ORIGINAL ARTICLE

Effect of Cholecalciferol on Proteinuria in Patients of Chronic Kidney Disease III & IV

MUHAMMAD MOHSIN RIAZ[1], GHULAM ABBAS QADRI[2], NABIHA RIZVI[3]
[1]*Senior Registrar Nephrology, Fatima Memorial Hospital, Shadman, Lahore.*
[2]*Senior Registrar Nephrology, Shaheed Muhtarma Benazir Bhutto Medical University Larkana*
[3]*Assistant Professor Nephrology, Central Park Teaching Hospital*
Correspondence to: Dr. Ghulam Abbas Qadri, Email: abbasqadri33@yahoo.com, Ph: 03116563958

ABSTRACT

Objective: To determine the mean decrease in spot urinary protein to creatinine ratio after cholecalciferol (vitamin D_3) replacement, in CKD III-IV patients with vitamin D deficiency/ insufficiency.

Methodology: This Quasi experimental study was conducted at Nephrology Department at Fatima Memorial Hospital, Lahore. We enrolled 100 cases with age range 18-70 yrs in both gender and those with CKD stage III and IV, and Vitamin D insufficiency and deficiancy. All cases with Vitamin D deficiency/ insufficiency were supplemented with cholecalciferol. Baseline levels of 25(OH) D, serum creatinine, urinary protein and creatinine (single spot urinary sample taken between 08-11 a.m.) was taken and later measured every two months, for a total period of six months.

Results: In our study, mean age was 49.81+13.10 years, 61%(n=61) were male and 39%(n=39) were females, 83%(n=83) had class III and 17%(n=17) had class IV, 79%(n=79) had vitamin D deficiency while 21%(n=21) had insufficiency, mean pre treatment creatinine values were calculated as 2.13+0.75 while 1.66+0.74 in post treatment period, p value was calculated as 0.0001, mean pre treatment protein to creatinine ratio was 1.97+0.34 while 0.46+0.10 in post treatment period, p value was calculated as 0.000, mean decrease in pre and post treatment serum creatinine level was recorded as 0.46+0.01, mean decrease in pre and post treatment serum protein to creatinine level was recorded as 1.51+0.28.

Conclusion: We concluded that a significant mean decrease in spot urinary protein to creatinine ratio after cholecalciferol (vitamin D3) replacement was recorded in CKD III-IV patients with vitamin D deficiency/ insufficiency but our reuslts are primary and multicenter trials are required to validate our findings.

Keywords: Chronic kidney disease, vitamin D deficiency/insufficiency, cholecalciferol, spot urinary protein to creatinine ratio

INTRODUCTION

Chronic kidney disease (CKD), defined as a decrease in the GFR to less than 60 ml per minute per 1.73 m^2 for three or more consecutive months. A recent survey suggested prevalence of 20% among population above 40 years.[1]

Vitamin D deficiency is prevalent in population worldwide and especially in CKD patients. In Pakistan 72.2% of adult population is estimated to be deficient of vitamin D.[2] It's insufficiency is more prevalent in CKD patients due to uraemia and proteinuria.[3-5] It reaches up to 79% and 85% in CKD stage III and IV respectively. Vitamin D deficiency is an independent risk factor for disease progression and mortality in patients of CKD.[6]

Proteinuria is an important surrogate marker for progress of CKD.[7] Decreasing proteinuria improves the outcome in patients of CKD.[8] Established regimes for decreasing proteinuria includes ACEi (Angiotensin Converting Enzyme inhibitors), ARBs (Angiotensin Receptor Blockers), and calcium channel blockers (CCB). They act by inhibiting the RAAS (Renin Angiotensin Aldosterone System) and decreasing inflammatory mediators independent of their anti-hypertensive effects.[9,10]

Studies have shown the renoprotective, antiproteinuric, anti-inflammatory and cardiovascular protective effects of activated vitamin D and its analogues. These effects are mediated through the activation of Vitamin D receptor (VDR).[2, 11-17] A recent study by Molina P et al., performed on 50 patients showed beneficial effects of cholecalciferol on decreasing albuminuria in CKD III and IV patients. It showed a decrease in spot urinary albumin to creatinine ratio of 117 ± 18.75 mg/g (i.e. 0.117 ± 0.02 g/g) from baseline over treatment duration of six months.[18]

Taken together above data suggests a therapeutic potential of vitamin D to delay progression of CKD.[19] Several therapeutic options are available to correct the Vitamin D levels including nutritional vitamin D, pro hormones and active hormones.[4] Nutritional Vitamin D has several advantages over activated vitamin D; it is cheaper and is safer in terms of mineral metabolism, therefore frequent monitoring is not required. Recent guidelines from Kidney Disease Outcome Quality Initiative (KDOQI) recommends the replacement of 25(OH) D_3 before treatment with active vitamin D analogues in stage III and IV.[19]

The rationale of this study is to evaluate the renoprotective effects of cholecalciferol in our population since no study is available in local literature. We will monitor decrease in proteinuria after replenishing vitamin D levels using oral cholecalciferol in CKD III & IV patients who are either insufficient or deficient of vitamin D, monitored by 25(OH) D levels.

METHODOLOGY

This Quasi experimental study was conducted at Nephrology Department at Fatima Memorial Hospital, Lahore. We enrolled 100 cases with age range 18-70 yrs in both gender and those with CKD stage III and IV, and Vitamin D insufficiency and deficiancy. We excluded all cases with Obstructive uropathy, female patients presenting with gestational amenorrhea and positive urine

pregnancy test, patients with CLD, having coarse echo textured liver and those with CHF having ejection fraction < 30%. All cases with Vitamin D deficiency/ insufficiency were supplemented with cholecalciferol. Baseline levels of 25(OH) D, serum creatinine, urinary protein and creatinine (single spot urinary sample taken between 08-11 a.m.) was taken and later measured every two months, for a total period of six months. We used 20th version of SPSS for analysis of data. Paired sample t test was applied to determine the significant difference pre and post treatment creatinine values.

RESULTS

Mean pre treatment creatinine values were calculated as 2.13+0.75 while 1.66+0.74 in post treatment period, p value was calculated as 0.0001, showing a significant difference, mean pre treatment protein to creatinine ratio was calculated as 1.97+0.34 while 0.46+0.10 in post treatment period, p value was calculated as 0.000, showing a significant difference. (Table No. 1)

Mean decrease in pre and post treatment serum creatinine level was recorded as 0.46+0.01, mean decrease in pre and post treatment serum protein to creatinine level was recorded as 1.51+0.28. (Table No. 2)

Table 1: Mean Pre and Post Serum Creatinine and Protein to Creatinine Ratio

Serum Creatinine Levels			P value
Pre and post treatment	Mean	SD	
Pre treatment	2.13	0.75	0.0001
Post treatment	1.66	0.74	
Serum creatinine and protein to creatinine ratio			0.000
Pre treatment	1.97	0.34	
Post treatment	0.46	0.10	

Table 2: Mean Decrease in Pre and Post Treatment Serum Creatinine and Protein to Creatinine Ratio

	Mean	SD
Serum creatinine	0.46	0.01
Serum Protein to creatinine	1.51	0.28

DISCUSSION

The current study was conducted with the view to evaluate the renoprotective effects of cholecalciferol in our population since no study is available in local literature. In our study, mean+sd was calculated as 49.81+13.10 years, 61%(n=61) were male and 39%(n=39) were females, 83%(n=83) had class III and 17%(n=17) had class IV, 79%(n=79) had vitamin D deficiency while 21%(n=21) had insufficiency, mean pre treatment creatinine values were calculated as 2.13+0.75 while 1.66+0.74 in post treatment period, p value was calculated as 0.0001, showing a significant difference, mean pre treatment protein to creatinine ratio was calculated as 1.97+0.34 while 0.46+0.10 in post treatment period, p value was calculated as 0.000, showing a significant difference, mean decrease in pre and post treatment serum creatinine level was recorded as 0.46+0.01, mean decrease in pre and post treatment serum protein to creatinine level was recorded as 1.51+0.28.

A recent study by Molina P et al., performed on 50 patients showed beneficial effects of cholecalciferol on decreasing albuminuria in CKD III and IV patients. It showed a decrease in spot urinary albumin to creatinine ratio of 117 ± 18.75 mg/g (i.e. 0.117 ± 0.02 g/g) from baseline over treatment duration of six months,[18] the findings of our study are in agreement with the above study which shows the efficayc of Colecalciferol.

Kim SM and ohters[20] in their trial evaluated supplementation effect of cholecalciferol and revealed that 52 cases(76.5%) reached levels of 25-hydroxy vitamin D (25(OH)D) of 30 ng/mL or more at 12 weeks, whereas after 24 weeks 89.7%(n=61) restored vitamin D levels.

Guillaume Jean and others in a recent trial explains that despite various unanswered queries, most of the data supports vitamin D supplementation in CKD patients.[21]

Cholecalciferol is prescribed as oral 100,000 IU monthly doses by French nephrologists and achieves normal level of 25(OH)D in more than 85% of the cases.[22]

The France nephrologists used to prescribe cholecalciferol as oral 100,000 IU monthly doses, which allow normalization of serum 25(OH)D level in >85% of cases.[23]

Another study by Matias PJ and colleagues[24] evaluated supplementation effect of oral cholecalciferol on inflammation, mineral metabolism and caradiac dimension parameters in cases with long hemodialysis and concluded that cholecalciferol was found to be easy and cost-effective way of treatment of CKD.

The limitation the current study includes that we did not record 25(OH) D after the six months of treatment, on the otherhand we are unable to compare the effect of cholecalciferol supplementation with regards to decrease in serum creatinine due to lack of availability of the data. However, our results may be considered as primary and multicenter trials on a larger sample size may be done to validate our findings.

CONCLUSION

We concluded that a significant mean decrease in spot urinary protein to creatinine ratio after cholecalciferol (vitamin D3) replacement was recorded in CKD III-IV patients with vitamin D deficiency/insufficiency but our reuslts are primary and multicenter trials are required to validate our findings.

REFERENCES

1. Jafar TH. The growing burden of chronic kidney disease in Pakistan. NEJM 2006;354;10:995-6
2. Mahmood K, Akhtar ST, Talib A, Haider I. Vitamin D status in a population of healthy adults in Pakistan**.** Pak J Med Sci 2009;25:545-50.
3. Dininz HF, Romao MF, Elias RM, Romao Junior JE. Vitamin D deficiency and insufficiency in patients with chronic kidney disease. J Bras Nephrol 2012;34:58-63.
4. Tang J. Vitamin D and Its Role in chronic kidney disease. 2009. www.nephrologyrounds.org;7.
5. Martin KJ, González EA. Vitamin D supplementation in CKD. Clinical Nephrology 2011;75:286-93.
6. Ravani P, Malberti F, Tripepi G, Pecchini P, Cutrupi S, Pizzini P. Vitamin d levels and patient outcome in chronic kidney disease. Kidney Int 2009;75:88-95.
7. Levey AS, Cattran D, Freidman A, Millae WG, Sedor J, Tuttle K. Proteinuria as a surrogate outcome in CKD:Report of a scientific workshop sponsored by the national kidney foundation and the US food and drug administration. AJKD 2009;54:205-26.

8. Jørgensen HS, Winther S, Povlsen JV, Ivarsen P. Effect of vitamin-D analogue on albuminuria in patients with non-dialyzed chronic kidney disease stage 4–5:a retrospective single center study. BMC Nephrology 2012;13:102.
9. Yilmaz MI, Carrero JJ, Martín-Ventura JL, Sonmez A, Saglam M, Celik T. Combined therapy with renin – angiotensin system and calcium channel blockers in type 2 diabetic hypertensivepatients with proteinuria:effect s on soluble TWEAK, PTX3, and flow-mediated dilation. Clin J Am Soc Nephrol 2010;5(7):1174-81.
10. Robert D, Toto, Tian M, Fakouhi K, Champion A, Becher P. Effects of calcium channel blockers on proteinuria in patients with diabetic nephropathy. JCH 2008;10:761-9.
11. Bonakdaran S, Hami M, Hatefi A. The effects of calcitriol on albuminuria in patients with type-2 diabetes mellitus. Saudi J Kidney Dis Transpl 2012;23:1215-20.
12. Yang L, Ma J, Zhang X, Fan Y, Wang L. Protective role of the vitamin D receptor. Cell Immunol 2012;279:160-6.
13. Sonneveld R, Ferre S, Hoenderop JG, Dijkman HB, Berden JH, Bindels RJ. Vitamin D down-regulates TRPC6 expression in podocyte injury and proteinuric glomerular disease. Am J Pathol 2013;182:1196-204.
14. Fukaqawa M, Komaba H, Hamano T. Vitamin D supplementation in renal disease:is calcitriol all that is needed? Scand J Clin Lab Invest Suppl 2012;243:120-3.
15. Liu LJ, Lv JC, Shi SF, Chen YQ, Zhang H, Wang HY. Oral calcitriol for reduction of proteinuria in patients with IgA nephropathy:a randomized controlled trial. Am J Kidney Dis 2012;59:67-74.
16. Dusso AS. Renal vitamin D receptor expression and vitamin D renoprotection. Kidney Int2012;81:937-9.
17. Krairittichai U, Mahannoupkul R, Bunnaq S. An open label, randomized controlled study of oral calcitriol for the treatment of proteinuria in patients with diabetic kidney disease. J Med Assoc Thai 2012;95:41-7.
18. Molina P, Górriz JL, Molina MD, Peris A, Beltrán S, Kanter J. The effect of cholecalciferol for lowering albuminuria in chronic kidney disease:a prospective controlled study. Nephrol Dial Transplant. 2014;29(1):97-109.
19. Kim SM, Choi HJ, Lee JP, Kim DK, Oh YK, Kim YS, Lim CS. Prevalence of vitamin D deficiency and effects of supplementation with cholecalciferol in patients with chronic kidney disease. J Ren Nutr. 2014;24(1):20-5.
20. Matias PJ, Jorge C, Ferreira C, Borges M, Aires I, Amaral T, Gil C, et al. Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters. Clin J Am Soc Nephrol. 2010;5(5):905-11.
21. Kim SM, Choi HJ, Lee JP, Kim DK, Oh YK, Kim YS, Lim CS. Prevalence of vitamin D deficiency and effects of supplementation with cholecalciferol in patients with chronic kidney disease. J Ren Nutr. 2014;24(1):20-5.
22. Jean G, Souberbielle JC, Chazot C. Vitamin D in Chronic Kidney Disease and Dialysis Patients. Nutrients. 2017;9(4):328.
23. Jean G., Souberbielle J.C., Chazot C. Monthly cholecalciferol administration in haemodialysis patients: A simple and efficient strategy for vitamin D supplementation. Nephrol. Dial. Transpl. 2009;24:3799–3805.
24. Matias PJ, Jorge C, Ferreira C, Borges M, Aires I, Amaral T, Gil C, et al. Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters. Clin J Am Soc Nephrol. 2010;5(5):905-11.