fracture risk and it worsens with the progression of CKD. Osteoporosis is a complex multi factorial disease that remains asymptomatic until a fracture occurs, and strategies need to be developed to accurately identify 'high risk' subjects who may benefit from preventive treatments before fractures occur. Considering that low BMD, osteopenia and osteoporosis are an increasing problem affecting the quality of life in CKD patients, there is a need to develop an effective strategy to improve BMD in these patients. There is a paucity of studies in the Indian literature regarding the role of bisphosphonates in improving BMD in pre dialysis patients with CKD and hence the present study was undertaken. Most of the studies were either of long duration, in patients with early CKD or in patients on haemodialysis. The present study was therefore carried out to assess the effect of short term alendronate therapy in predialysis patients with advanced CKD including stages 3 and 4.

REFERENCES

1. Eknoyan G, Lameire N, Barsoum R. The burden of kidney disease: improving global outcomes. Kidney Int 2004; 66: 1310-4.
2. Block GA, Cunningham J. Morbidity and mortality associated with abnormalities in bone and mineral metabolism in CKD. In: Olgard K (ed). Clinical Guide to the Basics of Bone and Mineral

Metabolism in CKD. National Kidney Foundation: New York, 2006, 77-92.

3. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int 2006; 69: 1945-53.
4. Ersoy FF, Passadakis SP, Tam P, Mammos ED, Katopodis PK, Ozener C et al. Bone mineral density and its correlation with clinical and laboratory factors in chronic peritoneal dialysis patients. J Bone Miner Metab 2006; 24(1): 79-86.
5. Lin JH. Bisphosphonates: a review of their pharmacokinetic properties. Bone 1996; 18(2) : 75-85.
6. Rodan GA, Fleisch HA. Bisphosphonates: Mechanisms of action. J Clin Invest 1996; 97: 2692-6.
7. Liberman UA, Weiss SR, Broll J. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis: The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995; 333: 1437-43.
8. Lomashvili KA, MonierFaugere MC, Wang X, Malluche HH, O'Neill WC. Effect of bisphosphonates on vascular calcification and bone metabolism in experimental renal failure. Kidney Int 2009; 75(6): 617-25.
9. Trabulus S, Altiparmak MR, Apaydin S. Treatment of renal transplant recipients with low bone mineral density: a randomized prospective trial of alendronate, alfacalcidol and alendronate combined with alfacalcidol. Transplant Proc 2008; 40: 160-6.
10. Negri AL. Vascular calcifications in chronic kidney disease: are there new treatments? Current Vascular Pharmacology. 2005; 3(2): 181-4.
11. Liu S, Gupta A, Quarles LD. Emerging role of fibroblast growth factor 23 in a bone-kidney axis regulating systemic phosphate homeostasis and extracellular matrix mineralization. Curr Opin Nephrol Hypertens 2007; 16: 329-35.
12. Klawansky S, Komaroff E, Cavanaugh PFJ, Mitchell DY, Gordon MJ, Connelly JE et al. Relationship between age, renal function and bone mineral density in the US population. Osteoporosis Int 2003; 14: 570-6.
13. Riggs BL, Melton LJ, Robb RA, Camp JJ, Atkinson EJ, McDaniel L et al. Population based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. J Bone Miner Res 2004; 19(12): 1945-54.
14. Harris ST, Gertz BJ, Genant HK, Eyre DR, Survill TT, Ventura JN et al. The effect of short term treatment with alendronate on vertebral density and biochemical markers of bone remodeling in early postmenopausal women. J Clin Endocrinol Metab 1993; 76: 1399-406.
15. Wetmore JB, Benet LZ, Kleinstuck D, Frassetto L. Effects of short-term alendronate on bone mineral density in haemodialysis patients. Nephrol 2005; 10(4): 393-9.
16. Shahbazian H, Tamadon MR, Mowla SK, Shayanpour S, Hayati F, Shojaii M et al. Effect and safety of alendronate on bone density in patients with chronic kidney disease; a controlled double blind randomized clinical trial. J Parathyroid Dis 2016; 4(1): 3-6.
17. Shahbazian H, Mowla K, Shahbazian HB, Peydayesh B, Ehsanpour A. Efficacy and safety of alendronate in the prevention of bone loss in renal transplant recipients. Indian J Nephrol 2007; 17: 61-5
18. Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A et al.. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. J Bone Miner Res 2007; 22(4): 503-8.
19. Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V. Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab 2004; 89(9): 4246-53.
20. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG. Effect of alendronate on vascular calcification in CKD stages 3 and 4: a pilot randomized controlled trial. Am J Kidney Dis 2010; 56(1): 57-68.
21. Ylitalo R, Kalliovalkama J, Wu X, Kankaanranta H, Salenius JP, Lahteenmaki T et al. Accumulation of bisphosphonates in human artery and their effects on human and rat arterial function in vitro. Pharmacol Toxicol. 1998; 83: 125-31.

Резиме

ЕФЕКТИ НА КРАТКОРОЧНОТО ВНЕСУВАЊЕ АЛЕНДРОНАТ ЗА МИНЕРАЛНАТА КОСКЕНА ГУСТИНА КАЈ ПАЦИЕНТИТЕ СО ХРОНИЧНА БУБРЕЖНА БОЛЕСТ

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Историја: Остеопорозата е многу распространета кај пациентите со хронична бубрежна болест (ХББ) и се карактеризира со ниска коскена маса, што доведува до намалена коскена сила. Таа е поврзана со зголемен ризик од фрактура, со што се зголемува морбидитетот и морталитетот. Внесувањето на бисфосфонат го намалува ризикот од фрактури кај постменопаузалните жени со остеопороза. Постојат ограничени студии кои покажуваат ефекти на краткотрајното внесување на алендронат за минералната коскена густина кај пациентите со остеопороза и со ХББ на преддијализа.

Методи: Оваа студија беше спроведена на педесет возрасни пациенти со хронична бубрежна болест. Пациентите беа поделени во две групи. Групата А се состоеше од седумнаесет пациенти со стадиум 3 на ХББ (eGFR 45-30 ml/min / 1,73 m^2), а групата Б имаше триесет и три пациенти со стадиум 4 на ХББ (eGFR 30-15 ml/min / 1,73 m^2). Студијата вклучуваше машки пациенти меѓу 18 и 75 години и предменопаузни небремени жени постари од 18 години. Сите пациенти беа со остеопороза со Т-резултат <-2,5 на DEXA-скенирање. На пациентите им беше давана таблета алендронат од 70 mg еднаш неделно во текот на шест недели. Реналните параметри, паратироидниот хормон, калциумот, фосфорот и нивоата на алкална фосфатаза беа анализирани во почетокот и на шест месеци. Нивото на серум (iPTH) (pg/ml) беше измерено со методот на хемилуминисцентен имунолошки тест (CLIA), а нивото на серумскиот 25 хидрокси витамин Д (ng/ml) се мереше со методот со ензимски поврзан имуносорбентен тест (ELISA). Минералната коскена густина на масата (BMD) беше измерена на почетокот и по шест месеци, со двојна енергетска рендген-апсорптиометрија кај лумбалниот ’рбет и вратот на бутната коска и беа вклучени најниските вредности. Резултатите беа добиени со Т-резултат, Z-резултат и минералната коскена густина (g/cm^2).

Резултати*:* Минералната коскена густина, Т-резултатот и Z-резултатот се зголемиле во двете групи по шест месеци со статистички значајна разлика во групата на третман. Во групата А, Т-резултатот, Z-резултатот и минералната коскена густина (g/cm^2) се зголемиле од -2,60 ± 0,086, -2,13 ± 0,28 и 0,80 ± 0,008 на почетокот до -2,57 ± 0,097, -2,11 ± 0,26 и 0,81 ± 0,008 по шест месеци. Во групата Б, Т-резултатот, Z-резултатот и минералната коскена густина (g/cm^2) се зголемиле од -3,17 ± 0,24, -2,82 ± 0,33 и 0,738 ± 0,03 до -3,16 ± 0,25, -2,66 ± 0,95 и 0,743 ± 0,03 по шест месеци со статистички значајна разлика. eGFR е намален кај двете групи, но со разлика што беше статистички незначајна (P>0,05). Серумските нивоа на iPTH се зголемиле по шест месеци кај двете групи со статистички незначителна разлика. По шест месеци имаше зголемување на серумскиот калциум и намалување на нивото на серумскиот фосфат, но разликата беше статистички незначајна (p>0,05). Вредностите на SAP се намалија по шест месеци и во двете групи со статистички незначителна разлика. Главниот несакан ефект во групата со алендронат беше појавата на симптоми на гастроезофагеален рефлукс кај двајца субјекти.

Заклучок*:* Алендронатот со ниски дози, кој се внесува со ограничено времетраење, се чини дека е добро толериран кај пациенти со ХББ. Минералната коскена густина се зголеми во двете групи, што сугерира за ефект на алендронатот за зачувување на коските.

Клучни зборови: Алендронат, остеопороза, хронична бубрежна болест, бисфосфонат.