Effect of Vitamin-D Therapy in Retarding the Progression of Diabetic Nephropathy: A Randomized Double-Blind Placebo-Controlled Trial

Biplob Kumar Barua[1*] Mohammad Abdul Kader[2] Syed Mahtab-Ul-Islam[3]
Marina Arjumand[4] Mohammad Mamunur Rashid[5] Md Faizur Rahman[6] Md Nurul Huda[7] Pradip Kumar Dutta[8]

Abstract

Background: The Renin–Angiotensin System (RAS) may contribute to proteinuria and progression of Diabetic Nephropathy (DN). Vitamin D therapy is found to have an inhibitory effect on the RAS. The aim of this study was to evaluate the effects of Vitamin D therapy in retarding the progression of DN.

Materials and methods: This was a single-center, double-blind, randomized placebo-controlled study conducted in Chittagong Medical College Hospital from June 2018 to May 2019. Thirty four eligible participants were randomly allocated to two groups in a 1:1 ratio. Experimental group received oral calcitriol 0.25 micro gm once daily and control group received placebo along with standard of therapy. Patients were evaluated at baseline and subsequently at 4th, 8th and 12th weeks for outcome evaluation. Serum creatinine, eGFR, uACR levels, serum calcium level, serum phosphate level, serum PTH level and any other tests as needed were done. Per protocol principle were used to analyze the data.

Results: Fifteen patients from each group were finally completed the study and included in analysis. After 12 weeks, uACR was decreased in experimental group (Median 40.8 µg/mg) and increased in control group (Median 43.3 µg/mg). It were highly significant in comparison between two groups ($p<0.001$). Significant decrease in serum creatinine and increase in the eGFR was observed in the treatment group while in the control group, serum creatinine was increased and eGFR was decreased and it were highly significant ($p<0.001$ & $p=0.001$ respectively). In other parameters (SBP, serum phosphate and PTH) were significant in comparison between two groups at the end of study. But, changes of parameters like DBP, serum albumin and calcium were similar between two groups after 12 weeks.

Conclusion: Vitamin D oral calcitriol 0.25 micro gm capsule given daily for 12 weeks reduces urine albumin and serum creatinine levels in patients with DN.

Key words : Diabetic nephropathy; Renin angiotensin system; Vitamin-D.

1. Registrar of Nephrology
Chittagong Medical College Hospital, Chattogram.
2. Assistant Registrar of Nephrology
Chittagong Medical College Hospital, Chattogram.
3. Assistant Professsor of Nephrology
Chittagong Medical College, Chattogram.
4. Junior Consultant of Nephrology
Chittagong Medical College Hospital, Chattogram.
5. Assistant Professor of Nephrology
National Kidney Foundation, Dhaka.
6. Assistant Professor (cc) of Nephrology
Rangamati Medical College, Rangamati.
7. Professor of Nephrology
Chittagong Medical College, Chattogram.
8. Professor of Nephrology
Marine City Medical College, Chattogram.

***Correspondence: Dr. Biplob Kumar Barua**
Cell : 01711 904 6 07
E-mail: biplob.barua.dr@gmail.com

Submitted on : 13.06.2024
Accepted on : 28.07.2024

Introduction

Diabetic Nephropathy (DN) is a frequent consequence of both type 1 and type 2 Diabetes Mellitus (DM). It is commonly defined as urine albumin excretion more than 30 mg/gm.[1] Globally, DM ranks fourth in terms of causes of mortality and is a significant non-communicable illness.

In order to lower the incidence and death rate of DN, it is critical to investigate affordable and efficient treatment options given the growing prevalence of diabetes and the high expense of ESRD care.[2]

Damage to the glomeruli of the kidneys' capillaries resulted in DN.[3] The progression of DM to DN starts with microalbuminuria, which is a mild increase in urine albumin excretion. This leads to macroalbuminuria, which is marked by an increasing glomerular filtration rate. Eventually, End-Stage Renal Disease (ESRD) develops, which is characterized by glomerulosclerosis and tubulointerstitial fibrosis.[4,5,6] The primary component and often utilized indicator of DN is albuminuria.[7,8,9] Strict blood pressure and glucose management, together with RAS suppression with Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) are the mainstays of current DN treatment strategies.[9] Nonetheless, DN patients treated with

ACEIs or ARBs experienced yearly renal event rates of 15% or higher and were unable to totally prevent proteinuria.[10,11] To lessen the burden on DN patients, further therapies that can improve proteinuria are thus required.

Vitamin D is fat-soluble vitamin which binds to Vitamin D Receptor (VDR) in target cells and plays role in calcium homeostasis.[12] Previous studies revealed that vitamin D treatment reduced urinary albumin and had the potential to prevent kidney damage in DN patients.[13,14,15]

As a negative endocrine regulator of the RAS, vitamin D binds to the promotor region of the renin gene, inhibiting the cyclic AMP response element's activity and lowering the production of renin on renal mRNA.[16] In individuals suffering from IgA nephropathy and ongoing proteinuria, it had a moderate antiproteinuric effect.[17] Subsequently, a pilot research conducted by Li et al. showed that 1, 25 dihydroxytherapy treatment has positive benefits on stopping the development of DN.[18]

However, there is scarcity of study regarding the role of vitamin D in DN in our country. Therefore, this study aimed to evaluate the efficacy of oral calcitriol as an adjuvant therapy for DN patients receiving standard treatment.

Materials and methods

It was a single center, randomized double-blind placebo-controlled trial, carried out in Department of Nephrology, Chittagong Medical College Hospital from June 2018 to May, 2019 after taking approval Ethical Review committee of Chittagong Medical College, Chattogram.

Thirty four qualifying patients with Type 2 Diabetes were purposefully chosen based on the inclusion and exclusion criteria listed below. Patients with T2DM and Diabetic Kidney Disease (DKD) were eligible if they met the following criteria: eGFR <90ml/min/1.73m^2, age 18, patients with vitamin D deficiency or insufficiency, urinary albumin excretion of 30-299 microgram/24 hours in a 24-hour urine collection, 20-199 microgram/min in a timed urine collection, or 30-299 microgram/mg creatinine in a spot urine collection on at least two occasions. Exclusion criteria were patients with hypercalcaemia (>10.0mg/dl), High serum phosphate (Serum phosphate >5.2 mg/dl), patients with systolic blood pressure ≥ 140 mm of Hg and diastolic blood pressure ≥ 90 mm of Hg, patients with acute renal injury, other serious co-morbidity such as severe heart failure and de-compensated liver failure, Any active malignant disease, uncontrolled diabetes mellitus, HbA1c: ≥ 8.0%, pregnancy, breastfeeding or planed pregnancy during the study, patients with history of receiving Vitamin-D or calcium.

Patients or attendees gave their informed written permission after being fully informed about the study's goals, risks and eventual conclusion. They were made aware of their freedom to leave the study at any time. They were then evenly assigned at random to the experimental and control arms. Baseline characteristics of patients such as age, sex, duration of DM, BP were recorded. At start of study following investigations were done: serum creatinine, urinary albumin, serum vitamin-D and serum parathormone, phosphate, calcium and serum albumin. Each of the selected patients of experimental group received capsule Calcitriol (0.25 microgram) orally daily along with the conventional treatment of DN and patients of control group received identical placebo capsule daily along with conventional treatment of DN. Conventional treatment included calcium, Proton Pump Inhibitor (PPI) Angiotensin Converting Enzyme Inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB). Patients will be evaluated at 4th week, 8th week and 12th week to assess the efficacy of the study drug. At each visit, blood pressure was measured and fasting blood samples were collected for the measurement of above investigations. Assessment consists of focused questions about drug compliance and adverse effects.

The master sheet was created by feeding data into an Excel sheet, and SPSS version 23.0 was used to analyze the data in accordance with procedure guidelines. When the data were skewed, continuous variables were given as medians and interquartile ranges or as means and standard deviation if the data were normally distributed. If the data were normally distributed, the paired sample 't' test was used for within-group comparisons; if not, the Wilcoxon Signed Rank test was used. If the continuous data were normally distributed, an independent sample t test was used to compare the groups, or if the data

were skewed, a Mann-Whitney 'U' test was used. Chi-square test was used to compare the counts and percentages of categorical variables between groups. The confidence interval was established at the 95% level and statistical significance was considered as p<0.05.

Results

Table I Socio-demographic, clinical and laboratory parameters at baseline

Variable (Unit)	Experimental Group (15)	Control Group (15)	p value
Age (Years)	57.1±8.3	54.7±11.1	0.510*
Sex			
Male	7 (46.7)	8 (53.3)	0.715†
Female	8 (53.3)	7 (46.7)	
Duration of Diabetes (years)			
≤5	3 (20.0)	1 (6.7)	0.682†
6-10	5 (33.3)	5 (33.3)	
11-15	4 (26.7)	4 (26.7)	
16-20	3 (20.0)	5 (33.3)	
Vitamin D status			
Insufficient (20-29.99 mg/dl)	8 (53.3)	4 (26.7)	0.136†
Deficient (10-19.99 mg/dl)	7 (46.7)	11 (73.3)	
Serum creatinine (mg/dl)	1.5±0.5	1.3±0.4	0.269*
eGFR (ml/min/1.73m^2)	37 (27-58)	42.0 (38.0-74.0)	0.161‡
uACR (µg/mg)	118.7 (88.4-498.1)	88.4 (39.7-349.3)	0.089‡
SBP (mm of Hg)	138.0±20.4	132.7±7.0	0.347*
DBP (mm of Hg)	78.7±8.3	79.3±4.6	0.788*
Serum albumin (gm/dl)	3.5±0.3	3.6±0.2	0.547*
Serum calcium (mg/dl)	8.6±0.9	9.1±0.4	0.061*
Serum phosphate (mg/dl)	5.0±0.7	4.7±0.6	0.291*
Serum PTH (pg/ml)	69.7 (41.5-101.2)	59.3 (27.4-145.6)	0.870‡

Data were presented as Mean±Standard deviation, Median (Interquartile range) Frequency (Percentage). *Independent t test, ‡Mann-whitney U test, †Chi-square test.

Both groups were comparable at baseline with respect to socio-demographic, clinical and laboratory parameters. In both groups most of the patients were ≥50 years of age group. Male and female representation was almost equal in both groups. Most of the patients of both groups had history of DM for ≥ 6 years (Table I).

Table II Change of laboratory parameters of both group from baseline to 12 weeks

Variables (Unit)	Group	Baseline	12 weeks	p value
Serum creatinine (mg/dl)	Experimental (15)	1.5±0.5	1.3±0.5	<0.001*
	Control (15)	1.3±0.4	1.6±0.6	<0.001*
eGFR (ml/min/1.73m2)	Experimental (15)	37 (27-58)	51 (35-66)	0.005†
	Control (15)	42.0 (38.0-74.0)	33.0 (32.0-56.0)	0.002†
uACR (µg/mg)	Experimental (15)	118.7 (88.4-498.1)	103.5 (73.1-385.2)	0.001†
	Control (15)	88.4 (39.7-349.3)	152.7 (108.5-478.3)	0.001†
SBP (mm of Hg)	Experimental (15)	138.0±20.4	133.3±10.5	0.301*
	Control (15)	132.7±7.0	140.7±8.0	0.003*
DBP (mm of Hg)	Experimental (15)	78.7±8.3	78.1±5.4	0.713*
	Control (15)	79.3±4.6	81.0±4.7	0.238*
Serum albumin (gm/dl)	Experimental (15)	3.5±0.3	3.6±0.6	0.242*
	Control (15)	3.6±0.2	3.6±0.3	0.618*
Serum calcium (mg/dl)	Experimental (15)	8.6±0.9	8.6±0.8	0.565*
	Control (15)	9.1±0.4	8.8±0.3	0.040*
Serum phosphate (mg/dl)	Experimental (15)	5.0±0.7	5.1±0.5	0.496*
	Control (15)	4.7±0.6	5.3±0.4	0.001*
Serum PTH (pg/ml)	Experimental (15)	69.7 (41.5-101.2)	71.0 (40.3-110.5)	0.233†
	Control (15)	59.3 (27.4-145.6)	73.7 (62.7-169.5)	0.001†

Data were presented as Mean±Standard deviation, Median (Interquatile range). *Paired t test, †Wilcoxon ranked signed test.

Serum creatinine was significantly decreased in experimental group (1.5±0.5 to 1.3±0.5 mg/dl, p<0.001) but increased in control group (1.3±0.4 to 1.6±0.6 mg/dl, p<0.001). In other hand, median eGFR was significantly increased in experimental group (37 to 51 ml/min/1.73 m^2, p=0.005) and decreased in control group (42 to 33 ml/min/1.73 m2, p=0.002). Median urinary ACR was also decreased in experimental group (118.7 to 103.5 µg/mg, p=0.001) and increased in control group (88.4 to 152.7 µg/mg, p=0.001). SBP (138.0±20.4 to 133.3±10.5 mm of Hg, p=0.301) and DBP (78.7±8.3 to 78.1±5.4 mm of Hg, p=0.713) were decreased in experimental group. But in control group, SBP was significantly increased at the end of study (132.7±7.0 to 140.7±8.0 mm of Hg, p=0.003) and DBP was also increased at the end of study (79.3±4.6 to 81.0±4.7 mm of Hg, p=0.238). Serum albumin was increased in experimental group but it was not significant (p=0.242). Serum calcium and phosphate were not changed significantly in calcitrol treated group (8.6±0.9 to 8.6±0.8 mg/dl, p=0.565 and 5.0±0.7 to 5.1±0.5 mg/dl, p=0.496 respectively). Serum calcium (9.1±0.4 to 8.8±0.3,

p=0.040) was decreased and serum phosphate was increased (4.7±0.6 to 5.3±0.4 mg/dl, p=0.001) significantly in placebo treated group at the end of study. Median serum PTH was not changed signifiacantly in experimental group (69.7 to 71.0 pg/ml, p=0.233) but increased significantly in control group (59.3 to 73.7 pg/ml, p=0.001) (Table II).

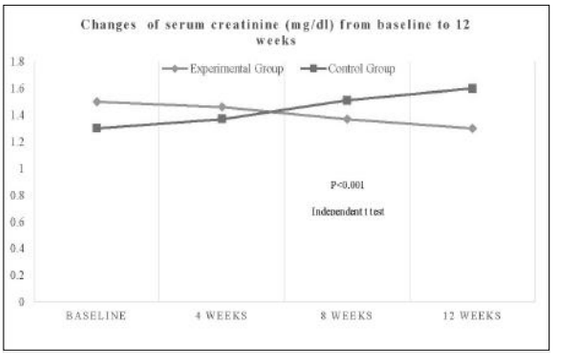

Figure 1 Comparison of changes of serum creatinine from baseline to 12 weeks of both groups

Serum creatinine was decreased in calcitriol treated group but increased in placebo treated group and comparison of both groups were statistically significant (p<0.001) (Figure 1).

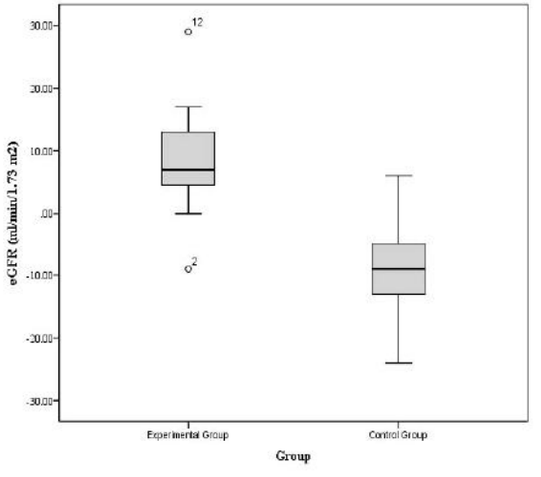

Figure 2 Comparison of changes of eGFR of both group 12 weeks

eGFR was increased in experimental group (Median 7.0 ml/min/1.73 m^2) and decreased in control group (median 9.0 pg/ml) at the end of study. Comparison of change between two groups were significant (p=0.001) (Figure 2).

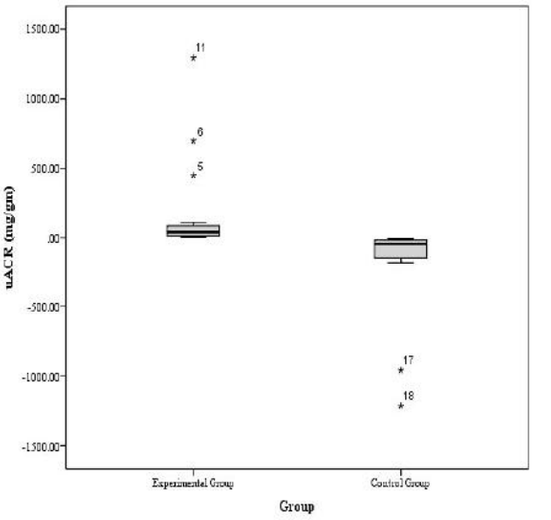

Figure 3 Comparison of changes of uACR of both groups at 12 weeks

Urinary ACR was decreased in experimental group (Median 40.8 µg/mg) and increased in control group (Median 43.3 µg/mg) at the end of 12 weeks. Comparison between two groups, it was highly significant (p<0.001) (Figure 3).

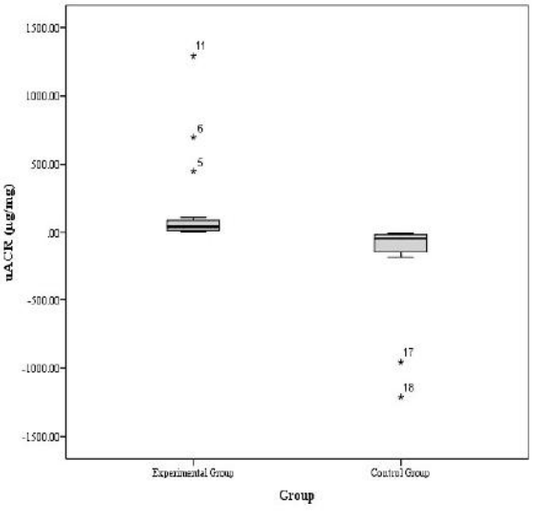

Figure 4 Comparison of changes of serum PTH of both groups at 12 weeks

Serum PTH was increased in both groups (Median 11.9 versus 39.3 pg/ml) and it was statistically significant (p=0.020) (Figure 4).

Table III Comparison of changes of secondary outcome of both groups at 12 weeks

Variable (unit)	Experimental Group (15)		Control Group (15)		p value
	Mean change	95% CI	Mean change	95% CI	
SBP (mm of Hg)	4.7	-4.7 – 14.0	0.3	0.01 – 0.5	0.015
DBP (mm of Hg)	0.6	-2.8 – 4.8	0.5	0.3 – 0.8	0.288
Serum albumin (gm/dl)	0.1	-0.1 – 0.4	0.04	-0.1 – 0.2	0.505
Serum calcium (mg/dl)	0.1	-0.2 – 0.3	0.04	-0.1 – 0.2	0.055
Serum phosphate (mg/dl)	0.1	-0.2 – 0.4	8.0	3.2 – 12.8	0.037

SBP was decreased in experimental group (Mean 4.7 mm of Hg) and increased in control group (mean 0.3 mm of Hg) and comparison of two groups were significant (p=0.015). DBP was also decreased in experimental group and increased in control group (Mean 0.6 versus 0.5 mm of Hg, p=0.288). In other hand, serum albumin was more increased in experimental group than control group but comparison of which were not significant (Mean 0.1 versus 0.04 gm/dl, p=0.505). Serum calcium was increased in calcitriol treated group and decreased in placebo group at the end of study (0.1 versus 0.04 mg/dl, p=0.055). Serum phosphate was less increased in experimental group than control group (Mean 0.1 versus 8.0 mg/dl, p=0.037) at the end of the study (Table III).

Discussions

Both the groups were comparable at the baseline in terms of age, gender, presence of HTN and duration of DM. The mean age of the patients was 55.87±9.75 years. Patient's characteristics of our study population were similar to the other studies conducted in this issue.[19,20]

The study results have shown that significant reduction of urine microalbumin could be achieved with the treatment of oral Calcitriol in DN patients who were on stable doses of ACE inhibitors and/or ARBs compared to placebo (p<0.001). This result was similar to previous studies.[19,21] Reduced kidney function is linked to increased proteinuria. For this reason, strategies to lower proteinuria are a key focus in the management of renal proteinuric disease.[22]

The treatment group saw a substantial rise in eGFR, whereas the control group experienced a significant decrease in eGFR (p=0.001). Serum creatinine significantly decreased in the treatment group while it rose in the control group (p<0.001). Previous research provided evidence for this.[20] In other studies, this result was not supported by some previous studies.[23,24,25] Potential explanations include the possibility that eGFR loss may occur in some diabetic patients even in the absence of albuminuria and that other risk factors (Such as blood pressure, blood lipids, and blood glucose) are correlated with the decline of renal function but were not taken into account in this meta-analysis.[26]

SBP and DBP were decreased in experimental group but increased in control group (p=0.015 and 0.288 respectively). In previous study Li et al. supported this findings.[27]

In the present study, serum PTH level was similar in both groups at baseline and at every follow-up. However, within group analysis indicated a significant increase of PTH in control group and no significant difference in the experimental group. Liyanage et al. observed a significant reduction of PTH in both experimental and control group with Vitamin D, 50000 IU (0.25 ml) IM monthly for 6 months.[20] Both the groups were comparable at the baseline in terms of age, gender, presence of HTN and duration of DM. The mean age of the patients was 55.87±9.75 years. Patient's characteristics of our study population were similar to the other studies conducted in this issue.[19,20]

Limitations

Small sample size. Short follow-up and we administered oral Vitamin D, the problems related to compliance and bioavailability may arise. Further, not including any marker of inflammation or method of endothelial function that could have been an explanation for reduction of albuminuria was another limitation of this study.

Conclusion

The outcome of this randomized double-blind placebo controlled clinical trial conducted among patients with DN and there was significant reduction of urine microalbumin after oral calcitriol therapy (0.25 microgram daily for 12 weeks). In addition, there was a significant reduction of serum creatinine and improvement of eGFR among patients who received Vitamin D. These results are supportive of the renoprotective effects of Vitamin D in diabetic patients with nephropathy who are on optimum medical therapy.

Recommendations

There is an urgent need for RCTs of larger sample size, placebo-controlled, comprehensive outcome measures, long term followed up and multi centered in order to clarify the real impact of calcitriol supplementation on indices of renal function and glycemic control in DM patients. Calcitriol supplementation would become a low-cost and convenient treatment strategy with social benefits in DN patients. If a clear conclusion is reached that Calcitriol supplementation prevents and treat DN.

Acknowledgements

Gratitude to all respondents and who assisted in this work.

Contribution of authors

BKB-Conception, acquisition of data, interpretation of data, drafting & final approval.
MAK-Acquisition of data, revision of content & final approval.
SMUI-Critical revision of content, design & final approval.
MA-Data analysis, revision of content & final approval.
MMR-Data analysis, critical revision of content & final approval.
MFR-Data analysis, drafting & final approval.
MNH-Conception, critical revision of content & final approval.
PKD-Conception, critical revision of content & final approval.

Disclosure

All the authors declared no conflict of interest.

References

1. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, De Boer IH, Goldstein-Fuchs J, Hirsch IB, Kalantar-Zadeh K, Narva AS, Navaneethan SD, Neumiller JJ. Diabetic kidney disease: A report from an ADA Consensus Conference. Diabetes care. 2014;37(10):2864-2883.

2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, AlMazroa MA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. The lancet. 2012;380(9859):2095-2128.

3. Saran R, Li Y, Robinson B, Ayanian J, Balkrishnan R, Bragg-Gresham J. US Renal Data System 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States [Internet]. Vol. 66. American Journal of Kidney Diseases. WB Saunders. 2015.

4. Alwakeel JS, Al-Suwaida A, Isnani AC, Al-Harbi A, Alam A. Concomitant macro and microvascular complications in diabetic nephropathy. Saudi journal of kidney diseases and transplantation. 2009;20(3):402-409.

5. Yokoyama H, Sone H, Oishi M, Kawai K, Fukumoto Y, Kobayashi M, Japan Diabetes Clinical Data Management Study Group. Prevalence of albuminuria and renal insufficiency and associated clinical factors in type 2 diabetes: the Japan Diabetes Clinical Data Management study (JDDM15). Nephrology Dialysis Transplantation. 2009;24(4):1212-1219.

6. Roscioni SS, Heerspink HJ, De Zeeuw D. The effect of RAAS blockade on the progression of diabetic nephropathy. Nature Reviews Nephrology. 2014;10(2):77-87.

7. Caramori ML, Fioretto P, Mauer M. The need for early predictors of diabetic nephropathy risk: is albumin excretion rate sufficient?. Diabetes. 2000;49(9):1399-1408.

8. Fineberg D, Jandeleit-Dahm KA, Cooper ME. Diabetic nephropathy: Diagnosis and treatment. Nature Reviews Endocrinology. 2013;9(12):713-723.

9. Gnudi L, Coward RJ, Long DA. Diabetic nephropathy: Perspective on novel molecular mechanisms. Trends in Endocrinology & Metabolism. 2016;27(11):820-830.

10. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, Jiang JP, Liang M, Wang GB, Liu ZR, Geng RW. Efficacy and safety of benazepril for advanced chronic renal insufficiency. New England Journal of Medicine. 2006;354(2):131-140.

11. Krairittichai U, Mahannopkul R, Bunnag 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(Suppl 3):S41-47.

12. Wu S, Sun J. Vitamin D, vitamin D receptor, and macroautophagy in inflammation and infection. Discovery medicine. 2011;11(59):325-335.

13. Plum LA, Zella JB. Vitamin D compounds and diabetic nephropathy. Archives of biochemistry and biophysics. 2012;523(1):87-94.

14. Santoro D, Caccamo D, Lucisano S, Buemi M, Sebekova K, Teta D, De Nicola L. Interplay of vitamin D, erythropoiesis, and the renin-angiotensin system. BioMed research international. 2015 ;2015.

15. Chokhandre MK, Mahmoud MI, Hakami T, Jafer M, Inamdar AS. Vitamin D & its analogues in type 2 diabetic nephropathy: A systematic review. Journal of Diabetes & Metabolic Disorders. 2015;14:1-0.

16. Richy F, Ethgen O, Bruyere O, Reginster JY. Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: A meta-analysis of their effects on bone mineral density and fracture rate. Osteoporosis international. 2004;15:301-310.

17. 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. American journal of kidney diseases. 2012;59(1):67-74.

18. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1, 25-Dihydroxyvitamin D 3 is a negative endocrine regulator of the renin-angiotensin system. The Journal of clinical investigation. 2002;110(2):229-238.

19. Agarwal R, Acharya M, Tian JI, Hippensteel RL, Melnick JZ, Qiu P, Williams L, Batlle D. Antiproteinuric effect of oral paricalcitol in chronic kidney disease. Kidney international. 2005;68(6):2823-2828.

20. Liyanage PL, Lekamwasam S, Weerarathna TP, Liyanage C. Effect of Vitamin D therapy on urinary albumin excretion, renal functions, and plasma renin among patients with diabetic nephropathy: A randomized, double-blind clinical trial. Journal of postgraduate medicine. 2018;64(1):10.

21. Alborzi P, Patel NA, Peterson C, Bills JE, Bekele DM, Bunaye Z, Light RP, Agarwal R. Paricalcitol reduces albuminuria and inflammation in chronic kidney disease: A randomized double-blind pilot trial. Hypertension. 2008 ;52(2):249-255.

22. Ruggenenti P, Perna A, Remuzzi G. Retarding progression of chronic renal disease: The neglected issue of residual proteinuria. Kidney international. 2003;63(6):2254-2261.

23. Wang Y, Yang S, Zhou Q, Zhang H, Yi B. Effects of vitamin D supplementation on renal function, inflammation and glycemic control in patients with diabetic nephropathy: A systematic review and meta-analysis. Kidney and Blood Pressure Research. 2019;44(1):72-87.

24. Xu L, Wan X, Huang Z, Zeng F, Wei G, Fang D, Deng W, Li Y. Impact of vitamin D on chronic kidney diseases in non-dialysis patients: A meta-analysis of randomized controlled trials. PloS one. 2013;8(4):e61387.

25. Zhang Q, Li M, Zhang T, Chen J. Effect of vitamin D receptor activators on glomerular filtration rate: a meta-analysis and systematic review. PloS one. 2016;11(1):e0147347.

26. Pugliese G. Updating the natural history of diabetic nephropathy. Acta diabetologica. 2014 ;51(6):905-915.

27. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1, 25-Dihydroxyvitamin D 3 is a negative endocrine regulator of the renin-angiotensin system. The Journal of clinical investigation. 2002;110(2):229-238.