VITAMIN D INSUFFICIENCY IN PATIENTS BY WAY OF CHRONIC KIDNEY DISEASE.

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ABSTRACT... Objectives: To measure Vitamin D levels in diabetic patients with and without kidney disease. Study Design: Prospective Case Control Study. Setting: Diabetic Clinic Ward 6, Nephrology Unit Ward 22 JPMC. Period: 2 year Jan 2016 to Dec 2017. Material & Methods: 102 subjects were enrolled for the study in which their anthropometry was recorded and blood samples were collected for hemoglobin A1C, fasting blood glucose, vitamin D levels, and blood Urea Nitrogen. Results: It is identified from the experiments that vitamin D deficiency links with a prior and an additional hostile inception of diabetes. In this research the levels of Vitamin D was measured in diabetic patients with and without kidney disease and then were correlated with disease severity. Conclusion: It is concluded that vitamin D deficiency in patients with CKD is not accepted so far. Whereas Patients with CKD might be connected with better existence rates, when matched to patients who did not consume vitamin D.

Key words: Blood Urea Nitrogen, Chronic Kidney Disease, Diabetes Mellitus, Vitamin D, VDBP

INTRODUCTION

Chronic kidney disease (CKD) has remained documented as a noteworthy worldwide health problem as for increased threat of over-all morbidity and death. Vitamin D shortage or inadequacy is shared in patients with CKD, and serum values of vitamin D seem to have a converse link through kidney function.¹ Vitamin D deficiency (VDD) has been in the spotlight as a major public healthcare issue with an estimated prevalence of more than a billion people worldwide. Among individuals with chronic kidney disease (CKD), VDD prevalence has been reported to be as high as 80%.(new) Escalating proof has shown that vitamin D deficiency may well add to declining renal function, as well as amplified disease and mortality in patients by means of CKD.² Current studies have proposed that management with active vitamin D or its equivalents can improve renal hurt by reducing fibrosis, apoptosis, and inflammation, this cure also reduces proteinuria and death in CKD patients.¹

Vitamin D acts as a major mediator of the concentration of calcium from the intestine and their reabsorption through the kidney. Two initial types of active vitamin D are Ergocalciferol (vitamin D₂) found in plants besides some fish, the other is Cholecalciferol (vitamin D₃), the root of which is either synthesis in human dermis cells by exposure to adequate sunlight or simply ingesting vitamin D.³ Ultraviolet (UV) β – rays are the only types of sunlight rays that can enable human skin to produce vitamin D₃. Cholecalciferol or vitamin D₃ needs activation, which is done by its passage through liver and kidneys. This active form is responsible for calcium regulation and bone mineralization. Apart from these well-known functions, vitamin D is also found to show a substantial role in the deterrence of many diseases over its anti-inflammatory and immune-modulating potentials.⁴ Regardless of its source, VD₂ and VD₃ are transported by a VD-binding protein (VDBP) in the liver where they undergo hydroxylation at the carbon 25 position by 25-hydroxylase (also known as CYP2R1) to become 25-hydroxyvitamin D [25(OH)-VD].⁵
VD and its plasma levels are routinely measured as a marker of VD status.⁶ Although 25(OH)-VD is considered the precursor of the active form 1,25(OH)₂-VD, it can also bind to vitamin D receptor (VDR), generating biological responses.⁷

The 1,25(OH)₂D₃, by way of VDR-associated modulation of calbindin manifestation, give the impression to control intracellular calcium flux in the islet cells, which, actually, upsets insulin discharge.⁸ In the 1,25(OH)₂D₃ deficiency of CKD, there is anomalous insulin secretion, a diminished reaction of the pancreatic β cells to glucose test, and insulin resistance.⁹ The 1,25(OH)₂D₃ deficiency yields to abnormal control of insulin secretion independent of modifications in VDR serum levels in pancreatic cells. Also, 1,25(OH)₂D₃ management corrects the irregular insulin secretion individualistic all of changes in serum levels of calcium or PTH.¹⁰ The discovery of 1-hydroxylase action in pancreatic cells (Koumenis et al., 2004). Boosts the likelihood of a dramatic autocrine regulation of insulin emission by 1,25(OH)₂D₃.

In recent studies, a weighty evidence was found that vitamin D also lowers thrombotic activity and hampers the inflammatory pathways, which could lead to coronary artery disease (CAD).¹¹ Similarly, it has been postulated that the microvascular complications in diabetic patients due to vitamin D deficiency are responsible for and may contribute to kidney failure. This is due to the fact that the incumbent vascular damage occurs as a result of by-activation of the renin-angiotensin-aldosterone system (RAAS), which ultimately ends up in abnormal protein excretion (proteinuria). Vitamin D is thought to prevent this loss by preventing RAAS hyper stimulation. Hence, vitamin D has a reno-protective role beyond what has already been known.¹² Reno-protective role of vitamin D analogues other than anti-fibrotic effects also includes straight antiproteinuric action through the protection of podocytes, interfaces with the renin–angiotensin–aldosterone system (RAAS), and anti-inflammatory special effects.¹³ Serum 1,25(OH)₂ vitamin D₃ surges are in reverse associated with renal inflammation in numerous sorts of kidney disease.¹⁴

Another important factor is the mediation of megalin through which the activation of vitamin D₃ takes place. Megalin expression is negatively affected by chronic exposure to albumin in diabetic patients. Various studies suggest that it negatively affects bone metabolism as well.¹⁴ Another mechanism of vitamin D scarcity in chronic renal malady is due to the loss of VDBP-vitamin D₃ complex at the tubular brush border of tubular epithelial cells. Normally, this albumin like protein to which vitamin D₃ binds (VDBP-25-hydroxyvitamin D₃ complex) is sieved at glomerulus along with its receptor facilitated uptake at the tubular brush border leaving only traces to be excreted into urine.¹⁵ Overall; it is obvious that vitamin D is a very central factor in sustaining the standard functioning of the renal system among diabetic patients and this dearth of vitamin D may lead to diabetic nephropathy.

Current guidelines suggest that patients with CKD stage 1–5 and VDD or VDI should receive supplementation using the same strategies as recommended for the general population.¹⁶,¹⁷,¹⁸ However, even for the general population, the optimal dosage of supplementation varies among the main guidelines. The KDOQI suggests 1000–2000 IU/d of VD₃ for VD repletion, but acknowledges that patients with CKD may require a more aggressive therapeutic plan.¹⁷ The National Institute for Clinical Excellence (NICE) in the UK suggests that people aged ≥ 65 years who are not exposed to much sun should take 400 IU of VD₃ daily, nevertheless, this guideline did not address VD supplementation in individuals with VDD or VDI.¹⁹,²⁰

Objective of the study
This study was conducted in order to measure the Vitamin D levels in diabetic patients having CKD and without kidney disease and then to correlate the levels with disease severity. Therefore, the key intention of this study was to determine the deficiencies of vitamin D amongst the individuals with chronic kidney diseases.

MATERIAL & METHODS
The present study was carried out at Jinnah Postgraduate Medical Center (JPMC), Karachi,
Pakistan, and a tertiary care hospital. Ethical permission for the study had been taken by the institutional review commission of the Basic Medical Sciences Institute, JPMC, Karachi, for piloting the research (Ref NO.F.2-81-IRB/2017/GENL/419/JPMC). Patients who fulfilled the following criteria were included: 35 to 65 years of age, identification of diabetes as per reference of American Diabetic Association.21 High risk diabetic kidney disease patients (family history, patients with micro-albuminuria, diabetes with <5 years and OR >5 years but < than 10 years.). All patients who had a chronic systemic disease (cardiovascular, urogenital, immunological etc.), chronic kidney disease (>10 years of DM), gestational diabetes, patient having CKD due to other causes and patients on nephrotoxic medications, anti-inflammatory drugs, vitamin supplements, vitamin D supplements, were excluded. Healthy non-diabetic patients were used as a control for this study. An overall of 132 individuals were identified using the selection criteria from the diabetic clinic from JPMC and AKU. Of these 102 subjects agreed to give their consent for the study in which their anthropometry was recorded and blood samples were collected for the blood tests relevant to the study.

To attain this foremost objective, researcher has divided the patients of JPMC and AKU into CKD without DM and CKD with DM groups. In this manner, researcher has conducted the cross-sectional study by comparing the data of both the groups. To gather the most relevant information related to the study, the data was collected on the basis of clinical characteristics, demographic information and laboratory examination of both the groups. The information related to clinical characteristics, demographic and laboratory examinations included age, body mass index (BMI), hemoglobin A1c, fasting blood glucose, vitamin D levels, and blood Urea Nitrogen. This helps the researcher to correlate the level of disease severity among the two sets.

For the Vitamin D levels the following literature based references were used.

but according to some standard reference range the level of vitamin D is considered as normal if it is 30 nanograms per millilitre to 100 nanograms per millilitre ml the level of vitamin D between 10 to 30 nanograms per millilitre is insufficient for the body and the parts of body which require vitamin D for their proper functioning will not function properly. If the level of vitamin D reference range will be less than 10 nanograms per millilitre than there is deficiency of vitamin D and it must be recovered otherwise it can be sever for the health and will give arise to multiple diseases. Vitamin D in excess is also harmful for body multiple disease also occur due to the accumulation of the excess amount of vitamin D due to intoxication caused by the excessive Vitamin D.

For native, seemingly healthy donors reference levels (serum) = 15- 60 ng/ml.

Statistical software SPSS version 21.0 was used for data record and analysis. A descriptive statistical exploration of continuous variables was accomplished. Facts on continuous variables i.e. biophysical and biochemical parameters were as Mean + standard deviation (SD) + standard error of mean (SEM). Statistical contrast were made by using One-way Analysis of Variance and Student t-test (paired for continuous/quantitative variables, Chi-square or Fischer exact test for categorical variables. In all statistical exploration, merely p-value < 0.05 was considered most important.

RESULTS
The outcomes of the descriptive analysis of the continuous variables is mentioned in the table below. For the variable of age the control group’s mean standard deviation was between 29.80 ± 16.40 when same thing is measured for the of Diabetes mellitus without CKD then the mean standard deviation for the age was between 45.81 ± 12.72. When and the 23 respondents in the group with CKD were tested the mean standard deviation for this group was identified between 52± 10.15.
The BMI of the control group was identified as 22.81 ± 2.69 whereas for the patients of Diabetes mellitus without CKD the mean of BMI deviated from the center by 28.16 ± 5.69 and it was greater than the deviation of control group however, it was less for among the patients of diabetes mellitus with CKD. The fasting and blood glucose are vital variables to consider and the mean standard deviation of the control group for the fasting blood glucose was 87.86 ± 9.08 when the same test was run for the patients of Diabetes mellitus without CKD, it is observed that MSD amplified in this group when compare to control set and that was 150.53 ± 43.48 same as it is observed among the patients OF Diabetes mellitus with CKD 159.88 ± 48.68.

Mean standard deviation for Hemoglobin A1C that is chemically linked to the sugar is identified to be increasing among three of the groups. For the control group it is identified between 5.18 ± 0.27, for the Diabetes mellitus patients without CKD it greater that was 7.45 ± 0.89 and for the Diabetes mellitus with CKD 7.78 ± 1.21 was the observed mean standard deviation. The mean standard deviation expected for level of vitamin D identified in the control group was 25.58 ± 22.68 whereas, the mean standard deviation for Diabetes mellitus without CKD was greater the control group and it was 39.18 ± 27.76 and the readings of Vitamin D in the Diabetes mellitus patients with CKD was a little low from the diabetes patients without CKD 28.99 ± 29.05. Blood urea Nitrogen was only 12.67 ± 3.47 in the control group and it did not increased in very large amount in the diabetes patients without CKD whereas among the diabetes patients with CKD the mean standard deviation highly elevated up to 57.93 ± 46.84.

DISCUSSION
This study showed a high prevalence of vitamin D lack/insufficiency in the local population and in sufferers with CKD. It is assessed that near 1 million people over the biosphere suffer vitamin D deficit. Serum vitamin D levels and metabolism are affected in nephropathy due to many reasons like deranged levels of vitamin D are possibly as a result of impaired glycemic parameter and many studies show the effect of renal dysfunction on vitamin D levels still exact etiology is unknown.

The current study found the lower serum vitamin D in control group as match to patients had DM CKD, but there was no significant difference (p value > 0.05). It can be understood that this was due to DN. However, for other group there is no plausible explanation for this effect other than the evidence that recent research studies found around the Western as well as the Eastern world. It is suggested a generalized vitamin D lack in otherwise in good health persons is highly prevalent.

Low vitamin D (<30ng/dl) is a shared discovery around the globe and it differs due to demographics food fortification, geographic setting, season. It has been predicted that around over one billion general public are suffering from low blood levels of vitamin D. The 25(OH) vitamin D is employed as the indicator of vitamin D in the body, rather than 1, 25(OH) vitamin D which symbolizes the on the go metabolite of vitamin D. Low 1, 25(OH) vitamin D is an anticipated and generally seen occurrence in CKD patients due to declined 1-alpha hydroxylase activity; nevertheless, the influence of CKD 25(OH) D is not as so far clear. A high frequency of 25(OH) D deficiency has been witnessed in CKD patients...
in abundant studies\textsuperscript{12,14,27}, and it has been understood that 25(OH) vitamin D deficiency get worse with advancement of CKD due to compromise in production of precursors of 25(OH) D. 25(OH) D is a sole predictors of kidney disease CKD patients (Sheikh et al., 2012). There have been sprouting evidence that kidneys show functional vitamin D receptors (VDRs) and react to cure with active vitamin D and studies suggest the vitamin D axis has a kidney-protective role.\textsuperscript{28}

Conservation of acceptable serum vitamin D therefore, be of particular significance for renal disease patients, not only for the avoidance of bone disease, but also for saving renal function. Emergent confirmation specifies that vitamin D analogues may have favorable effects in patients of CKD and longer survival among nephropathy patients.\textsuperscript{29}

Our results are in concurrence with several other studies.\textsuperscript{3,4,29} Nevertheless, few studies have contradictory evidence that urinary VDBP (vitamin D binding protein) elimination is strikingly increased in proteinuria and reacts to anti protein uric medicines. Urinary VDBP loss is not connected with plasma VDBP or vitamin D3 levels, proposing that renal loss of VDBP does not upset vitamin D (Doorenbos et al., 2012). Few studies reported that bigger renal impairment is allied with reduced circulating levels of 1,25(OH)\textsubscript{2}D.\textsuperscript{27} Accordingly; El-Ashmawy, et al., reported that urinary VDBP is accompanying with interstitial inflammation autonomous of albuminuria rendering VDBP an even new thought-provoking biomarker.\textsuperscript{30}

Table shows the demographic distribution of all groups. The mean ages of groups DM with and without CKD were equivalent (p>0.05) control group on the low age group (p=0.01). A comparison of the data shows that patients with DM without CKD had normal levels of Vitamin D levels, whereas the patients having DM and CKD had low levels of Vitamin D in their blood.

Like the current study, other studies also noted a major increase in fasting plasma glucose and HbA1c (p-value <0.001) among DM patients with and without nephropathy compared to control group.\textsuperscript{30}

While conducting the following research few confines faced at different stages. The main limitation of this research is that all the participants were of the same hospital so it confined the variance in the data whereas there is no doubt that the patients were of different family backgrounds. Another limitation of the study was low funding for that purpose less budget was allocated for the following research study. In addition lack of time was also constrain for the study and this effected the reliability and credibility of the study. Moreover, researcher used quantitative research design, If the study was conducted by mixed method approach which included and quantitative and qualitative studies then this enables researcher to add more data about the previous researches which were relevant to the study and if the finding of the current study were also analyzed according to the previous studies more comprehended and accurate solution for the research problem would be identified by the researcher. Furthermore the research had been restricted towards the use of only one of data collection method which was primary however the usage of the secondary method of data collection would enable the researcher to gain data from the other sources as well including book, from databases of the hospital and from general articles.

**CONCLUSION**

The overall analysis and discussion of research findings reveals that there is high prevalence of vitamin D inadequacy in the general people and in patients of CKD. In addition to that it is concluded from the study that lower serum intensities of vitamin D in control group as related to patients had diabetes mellitus CKD. Multiple emerging evidence are identified that kidneys has functional vitamin D receptors and react to usage with active vitamin D and it is concluded from the study that vitamin D axis has a nephron-protective role. In addition to this it is identified that conservation of ample serum vitamin D levels may, therefore, be of precise standing meant for patients with renal ailment, not only for the avoidance of bone problem, but also for the safety of renal function. In addition to that it is identified that vitamin D equivalents may have advantageous effects in patients with CKD and longer survival among
nephropathy patients. To sum up the distresses of vitamin D lack in patients with CKD are not proven up till now. Patients with CKD might be concomitant with improved survival, when related to patients who did not take any vitamin D analogues.\textsuperscript{23}

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REFERENCES

1. Kim CS, Kim SW. Vitamin D and chronic kidney disease. Korean J Intern Med. 2014; 29:416427.

2. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357:266.

3. Allegra V, Luisetto G, Mengozzi G, Martimbianco L, Vasile A. Glucose-induced insulin secretion in uremia: role of 1α, 25 (HO) 2-vitamin D3. Nephron. 1994; 68(1):41-7.

4. Allegra V, Mengozzi G, Martimbianco L, Vasile A. Glucose-induced insulin secretion in uremia: effects of aminophylline infusion and glucose loads. Kidney international. 1990 Dec 1;38(6):1146-50.

5. Dusso, A.S., Brown, A.J., Slatopolsky, E. Vitamin D. Am. J. Physiol. Ren. Physiol. 2005, 289, F8–F28.

6. Jean, G., Souberbielle, J.C., Chazot, C. Vitamin D in chronic kidney disease and dialysis patients. Nutrients2017, 9, 328.

7. Lou, Y.R., Molnár, F., Peräkylä, M., Qiao, S., Karleff, A.V., St-Arnaud, R., Carlberg, C., Tuohimaa, P. Hydroxyvitamin D3 is an agonistic vitamin D receptor ligand. J. Steroid Biochem. Mol. Biol. 2010, 118, 162–170.

8. Christakos S, Friedlander EJ, Frandsen BR, Norman AW. Studies on the mode of action of calciferol. XIII. Development of a radioimmunoassay for vitamin D-dependent chick intestinal calcium-binding protein and tissue distribution. Endocrinology. 1979 May 1;104(5):1495-503.

9. Alvestrand A, Mujagic M, Wajngot A, Efendic S. Glucose intolerance in uremic patients: the relative contributions of impaired beta-cell function and insulin resistance. Clinical nephrology. 1989 Apr;31(4):175-83.

10. Chertow BS, Sivitz WI, Baranetsky Ng, Clark Sa, Waite A, Deluca Hf. Cellular mechanisms of insulin release: the effects of vitamin D deficiency and repletion on rat insulin secretion. Endocrinology. 1983 Oct 1;113(4):1511-8.

11. Quesada JM, Martin-Malo A, Santiago J, Hervas F, Martinez ME, Castillo D, Barrio V, Aljama P. Effect of calcitriol on insulin secretion in uremia. Nephrology Dialysis Transplantation. 1990 Jan 1;5(12):1013-7.

12. Lowrie EG, Soeldner JS, Hampers CL, and Merrill JP, 1970. Glucose metabolism and insulin secretion in uremic, prediabetic, and normal subjects. J Lab Clin Med 76: 603–615.

13. Schwartz GG, Eads D, Rao A, Cramer SD, Willingham MC, Chen TC, Jamieson DP, Wang L, Burnstein KL, Holick MF, Koumenis C. Pancreatic cancer cells express 25-hydroxyvitamin D-1α-hydroxylase and their proliferation is inhibited by the prohormone 25-hydroxyvitamin D 3. Carcinogenesis. 2004 Jun 1;25(6):1015-26.

14. Gois F, Henrique P, Wolley M, Ranganathan D, Seguro AC. Vitamin D deficiency in chronic kidney disease: recent evidence and controversies. International journal of environmental research and public health. 2018 Aug; 15(8):1773.

15. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease—Mineral and Bone Disorder (CKD-MBD). Kidney Int. Suppl. 2017, 7, 1–59.

16. National kidney foundation evaluation and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Available online: https://www.kidney.org/sites/default/files/02-10-390B_LBA_.

17. Chan, A.M., Johnson, D. Vitamin D Therapy (Supplementation) in early chronic kidney disease. The CARI Guidelines. Available online: http://www.cari.org.au/CKD/CKD%20early/Vitamin_D_TherapY.

18. National Kidney Foundation Evaluation and Treatment of Chronic Kidney Disease-Mineral and Bone (CKD-MBD). Available online: https://www.kidney.org/sites/default/files/02-10-390B_LBA_.

19. National Institute for Health and Care Excellence. Vitamin D: Implementation of Existing Guidance to Prevent Deficiency. Available online: https://www.nice.org.uk/guidance/ph56/resources/implementingvitamin-d-guidance-draft-guideline2.

20. Moscovic A, Sprague SM. Role of vitamin D deficiency in chronic kidney disease. Journal of Bone and Mineral Research. 2007 Dec; 22(S2):V91-4.

21. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2018. (2017). Diabetes Care, 41(Supplement 1), S13-S27. doi:10.2337/dc18-s002.
22. Higgins DM, Wischmeyer PE, Queensland KM, Sillau SH, Sufit AJ, Heyland DK. Relationship of vitamin D deficiency to clinical outcomes in critically ill patients. Journal of Parenteral and Enteral Nutrition. 2012 Nov; 36(6):713-20.

23. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. In Mayo Clinic Proceedings 2010 Aug 1 (Vol. 85, No. 8, pp. 752-758). Elsevier.

24. Larson-Meyer DE, Willis KS. Vitamin D and athletes. Current sports medicine reports. 2010 Jul 1;9(4):220-6.

25. Le Fevre ML. Screening for vitamin D deficiency in adults: US Preventive Services Task Force recommendation statement. Annals of internal medicine. 2015 Jan 20; 162(2):13340.

26. Restrepo Valencia CA, Aguirre Arango JV. Vitamin D (25 (OH) D) in patients with chronic kidney disease stages 2-5. Colombia Médica. 2016 Sep; 47(3):160-6.

27. Kosmadakis G, Duja S, Basta M, Iqbal J, Warwick G, Medcalf JF. 25 (OH) vitamin D deficiency among SE Asians and Caucasians with CKD 3 and 4, and its role in hyperparathyroidism. Kidney international. 2008 Feb 1; 73(3):360.

28. Jhee JH, Kim H, Park S, Yun HR, Jung SY, Kee YK, Yoon CY, Park JT, Han SH, Kang SW, Yoo TH. Vitamin D deficiency is significantly associated with depression in patients with chronic kidney disease. PloS one. 2017 Feb 13; 12(2):e0171009.

29. Teng M, Wolf M, Ofsthun MN, Lazarus JM, Hernán MA, Camargo CA, Thadhani R. Activated injectable vitamin D and hemodialysis survival: a historical cohort study. Journal of the American Society of Nephrology. 2005 Apr 1;16(4):1115-25.

30. London GM, Guérin AP, Verbeke FH, Pannier B, Boutouyrie P, Marchais SJ, Métivier F. Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. Journal of the American Society of Nephrology. 2007 Feb 1;18(2):613-20.

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