Research article

Vitamin D deficiency in patients with Type 2 diabetes mellitus: its association with microvascular complications

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ABSTRACT

Introduction and Aim: A worldwide epidemic, type 2 diabetes affects 382 million people. Nephropathy, neuropathy, and retinopathy are examples of microvascular consequences. According to estimates, 1 billion people, or close to 15% of the world's population, are vitamin D deficient. There is proof that inadequate vitamin D levels are linked to poor glycaemic management. However, there is a dearth of information from India on a potential connection between a vitamin D deficit and microvascular problems. Therefore, the purpose of our study was to determine if individuals with microvascular consequences of diabetes are more likely to suffer from vitamin D insufficiency.

Materials and Methods: This cross-sectional study was done on 72 diabetic subjects availing the inpatient services of Father Muller Medical College Hospital. Diabetes was diagnosed as per American Diabetes Association guidelines. Subjects were examined for presence of neuropathy, nephropathy and retinopathy by nerve conduction study, urine protein creatinine ratio and fundus examination respectively. Serum vitamin D levels were assessed. Data was recorded and statistically analysed.

Results: Seventy-two patients fulfilling the selection criteria were recruited for this study. 77.8% of subjects had poorly controlled diabetes and 66.66% had vitamin D deficiency. 39 (54.16%) of subjects had microvascular complications of which 28 (38.8%) had neuropathy, 14 (19.4%) had retinopathy and 28 (38.9%) had nephropathy. 71% of patients with microvascular complications had vitamin D deficiency.

Conclusion: Poor glycemic control is strongly correlated with vitamin D insufficiency. Individuals who suffer from microvascular problems tend to have inadequate levels of vitamin D more frequently than people without such difficulties.

Keywords: Diabetes; microvascular complications; neuropathy; nephropathy; retinopathy; Vitamin D.

INTRODUCTION

A worldwide epidemic, type 2 diabetes mellitus affects 382 million individuals (1). Chronic microvascular and macrovascular consequences of Type 2 Diabetes mellitus include diabetic retinopathy, nephropathy, neuropathy, cardiovascular, cerebrovascular, and peripheral vascular disease (2). One billion people, or around 15% of the world's population, are thought to be 25-hydroxyvitamin D deficient (3).

Vitamin D can regulate glucose metabolism by improvement in insulin exocytosis, by stimulating the insulin receptor directly, by decreasing insulin resistance and by improving glucose uptake in peripheral tissues. Studies revealed that the insulin receptor gene promoter contains a vitamin D sensitive element. By regulating the production and activity of cytokines, vitamin D can reduce systemic inflammation. It also has immune regulating actions that are unrelated to cytokines (4-6).

The development of diabetes' microvascular problems is frequently linked to vitamin D. According to recent research, inadequate vitamin D levels may contribute to poor glycaemic management. However, there is a paucity of South Indian research on the origins of vascular problems of diabetes caused by a lack of 25-hydroxyvitamin D. We conducted this study to investigate the relationship between vitamin D insufficiency and T2DM microvascular consequences. The objectives of the study were to measure levels of 25 hydroxy vitamin D in patients with T2DM; evaluate the severity of microvascular complications in patients with T2DM and ascertain whether there is a relationship between those levels of 25-hydroxy vitamin D and microvascular complications in T2DM patients.

MATERIALS AND METHODS

This 19-month cross-sectional study involved 72 T2DM patients who received IP/OP care at Father Muller Medical College Hospital. After receiving approval from the institutional ethics committee and obtaining the participants' written informed agreement, the patients were added to the research.

Inclusion criteria

All patients aged more than 18 years with type 2

diabetes mellitus who fulfilled ADA criteria.

Exclusion criteria

1. Disorders which affect vitamin D metabolism including CKD, chronic liver disease.
2. Patients on vitamin D, calcium supplementation, steroids, antiepileptics
3. Pre-existing parathyroid disorders.
4. Patients with a history of cerebrovascular accidents.

Methods

Patients who fulfilled inclusion and exclusion criteria were recruited for the study.

Physical examination and investigations were done including:

- Blood pressure measurement.
- Examination for anaemia and oedema.
- Dilated fundus examination by ophthalmologist.
- Peripheral neuropathy was checked by SWM examination.
- Presence or absence of neuropathy was confirmed by nerve conduction study of both feet performed by a qualified neurologist with the machine NIHON KOHDEN NEUROPACK.
- Urine was tested for protein creatinine ratio. Urine PCR ≥0.3 was considered to be indicative of nephropathy and those with ≤0.2 was considered normal.
- 25 Hydroxy vitamin D levels were analysed by Electrochemiluminescence method with machine COBAS 6000.
- Vitamin D levels were considered normal when they were ≥30 ng/ml and insufficient when between 20-29 ng/ml. However, for this study we considered vitamin D deficiency as <20 ng/ml.
- The data was analysed by mean standard deviation; frequency percentage; chi square test.

RESULTS

The research comprised a total of 72 patients who met the eligibility requirements. With a range of ages from 33 to 77, the average age was 58.15 ±10.35. In all, 40.27% of the participants were between the ages of 61 and 70. Of the participants, 50 (69.4%) were men and 22, or 30.6%, were women. 1:0.44 was the male to female ratio.

Inadequate vitamin D status was associated with an average age of 57.9± 10.85, and levels below 20 ng/ml of vitamin D were associated with an average age of 58.67 ±9.49.

Thirty-one males (62%) and 17 females (77.27%) had vitamin D deficiency. This difference was statistically not significant. (P value 0.768). The mean BMI of subjects was 24.08±2.83. Mean BMI of subjects with vitamin D deficiency was 23.64±3.01, and of those with ≥20 ng/dl was 24.96±2.26 - this difference was not statistically significant.

Table 1: Glucose level and vitamin D

Parameters	Vitamin D<20	Vitamin D≥ 20	P value
FBS mg/dL	209.38±87.39	160.83±49.05	0.004
PPBS mg/dL	246.58±101.39	175.54±56.64	<0.001
HbA1c %	10±3.3	8.33±2.27	0.029

56 (77.8%) of our subjects had a glycosylated haemoglobin of >7 and most (41/73.21%) of them had vitamin D deficiency.

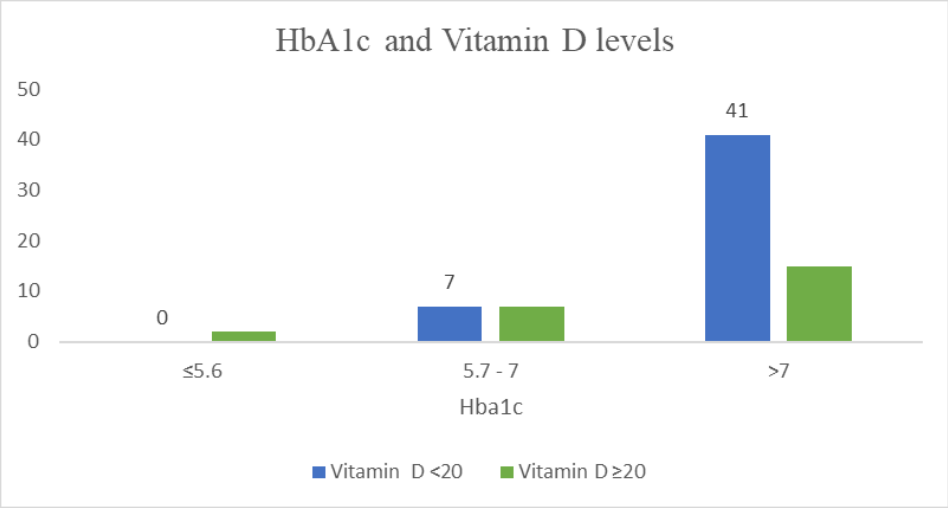

Fig. 1: HbA1c and vitamin D levels

The average duration of diabetes in our subjects was 7.51±6.37 years. 28(38.9%) had diabetes for less than 5 years. The number of patients with vitamin D deficiency tended to increase when the duration of diabetes was more than 5 years. However, this result did not reach statistical significance (p – 0.113). Mean vitamin D level of our subjects was 17.28 ±7.8. 48(66.66%) subjects had vitamin D deficiency compared to 24 subjects who had vitamin D level more than 20 ng/ml.

Of the 39(54.16%) subjects with microvascular complications, most 28(71%) had vitamin D deficiency.

Table 2: Vitamin D and microvascular complications

Variables	Vitamin D<20	Vitamin D≥ 20	Total
No microvascular complications	20	13	33
Some microvascular complications	28	11	39
Total	48	24	72

SWM test detected neuropathy in 27(37.5%) subjects. NCS was slightly more sensitive and detected neuropathy in 28 (38.8%) subjects. Out of the 28 subjects with neuropathy 75% Vitamin D deficiency (p value 0.231).

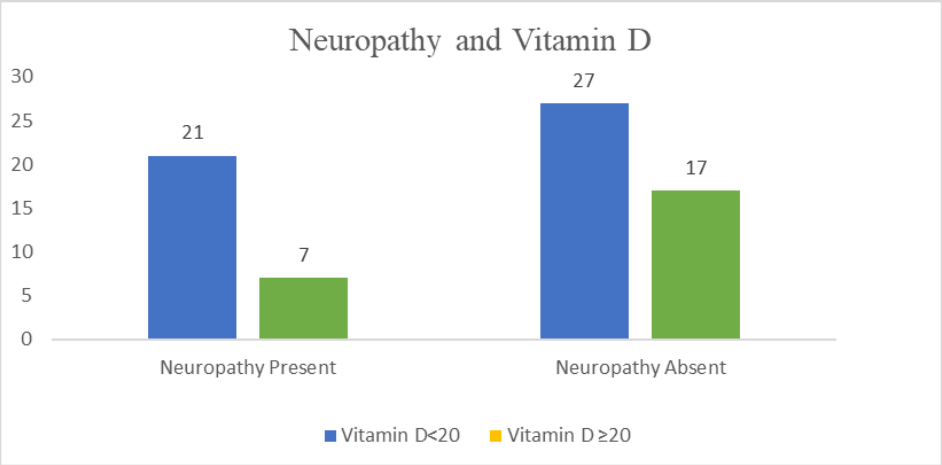

Fig. 2: Neuropathy and vitamin D

Out of 72 subjects, 14 patients had retinopathy, 10 of these subjects had mild NPDR (non-proliferative diabetic retinopathy), 1 moderate NPDR and 3 had PDR. Out of the 10 mild NPDR subjects, 8 had Vitamin D deficiency and all moderate NPDR and PDR (proliferative diabetic retinopathy) subjects had Vitamin D deficiency. However these values did not reach statistical significance (p value 0.092).

Table 3: Diabetic retinopathy and vitamin D

Retinopathy grading	Vitamin D <20	Vitamin D≥20	Total
No retinopathy	36	22	58
Mild NPDR	8	2	10
Moderate NPDR	1	0	1
Severe NPDR	0	0	0
PDR	3	0	3
Total	48	24	72

Twenty-eight (38.8%) of subjects had nephropathy. Of these 71.42 % had vitamin D deficiency (p value 0.494).

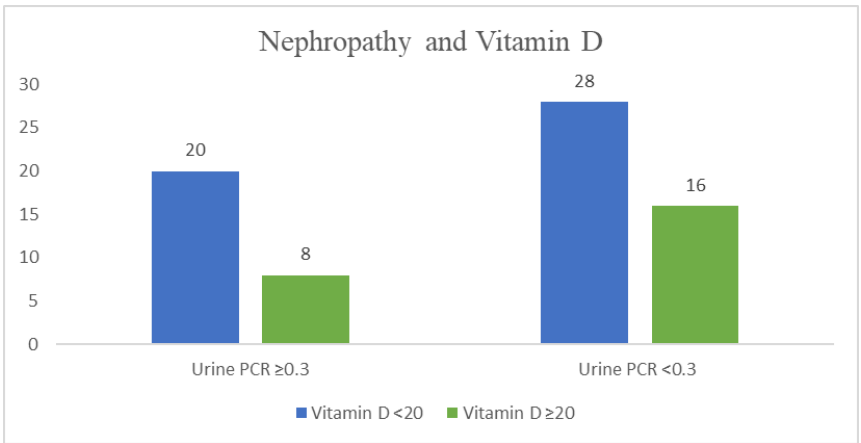

Fig. 3: Nephropathy and vitamin D

DISCUSSION

Numerous studies have been done on the role that vitamin D deficiency plays in diabetes and its control. Although it has been established that vitamin D insufficiency plays a part in the development of diabetes, there is currently no conclusive evidence linking this condition to the microvascular complications of diabetes. Our study aimed to determine whether Vitamin D deficiency and the microvascular complications of diabetes are linked.

We compared vitamin D levels in patients with and without microvascular complications. 66.66% of our subjects had vitamin D deficiency. Vitamin D deficiency was significantly associated with poor glycaemic control. We found that the odds of patients with microvascular complications having vitamin D deficiency was higher, though this did not reach statistical significance. Additionally most patients with diabetic retinopathy had vitamin D deficiency

Our study indicated that 66.66% of T2DM participants had vitamin D insufficiency, which is comparable to an Indian study's finding that the prevalence was 59.49% (7). Comparatively, research by Zoppini *et al.*, (8) found that 36.66% of people had the condition. In our investigation, the incidence of insufficiency was much greater, which might be attributed to increased skin pigmentation impairing vitamin D absorption (9). A variation in the vitamin D binding protein gene (10) may also be a contributing factor to the greater frequency of vitamin D insufficiency in those with dark skin.

Among our study subjects 62 % males and 77.27% females had Vitamin D deficiency. This difference was not statistically significant. Though there were more male diabetics in our study, the percentage of female subjects with vitamin D deficiency was greater. Similar results were observed in other research (11). This gender predisposition is not universal, with some studies showing that males had a higher prevalence of vitamin D deficiency probably due to low intake of milk, central obesity and lack of vitamin D supplementation (12,13).

Elderly people produce less vitamin D through their skin and kidneys, which exacerbates the effects of inadequate levels of vitamin D in this group as a whole (14). In light of this, it is sensible to assume that vitamin D deficiency would be more prevalent among the elderly, and some studies support this (11). In our research, the older age group had somewhat greater vitamin D levels. In the group with insufficient levels of vitamin D, the mean age was 57.9 ±10.85, whereas it was 58.67 ±9.49 in the group with adequate levels. Given the significance level of 0.768, this difference was not statistically significant. Other published works (12) show similar outcomes.

We found no significant difference in the BMI of subjects with or without Vitamin D deficiency (BMI 23.64 when vitamin D < 20, BMI 24.96 when vitamin D ≥ 20, p value: 0.069). Most published research shows that vitamin D deficiency is more common in the overweight and obese (15,16). Vitamin D deficiency in obese subjects is perhaps due to accumulation of vitamin D in body fat, resulting in decreased bioavailability (17). This result in our study is difficult to explain, but may be related to varying body fat percentages in different ethnicities. We did not measure body fat percentage in our subjects. Vitamin D deficiency may be more related to the body fat percentage and not the actual BMI (18).

We found a statistically significant association between Vitamin D deficiency and higher HbA1c, higher fasting, postprandial sugars. This association has been seen in numerous studies as well (19,20). A statistically significant negative correlation was found between glycaemic control and Vitamin D deficiency in pregnant women (21). However, in adults without diabetes, correction of Vitamin D deficiency does not affect blood glucose or insulin sensitivity (22). Vitamin D supplementation also did not further improve glycaemic control in adults with well controlled diabetes (23).

We found no association between duration of diabetes and vitamin D deficiency. This is similar to results observed in studies done by Zoppini *et al.*, (8). However other studies showed that duration of diabetes and vitamin D levels are inversely proportional (24).

Thirty-nine (54.16%) of our subjects had microvascular complications. The global prevalence of microvascular complications has been reported as 18.8%, of which – neuropathy has a prevalence of 7.7%, CKD – 5 %, albuminuria 4.3% (25). A higher percentage of our patients with complications may be explained by the longer mean duration of diabetes in our study – 7.51 years as opposed to 4.1 in the above quoted study.

Twenty-eight (38.8%) of our subjects had neuropathy either alone or in combination with other microvascular complications. There was a vitamin D deficiency in 21 of these (75%). A lack of vitamin D has also been linked in other studies to diabetes-related peripheral neuropathy (26). Vitamin D deficiency not only predicts the occurrence of neuropathy, it is related to the severity as well (27). However, Vitamin D supplementation did not improve neuropathy as measured by NCS (28).

Fourteen (19.4%) study subjects had retinopathy. Though there was no statistically significant association between Vitamin D deficiency and retinopathy (p-0.092), we found that Vitamin D deficiency tended to correlate with the severity of retinopathy, with 100% of patients with moderate NPDR and PDR having Vitamin D deficiency. Other published literature confirms the association of

Vitamin D deficiency with the presence and severity of diabetic retinopathy (29). This association is not invariable, however, with some studies showing no correlation (30).

Twenty-eight (38.8%) of our subjects had nephropathy. 71.42 % of these had vitamin D deficiency. However, we did not find a significant difference in vitamin D levels between those with or without nephropathy. This is in contrast to studies by Bonakdaran *et al.*, (31). This discrepancy is difficult to explain.

Limitations of the study

This study was limited by the fact that we correlated only vitamin D deficiency (< 20 ng/ml) and not insufficiency (between 20 and 30 ng/ml) with the presence or absence of complications.

Most of our subjects had poor glycaemic control, which may have influenced the results.

Additionally, we did not correlate the severity of neuropathy and nephropathy with vitamin D deficiency. We measured only BMI and did not check body fat percentage, which might have yielded further information. Although a correlation between vitamin D deficiency and microvascular problems was found due to the observational approach of the study, a causal link could not be established.

CONCLUSION

In spite of these limitations, some important conclusions can be drawn from this study namely that vitamin D deficiency is significantly associated with poor glycaemic control in Type 2 DM. It is more common in patients with microvascular complications than in those without, and was present in all patients with moderate NPDR and PDR in our study. Hence, estimation and correction of vitamin D deficiency may be beneficial in patients with early type 2 DM to prevent microvascular complications.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

REFERENCES

1. van Dieren, S., Beulens, J. W., van der Schouw, Y. T., Grobbee, D. E., Neal, B.The global burden of diabetes and its complications: an emerging pandemic. European journal of cardiovascular prevention and rehabilitation: official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology. 2010; 17 Suppl 1: S3-S8.
2. Gaede, P., Vedel, P., Larsen, N., Jensen, G. V., Parving, H. H., Pedersen, O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. The New England Journal of Medicine. 2003;348(5): 383–393.
3. Holick, M. F. Vitamin D deficiency. The New England Journal of Medicine. 2007; 357(3): 266-281.
4. Zeitz, U., Weber, K., Soegiarto, D.W., Wolf, E., Balling, R., Reinhold, G.E. Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. FASEB J. 2003;17(3):509-511.
5. Maestro, B., Dávila, N., Carranza, M.C., Calle, C. Identification of a Vitamin D response element in the human insulin receptor gene promoter. The Journal of Steroid Biochemistry and Molecular Biology. 2003; 84(2):223-230.
6. Song, Y., Wang, L., Pittas, A.G., Del Gobbo, L.C., Zhang, C., Manson, J. E., et al., Blood 25-hydroxy vitamin D levels and incident type 2 diabetes. Diabetes Care. 2013; 36(5):1422-1428.
7. Bajaj, S., Singh, R., Dwivedi, N., Singh, K., Gupta, A., Mathur, M. Vitamin D levels and microvascular complications in type 2 diabetes. Indian J Endocrinol Metab. 2014;18(4):537-541.
8. Zoppini, G., Galletti, A., Targher, G., Brangani, C., Pichiri, I., Trombetta, M., et al., Lower levels of 25-hydroxyvitamin D 3 are associated with a higher prevalence of microvascular complications in patients with type 2 diabetes. BMJ. 2015;3:1-6.
9. Clemens, T.L., Adams, J., Henderson, S., Holick, M. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. Lancet. 1982;319(8263):74-76.
10. Powe, C.E., Evans, M.K., Wenger, J., Zonderman, A.B., Berg, A.H., Nalls, M., et al., Vitamin D-binding protein and vitamin D status of black Americans and white Americans. N Engl J Med. 2013;369(21):1991-2000.
11. Chen, J., Yun, C., He, Y., Piao, J., Yang, L., Yang, X. Vitamin D status among the elderly Chinese population: A cross-sectional analysis of the 2010-2013 China national nutrition and health survey (CNNHS). Nutr J. 2017;16(1):1-8.
12. AlQuaiz, A.J.M., Kazi, A., Fouda, M., Alyousefi, N. Age and gender differences in the prevalence and correlates of vitamin D deficiency. Arch Osteoporos. 2018;13(1):1-11.
13. Sanghera, D.K., Sapkota, B.R., Aston, C.E., Blackett, P.R. Vitamin D Status, Gender Differences, and Cardiometabolic Health Disparities. Ann Nutr Metab. 2017;70(2):79-87.
14. Gallagher, J.C. Vitamin D and Aging. Endocrinol Metab Clin North Am. 2013;42(2):1-18.
15. Lagunova, Z., Porojnicu, L.C., Lindberg, F., Hexeberg, S., Moan, J. The dependency of vitamin D status on body mass index, gender, age and season. Anticancer Res. 2009;29(9):3713-3720.
16. Cheng, S., Massaro, J.M., Fox, C.S., Larson, M.G., Keyes, M.J., McCabe, E.L., et al., Adiposity, cardiometabolic risk, and vitamin D status: The Framingham heart study. Diabetes. 2010;59(1):242-248.
17. Wortsman, J., Matsuoka, L.Y., Chen, T.C., Lu, Z., Holick, M.F. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000;72(3):690-693.
18. Arunabh, S., Pollack, S., Yeh, J., Aloia, J.F. Body fat content and 25-hydroxyvitamin D levels in healthy women. J Clin Endocrinol Metab. 2003;88(1):157-161.
19. Wu, C., Qiu, S., Zhu, X., Li, L. Vitamin D supplementation and glycemic control in type 2 diabetes patients: A systematic review and meta-analysis. Metabolism. 2017;73:67-76.
20. Mirhosseini, N., Vatanparast, H., Mazidi, M., Kimball, S.M. Vitamin D supplementation, glycemic control, and insulin resistance in prediabetics: A meta-analysis. J Endocr Soc. 2018;2(7):687-709.
21. Lithy, A. El., Abdella, R.M., El-Faissal, Y.M., Sayed, A.M., Abdel Samie, R.M. The relationship between low maternal serum vitamin D levels and glycemic control in gestational diabetes assessed by HbA1c levels: An observational cross-sectional study. BMC Pregnancy Childbirth. 2014;14(1):2-6.
22. Pittas, A.G., Harris, S.S., Stark, P.C., Dawson-Hughes, B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. Diabetes Care. 2007;30(4):980-986.
23. Krul-Poel, Y.H.M., Westra, S., Boekel, E. T., Wee, M.M.T., Van Schoor, N.M., Van Wijland, H., et al., Effect of Vitamin D supplementation on glycemic control in patients with type 2 diabetes (SUNNY Trial): A randomized placebo-controlled trial. Diabetes Care. 2015;38(8):1420-1426.

24. Scragg, R., Holdaway, I., Singh, V., Metcalf, P., Baker, J., Dryson, E. Serum 25-hydroxyvitamin D3 levels decreased in impaired glucose tolerance and diabetes mellitus. Diabetes Res Clin Pract. 1995;27(3):181-188.
25. Kosiborod, M., Gomes, M.B., Nicolucci, A., Pocock, S., Rathmann, W., Shestakova, M. V., et al., Vascular complications in patients with type 2 diabetes: Prevalence and associated factors in 38 countries (the DISCOVER study program). Cardiovasc Diabetol. 2018;17(1):1-13.
26. He, R., Hu, Y., Zeng, H., Zhao, J., Zhao, J., Chai, Y., et al., Vitamin D deficiency increases the risk of peripheral neuropathy in Chinese patients with type 2 diabetes. Diabetes Metab Res Rev. 2017;33(2):1-8.
27. Pinzon, R.T., Gelgel, P.C.S. The correlation between vitamin D deficiency and the severity of painful diabetic neuropathy in patients with type 2 diabetes mellitus (T2DM). J Gizi Klin Indones. 2020;17(1):9-14.
28. Shehab, D., Al-Jarallah, K., Mojiminiyi, O.A., Al Mohamedy, H., Abdella, N.A. Does Vitamin D deficiency play a role in peripheral neuropathy in Type 2 diabetes? Diabet Med. 2012;29(1):43-49.
29. Alcubierre, N., Valls, J., Rubinat, E., Cao, G., Esquerda, A., Traveset, A., et al., Vitamin D deficiency is associated with the presence and severity of diabetic retinopathy in type 2 diabetes mellitus. J Diabetes Res. 2015;2015:1-8.
30. Bonakdaran, S., Shoeibi, N. Is there any correlation between vitamin D insufficiency and diabetic retinopathy? Int J Ophthalmol. 2015;8(2):326-331.
31. Bonakdaran, S., Hami, M., Hatefi, A. The Effects of Calcitriol on Albuminuria in Patients with Type-2. Saudi J kidney Dis Transplant. 2012;23(6):1215-1220.