



# Safety & Efficacy of Denosumab in Chronic Kidney Disease Patients in Dubai Hospital: Single Center Experience

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**Abstract:** Chronic kidney disease (CKD) patients has not only higher risk of bone fractures due to low bone mineral density & poor bone quality, but also carries high risk of cardiovascular disease due to soft tissue calcification in conjunction with secondary hyperparathyroidism and high phosphate. Bisphosphonates use was limited in CKD patients due to nephrotoxicity while Denosumab were found safe & effective. Purpose of study was to report efficacy & safety of denosumab in different stages of CKD, also to compare it with normal renal function patients. With help of medical software, data was collected for patients who received denosumab for osteoporosis, osteopenia or fragile fractures at least for 6 months. 90 patients were included (Osteoporosis 53.34%, fractures 25.56% & osteopenia 21.11%), 80% had CKD (Stage III: n=32,44.44%, Stage V: n=23, 31.94% & Stage IV n=11, 15.27%) while 20% had normal renal functions (NKF). CKD patients belonged to older age group than NKF patients ( $79\pm 13$  vs  $73.06\pm 13.63$ ,  $p<0.05$ ). Osteoporosis (CKD vs NKF: 47.22% vs 77.78%,  $p<0.05$ ) & Osteopenia (CKD vs NKF: 20.83% vs 22.22%,  $p>0.05$ ) were more common in NKF patients, while fractures were more common in CKD patients (CKD vs NKF: 29.16% vs 11.11%  $p=>0.05$ ). After denosumab therapy, there was not much improvement in osteopenia (pre & post in CKD: 20.83% vs 19.45%,  $p>0.05$ ) or osteoporosis (pre & post 47.22% vs 45.80%  $p=>0.05$ ) in CKD patients, while fracture frequency increased (pre & post in CKD: 29.16% vs 34.70%,  $p=>0.05$ ) however these findings were not statistically significant. After Denosumab therapy, there was significant drop in median (IQR) corrected serum calcium {pre & post: 9.4(0.68) vs 9.2 (0.72),  $p<0.05$ }, while increase in parathyroid hormone {PTH pre & post: 46.5(74.77) vs 68.25(157.17),  $p<0.05$ } & 25 hydroxy vitamin D {pre & post denosumab: 28.50(17.65) vs 37.45(25.12),  $p<0.05$ } in CKD patients, whereas there was no significant change in phosphate. Positive effects of denosumab on BMD were not appreciated in our CKD population. Hypocalcemia is significant side effect and can be dealt with close monitoring, aggressive diet to provide calcium & vitamin D, awareness of doctors & health care professionals to set up integrated multidisciplinary care.

**Keywords:** Osteoporosis, Osteopenia, Denosumab, Chronic Kidney disease.

## INTRODUCTION

Osteoporosis and impaired kidney functions exert negative impact on bone health (1). Chronic kidney disease (CKD) patients has higher risk of bone fractures & associated with morbidity & mortality due to low bone mineral density & poor bone quality (2,3). World Health organization set the the T-score  $\leq 2.5$  as diagnostic limit of osteoporosis (4). Bone mineral disorders associated with CKD includes mineral metabolism disorder, soft tissue

calcification in conjunction with secondary hyperparathyroidism and high phosphate, carries high risk of cardiovascular disease (5,6). Keeping strong association between CKD & osteoporosis in mind, such medicine is needed that can effectively & safely treat osteoporosis without further causing deterioration of renal functions. Endocrinology scientific society established osteoporosis treatment guidelines on the basis of glomerular filtration rate, also advise not to use certain treatment options in advance CKD (7). Nitrogen containing bisphosphonates introduction was a major step in osteoporosis treatment, however its use was limited in CKD patients due to fear of nephrotoxicity and lack of clear recommendation (8). Denosumab is human monoclonal antibody directed against RANKL (receptor activator of nuclear factor kappa B ligand) reduce function & formation of osteoclast (9), was approved for use in osteoporosis in 2010, and for osteoporosis in CKD in 2018 (10). In this Study, we compare the efficacy & safety of denosumab in different stages of CKD with normal renal function patients.

## **METHODS**

### **Study Design**

This retrospective observational study was performed for a period from 01/01/2018 to 1/6/2024. Osteoporosis or osteopenia patients were included in study from Rheumatology clinic, Dubai hospital who received denosumab for T score of <2.5 or for fragile fractures due to osteopenia. As per unit protocol for treatment of osteopenia or osteoporosis, Denosumab was prescribed 60 mg monthly for at least 6 months. With help of medical software Epic, Patient's data was analyzed and divide patients into two groups according to normality of renal functions i.e. CKD & Normal renal functions (NKF). Primary goal of study was to report improvement in T score & reduction in fracture recurrence in CKD patients after denosumab treatment, also to observe changes in serum calcium, 25 hydroxy vitamin D & parathyroid hormone level after denosumab treatment in both groups.

### **Statistical Methods**

Mean  $\pm$  standard deviation is used to describe continuous variables and for normally distributed as well as non-normally distributed data median with interquartile range (IQR) values are used. Categorical variables were expressed as frequency and percentage. For normally distributed and non-normally distributed continuous variables, Independent t-test and Mann-Whitney test were used respectively, also Pearson's  $\chi^2$  test or Fischer's exact test were used to compare categorical data. A p-value of <0.05 was considered statistically significant. SPSS (Statistical Package for the Social Sciences) version 20 was used for statistical analysis.

## **RESULTS**

Total 90 patients received denosumab in study period, their mean age was  $76.20 \pm 12.33$  years and 68.88% (n=62) were female. Chronic kidney disease (CKD) was most common comorbid (80%, n=72), followed by hypertension (77.78%, n=70), ischemic heart disease (22.22%, n=20), heart failure (8.89%, n=8), diabetes mellitus & chronic obstructive pulmonary disease (6.67%, n=6 each). Osteoporosis was reported in 48 (53.34%) patients,

while fractures & osteopenia was observed in 25.56% (n=23) & 21.11% (n=19) patients respectively. Before denosumab therapy, median (IQR) corrected serum calcium, parathyroid hormone & 25 hydroxy vitamin D was 9.4 (0.78) mg/dl, 21.5(73.15) & 28.65(20) respectively, also mean phosphate was  $3.88 \pm 0.94$  mg/dl. In Our study population, 80% (n=72) patients were suffering from CKD while 20% (n=18) patients had normal renal functions (NKF). Among CKD patients, 32(44.44%) patients were suffering from stage III, and 31.94% (n=23) were suffering from stage V & 15.27% (n=11) from stage IV. CKD patients belonged to elder age group than NKF patients (Mean $\pm$ SD age in Years CKD vs NKF:  $79 \pm 13$  vs  $73.06 \pm 13.63$ ,  $p < 0.05$ ), also female were predominant gender in both group of patients (Female gender CKD vs NKF: 50(69.44%) vs 12(66.67%),  $p > 0.05$ ). Osteoporosis & Osteopenia were more common in NKF patients {Osteoporosis CKD vs NKF: 34 (47.22%) vs 14 (77.78%),  $p < 0.05$ }, Osteopenia CKD vs NKF: 15 (20.83%) vs 4 (22.22%),  $p > 0.05$ }, while fractures were more common in CKD patients (Fractures CKD vs NKF: 21 (29.16%) vs 2 (11.11%),  $p > 0.05$ ). Before denosumab therapy in CKD patients, median (IQR) corrected serum calcium, parathyroid hormone & 25 hydroxy-vitamin D was 9.4(0.68) mg/dl, 46.5(74.77) & 28.50(17.65) respectively, also mean phosphate was  $3.95 \pm 0.99$  mg/dl. After denosumab therapy, there was not much improvement in osteopenia or osteoporosis in CKD patients {Osteoporosis pre & post denosumab in CKD: 34 (47.22%) vs 33(45.80%)  $p = > 0.05$ , Osteopenia pre & post denosumab in CKD: 15 (20.83%) vs 14(19.45%),  $p > 0.05$ }, while fracture frequency increased (Fractures pre & post denosumab in CKD: 21 (29.16%) vs 25(34.70%),  $p > 0.05$ ) however these findings were not statistically significant. After Denosumab therapy, there was significant drop in median (IQR) corrected serum calcium {median (IQR) Ca mg/dl in CKD pre & post denosumab: 9.4(0.68) vs 9.2 (0.72),  $p < 0.05$ }, while increase in parathyroid hormone & 25 hydroxy vitamin D in CKD patients {PTH in CKD pre & post denosumab: 46.5(74.77) vs 68.25(157.17),  $p < 0.05$ , 25 OH Vit D in CKD pre & post denosumab: 28.50(17.65) vs 37.45(25.12),  $p < 0.05$ }, whereas there was no significant change in phosphate.

## DISCUSSION

The positive effects of long term use of denosumab in context of increasing bone mineral density & reducing fractures were already authenticated by large clinical trials (11,12), also adherence & cost effectiveness may be better for denosumab as compared to bisphosphonates (13). Denosumab effectively increases BMD also lack of metabolism & clearance by kidneys makes it suitable candidate to use in CKD patients as compared to bisphosphonates (14,15). Block et al and others observed no effect on denosumab pharmacokinetics or pharmacodynamics while using in CKD patients suggested that dose adjustment was not required, also they found it not dialysable (16-18). We used denosumab at standard dose in CKD as well as NKF patients, did not notice adverse events or serious infections, also kidney functions remain stable over study period, similar results were observed by Bonani et al (19).

### **Efficacy of Denosumab**

Superiority of denosumab in improving femoral bone mineral density in CKD stage II-V & renal transplant patients was appreciated by Chen et al in his systematic review of 17 studies

in 2022 (20A). Iseri et al (21A). compared denosumab & alendronate in hemodialysis patients in his randomized controlled trial, observed denosumab induced significantly reduction in bone resorption markers & increase in lumbar spine bone mineral density (BMD). Bonani et al (19) reported improved BMD in lumbar spine & total hip after one year denosumab treatment in renal transplant recipients. In our study, there was no statistically significant improvement in BMD after denosumab treatment in CKD patients, rather increase in incidence of fractures was observed.

### **Denosumab Associated Hypocalcemia (DAH) & Changes in Parathyroid Hormone (iPTH):**

The reported incidence of DAH is up to 42%, usually occur 7-20 days after initiation of denosumab, and touches to lowest point in first two weeks to two months according to meta analysis of six observational studies including 84 dialysis dependent patients (18). Festuccia et al reported lower incidence of DAH (25%) in his retrospective study and there was no hospital admissions needed (20). We have observed incidence DAH 22.20% in CKD patients (43.47% in GFR <15 ml/min & 12.24% in GFR >15 ml/min), significant drop in corrected serum calcium level despite patients were on cholecalciferol and calcium carbonate, lowest corrected serum calcium level was 5.7 mg/dl. Iseri et al reported that secondary hyperparathyroidism patients are more prone to develop DAH (21), they also found denosumab safe to use in hemodialysis patients & successfully prevented DAH with two weeks course of calcium supplement (21), however Kunizawa et al found dialysis patients at high risk of DAH despite receiving active vitamin D and/or calcium carbonate (22), also Nanmoku et al used this side effect of denosumab to treat hypercalcemia in renal transplant recipients (23). Intravenous Iron use in combination with denosumab is reported risk factor of severe hypocalcemia by Smyth et al (24), and possible culprit is fibroblast growth factor, higher levels were observed in these patients also lead to hypophosphatemia that weakens parathyroid hormone (PTH) response and causes DAH (25). We have observed significant increase in PTH in 22.20% CKD patients after denosumab injection, this could be due to compensatory low serum calcium levels (26). Post denosumab Increase in PTH is also reported in many case reports and clinical trials (16-19, 21,27), it can occur within first week of denosumab and effect last up to 6 months (26,28-29). Calcium & calcitriol is advised by some authors to avoid hypocalcemia & compensatory increase in Parathyroid hormone. Chen et al reported hypocalcemia (DAH) in one third of dialysis patients and was corrected with calcium & calcitriol, also later helped in controlling PTH surge. Use of Calcitriol & calcium for prevention must be according to patient's calcium and PTH profile (29). In Kidney transplant recipients on denosumab, addition of calcitriol with cholecalciferol was necessary to deal with DAH & compensatory rise in PTH. Secondary increase in PTH induced by DAH may be used in adynamic bone disease patients (30). *Relapse of bone turnover & fracture risk after discontinuation of denosumab is observed by Broadwel et al (11), Cummings et al emphasized that in case of contraindication for denosumab or drug to be stopped must be switched with antiabsorptive agent (12).*

### **CONCLUSION**

Due to effects on bone mineral dynamics, osteoporosis is quite common in CKD patients. Compared to bisphosphonates, Denosumab increases bone density, also it is neither

metabolized or excreted by the kidneys nor affect renal functions, so found safe to use in CKD patients, however its positive effects on BMD were not appreciated in our CKD population. Hypocalcemia is significant side effect of denosumab, and can be dealt with close monitoring, aggressive diet to provide calcium & vitamin D, awareness of doctors & health care professionals to set up integrated multidisciplinary care. The occurrence of DAH in advance CKD patients especially is a concern, further research is needed to comprehend long term side effects of denosumab in CKD and dialysis patients.

**Table 1: Characteristics of patients**

	Total Patients (n=90)	CKD (n=72, 80%)	NFK (n=18, 20%)	p-value
Age in Years Mean±SD	76.20±12.33	79±13	73.06±13.63	0.30349201
Gender				
Female	62(68.88)	50(69.44)	12(66.67)	0.819886254
Co-morbid				
Diabetes Mellitus	6 (6.67)	5(6.95)	1(5.56)	0.832662106
Hypertension	70(77.78)	56(77.78)	14(77.78)	1
Heart failure	8(8.89)	7(9.72)	1(5.56)	0.578485769
IHD	20(22.22)	16(22.20)	4(22.20)	1
COPD	6 (6.67)	5(6.95)	1(5.56)	0.832662106
Chronic Kidney disease (CKD)	72(80)			
CKD-II	6(8.33)			
CKD-III	32(44.44)			
CKD-IV	11(15.27)			
CKD-V	23(31.94)			
Dexa scan results				
Osteopenia: 17	19(21.11)	15 (20.83)	4 (22.22)	0.897241106
Osteoporosis: 43	48 (53.34)	34 (47.22)	14 (77.78)	<0.05
Fracture	23 (25.56)	21 (29.16)	2 (11.11)	0.116218692

**Table 2: Calcium, phosphate & PTH for CKD patients, pre & Post Denosumab**

	CKD (n=72, 80%)		
Age in Years Mean±SD	79±13		
Gender			
Female	50(69.44)		
Co-morbid			
Diabetes Mellitus	5(6.95)		
Hypertension	56(77.78)		
Heart failure	7(9.72)		
IHD	16(22.20)		
COPD	5(6.95)		
Chronic Kidney disease (CKD)			
CKD-II	6(8.33)		
CKD-III	32(44.44)		
CKD-IV	11(15.27)		
CKD-V	23(31.94)		
	Before Denosumumab	After Denosumamb	
Osteopenia: 17	15 (20.83)	14(19.45)	
Osteoporosis: 43	34 (47.22)	33(45.80)	
Fracture	21 (29.16)	25(34.70)	
Calcium mg/dl, Median (IQR)	9.4(0.68)	9.2 (0.72)	<0.05
< 8.5 mg/dl	5(6.94)	16(22.20)	
8.5-10.2 mg/dl	61(84.72)	51(70.80)	
>10.2 mg/dl	6(8.33)	5(6.95)	

Phosphatmg/dl, Mean±SD	3.95±0.99	3.80±0.54	
< 3.5:	17(23.61)		
3.5-5.5:	49(68.05)		
>5.5:	6(8.33)		
PTH, Median (IQR)	46.5(74.77)	68.25(157.17)	<0.05
Hi:	16(22.20)	7(9.52)	
Low:	43(59.70)	36(50)	
N:	13(18.05)	29(40.48)	
25 OH VitD, Median (IQR)	28.50(17.65)	37.45(25.12)	<0.05
>30:	33(45.83)	43(59.67)	
20-30:	25(34.70)	17(24.20)	
<20:	14(19.40)	12(16.12)	

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**Statement of Ethics & Ethical Approval:** This research complies with the guidelines for human studies and is conducted ethically in accordance with the Declaration of Helsinki. The study was approved by Dubai Scientific Research Ethics Committee, Decision DSREC-12/2024\_11, Date December 17, 2024. Patients who visited Dubai Hospital in Dubai Health Authority signed a general informed consent submitted in the EMR (SALAMA) to use their de-identified data for Research and Education purposes.

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**Data Sharing Statement:** Research data is not available publicly due to ethical & legal reasons, however it is available on request from corresponding author.

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