ORIGINAL ARTICLE

Vitamin D deficiency: Correlation with diabetic retinopathy in diabetes type-II

Mashhood-uz-Zafar Farooq, Shama Mashhood, Aisha Kaleem, Mir Amjad Ali, Muhammad Faisal Fahim, Abdul Rafiu Soomro

Received
Date: 17th May, 2020
Accepted
Date: 2nd June, 2021

Karachi Institute of Medical Sciences, Karachi
MZ Farooq

Karachi Medical & Dental College, Karachi
S Mashhood

Mohsin Family Health Clinic, Karachi
A Kaleem

Sir Syed Medical College, Karachi
MA Ali

Bahria University Medical & Dental College, Karachi
MF Fahim

Suleman Roshan Medical College, Tando Adam.
AR Soomro

Correspondence:
Dr. Mashhood uz Zafar Farooq
Department of Ophthalmology, Karachi Institute of Medical Sciences, Malir Cantonment, Karachi.
Cell No:+92
email: drmzafarfarooq@gmail.com

Abstract:

Background: Vitamin D is identified to have an important association with diabetic retinopathy (DR). Several vitro and vivo studies support this evidence. Diabetic retinopathy is identified as one of the leading causes of blindness. Diabetic retinopathy poses economic and social implications. Visual loss secondary to diabetic retinopathy is avoidable and/or treatable with timely intervention. Different risk factors have been identified for causing diabetic retinopathy. Recently, vitamin-D is also identified as a risk factor for diabetic retinopathy in patients suffering from diabetes mellitus type-II. Large number of studies has identified vitamin D deficiency in different countries affecting all ages. Where several studies have found correlation of vitamin-D deficiency with diabetic retinopathy, some studies have found no relationship between vitamin-D deficiency and diabetic retinopathy.

Objective: To find a relationship between levels of vitamin-D and state of retinopathy among patients suffering from type-II diabetes mellitus (DM).

Material & Methods: This was a retrospective study with non-probability purposive sampling carried out at Mohsin Family Health Clinic, Karachi. Records of patients were traced out from January 2017 to December 2019.

Results: A total of 497 patient records were traced out for analysis during the study period. Mean age was 61.17±6.3 with range of 41 to 70 years. Male to female ratio was 4.3:1. Vitamin D levels were assessed with Diabetic retinopathy status. There were 17 (27.0%) NPDR cases found with normal vitamin D level, 133 (53.2%) patients observed with NPDR and insufficiency level and 115 (62.5%) found with NPDR and deficiency level of vitamin D.

Conclusion: There is an association between low levels of vitamin D and retinopathy in type II diabetes mellitus. Vitamin D has potential role in developing diabetic retinopathy.

Keywords: Diabetic retinopathy, type 2 diabetes mellitus, visual loss, vitamin D, Nonproliferative diabetic retinopathy (NPDR).

Introduction:

Diabetic retinopathy (DR) is an important complication of diabetes. Diabetic retinopathy is found to be a leading cause of visual loss and blindness.[1] The population affected by the disease belong to the working group.[2] The effect of the disease is not only limited to vision, but it also has great social and economic impact. Diabetic complications are expected to rise in view of increased prevalence of diabetes.[3] Diabetes has affected about seven hundred thousand people, who are suffering from the disease. In Pakistan about 7 million population is having diabetes.[4] Blindness secondary to retinopathy is a disastrous serious complication of diabetes.[5] Severity of DR is classified by Early Treatment Diabetic Retinopathy Study (EDTRS).[6] Patients are categorized as having Nonproliferative diabetic retinopathy (NPDR) and Proliferative diabetic retinopathy (PDR). It is pertinent to note that visual loss secondary to diabetic retinopathy is avoidable. It therefore becomes important to devise strategies to decrease or prevent this serious complication. Long duration

of diabetes, raised blood glucose level secondary to poor glycemic control, hyperlipidemia, systemic hypertension, obesity and positive family history of diabetes have all been identified as important risk factors for causing DR in patients suffering from type II diabetes mellitus (T2DM).[7-13] Early identification of risk factors is important as this permit for timely intervention in reducing the burden of diabetic retinopathy. Recent studies have identified vitamin D deficiency as an important risk factor for developing diabetic retinopathy.[14-18] Vitamin D deficiency has emerged as a global health issue. Work of Van der Meer IM et al., found that population of different countries is suffering from low levels of vitamin D.[19] Researchers have estimated that over half of the population is at risk of suffering from deficiency of vitamin D globally.[20] Pakistan is one of the countries where vitamin D deficiency is prevalent.[21] Where several studies have found correlation of vitamin D deficiency with diabetic retinopathy in T2DM, some studies have not found this association.[22-23] Therefore, present study was designed to investigate relationship between low level of Vitamin D and diabetic retinopathy in patients with T2DM in our outpatient population.

Materials and Methods:

This was a retrospective study with non-probability purposive sampling carried out at Ophthalmology and Family Physician outpatient department of Mohsin Family Health Clinic, Karachi. A prior Ethical approval was taken from the Institutional Review Committee of the Institute and study was conducted as per principles of Helsinki Declaration of 1975 as revised in 2000. Records of patients were traced out from January 2017 to December 2019. In view of the prevalence of vitamin D deficiency, all patients who attend family physician clinic are assessed for vitamin D deficiency irrespective of their history. All diabetic patients who attend either the family physician clinic or ophthalmology clinic are assessed for vitamin D levels. Data of patients having age between 40-70 years of age and suffering from T2DM were included for analysis. Exclusion criteria of study were Type 1 diabetes mellitus, any ocular disorder other than diabetic retinopathy, poor health that limited out-door activities, any systemic disorders other than T2DM that could affect the retinal microvascular structure like cardiovascular, renal, behavioural, liver, cancer, tuberculosis, hyper or hypothyroidism, and epilepsy. Drug intake that could affect vitamin D metabolism like vitamin supplements, antioxidants, pregnant and lactating females, incomplete records and missing information. After considering the inclusion and exclusion criteria, clinical data of these patients with respect to age, gender, duration of diabetes, retinopathy status and level of vitamin D were analysed. The patients record was coded and deidentified. A complete sample of 497 eligible subjects were analysed.

Data collection procedure: Ophthalmic evaluation was performed with visual acuity assessment with Snellen`s chart and detailed ocular examination. Fundus examination with slit lamp bio-microscopy using 90 D lens and indirect ophthalmoscope was done. Retinopathy status was assessed and recorded. Classification by Early Treatment Diabetic Retinopathy Study (EDTRS) for severity of diabetic retinopathy was used and patients were categorized as suffering from no Retinopathy, Non-proliferative diabetic retinopathy (NPDR) and Proliferative diabetic retinopathy (PDR).[6] Detailed physical examination was performed, and blood sample was taken using all aseptic precautions for measuring vitamin D status. Serum or plasma concentration of 25(OH)D is the best indicator of vitamin D status and is considered normal with value of 25-OHD = or > 30ng/ml, insufficiency with level 20.1-29.9 ng/ml and deficiency with value < 20ng/ml.[24]

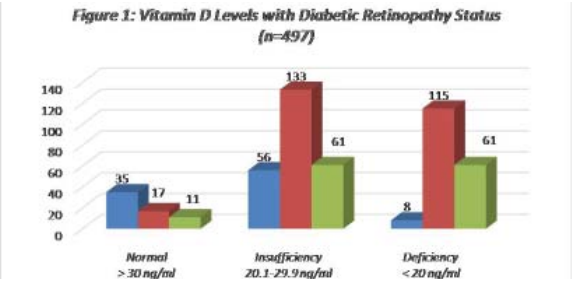
Statistical analysis: Data was entered and analyze through software SPSS version 23.0. All continuous variables were presented as mean± standard deviation. For categorical variables frequency and percentages were reported. To see the significance between vitamin D levels and Status of Diabetic Retinopathy Chi-Square test or Fischer Exact test was applied. P-value ≤ 0.05 considered to be statistically significant.

Table 1: Indicates Vitamin-D levels with Diabetic Retinopathy in relation to age (years)

		Vitamin D Levels			
Age Group	**Diabetic Retinopathy Status**	**Normal > 30ng/ml (n=63)**	**Insufficiency 20.1-29.9 ng/ml (n=250)**	**Deficiency < 20ng/ml (n=184)**	**P-value**
41 - 50	NPDR	0	2	2	0.182
		0%	16.7%	50.0%	
	PDR	0	10	2	
		0%	83.3%	50.0%	
51 - 60	No DR	20	22	2	0.000
		71.4%	28.9%	2.8%	
	NPDR	2	29	50	
		7.1%	38.2%	69.4%	
	PDR	6	25	20	
		21.4%	32.9%	27.8%	
61 - 70	No DR	15	34	6	0.000
		42.9%	21.0%	5.6%	
	NPDR	15	102	63	
		42.9%	63.0%	58.3%	
	PDR	5	26	39	
		14.3%	16.0%	36.1%	

Table 2: Vitamin D levels with Diabetic Retinopathy in relation with Gender

		Vitamin D Levels			
Gender	**Diabetic Retinopathy Status**	**Normal > 30ng/ml (n=63)**	**Insufficiency 20.1-29.9 ng/ml (n=250)**	**Deficiency < 20ng/ml (n=184)**	**P-value**
Male	No DR	27	48	8	0.000
		52.9%	24.6%	5.1%	
	NPDR	17	104	102	
		33.3%	53.3%	64.6%	
	PDR	7	43	48	
		13.7%	22.1%	30.4%	
Female	No DR	8	8	0	0.000
		66.7%	14.5%	0.0%	
	NPDR	0	29	13	
		0.0%	52.7%	50.0%	
	PDR	4	18	13	
		33.3%	32.7%	50.0%	



Results:

A total of 497 patient records were traced out for analysis during the study period. Mean age was 61.17±6.3 with range of 41 to 70 years. Male to female ratio was 4.3:1. Vitamin D levels were assessed with Diabetic retinopathy status. There were 17 (27.0%) NPDR cases found with Normal Vitamin D level,

Out of 250 patients having insufficiency of vitamin D, 53.2% were having NPDR and 24.4% were having PDR. Deficiency of vitamin D was observed in 184 patients, out of which 62.5% were having NPDR and 33.1% were having PDR. (Figure 1)

All patients in age group 41-50 demonstrated low levels of vitamin D with evidence of NPDR and PDR with p-value 0.182. Age group 51-60 year patients were 6 (21.4%) with PDR and normal vitamin D level, 25 (32.9%) patients with PDR and Insufficiency level of vitamin D and 20 (27.8%) patients with PDR and Deficiency level of vitamin D with significant P-value <0.0001. Age group of 61-70 year patients were 15 (42.9%) with NPDR and normal Vitamin D level, 102 (63.0%) patients with NPDR and Insufficiency level of vitamin D and 63 (58.3%) patients with NPDR and Deficiency level of vitamin D with significant P-value <0.0001. (Table 1)

Gender based analysis was also performed. In male, status of NPDR was seen in 17 (33.3%) patients with Normal Vitamin D level, 104 (53.3%) with i nsufficiency level of vitamin D and 102 (64.6%) patients found deficiency level of vitamin D with significant P-value <0.0001. In Female, there were no cases of NPDR in Normal Vitamin D level, 29 (52.7%) patients with Insufficiency level of vitamin D and 13 (50.0%) patients Deficiency level of vitamin D with significant P-value <0.0001. (Table 2)

With regards to duration of diabetes, most patients were lying in the category of 3-5 years of diabetes. NPDR follows 8 (17.8%) with normal vitamin D level, 40 (32.5%) with insufficiency level of vitamin D and 25 (71.4%) found with deficiency level of vitamin D with not-signif-

Table 3: Vitamin D levels with Diabetic Retinopathy in relation with Duration of Diabetes

		Vitamin D Levels			
Duration of Diabetes	**Diabetic Retinopathy Status**	**Normal > 30ng/ml (n=63)**	**Insufficiency 20.1-29.9 ng/ml (n=250)**	**Deficiency < 20ng/ml (n=184)**	**P-value**
3-5 years	No DR	30	47	3	
		66.7%	38.2%	8.6%	
	NPDR	8	40	25	0.283
		17.8%	32.5%	71.4%	
	PDR	7	36	7	
		15.6%	29.3%	20.0%	
5-10 years	No DR	5	9	5	0.000
		33.3%	8.8%	4.6%	
	NPDR	9	81	73	
		60.0%	79.4%	67.0%	
	PDR	1	12	31	
		6.7%	11.8%	28.4%	
> 10 years	NPDR	0	12	17	0.000
		0.0%	48.0%	42.5%	
	PDR	3	13	23	
		100.0%	52.0%	57.5%	

icance P-value of 0.283. However there were significant differences found among patients having diabetes from 5-10 years and > 10 years. (see Table 3)

Discussion:

The results of our study are in line with previous reports that show lower levels of vitamin D with retinopathy and confirm that there is an association of vitamin D deficiency with diabetic retinopathy. The severity of diabetic retinopathy is also associated with lower levels of 25(OH) D. Deficiency of vitamin D has now become a worldwide involving all ages.[24] In Pakistan vitamin D deficiency has now become a public health problem.[25] Retinal neo-vascularization is basic mechanism for development of retinal complication of diabetes and serves as a major cause of visual loss. Hyperglycemia is established risk factor for developing diabetic retinopathy in T2DM. Elevated blood glucose level in DM is caused by poor glucose metabolism due to lack of insulin. Lack of insulin in diabetes has been linked to vitamin D deficiency as demonstrated by Mathieu C et al.[26] Beside other effects, Vitamin D possesses anti-inflammatory effect.[27] The work of Albert D.M et al and Zittermann A. et al. have demonstrated potent anti-inflammatory effect of vitamin D on retinal neovascularization.[28,29] According to results of studies by Jiao Jet al., Zhang Y et al. and Taverna MJ et al., diabetic retinopathy is found to have significant association with vitamin D receptor gene FokI- and TaqI polymorphism.[30-32] Study of Hong YJ et al. on Korean population found Bsm1 Polymorphism in Vitamin D Receptor Gene and diabetic retinopathy of T2DM.[33] However, in a study conducted in Pakistan, no evidence of association was found of VDR gene BsmI polymorphism with T2DM.[34] Study results of Nadri G et al. found serum level of vitamin D to be a biomarker for PDR.[35] Efficient insulin secretion is dependent upon adequate level of Vitamin D as reflected in the studies of Danescu L.G. et al., Cavalier E. et al and Michos E.D.[36-38]

Association of low vitamin D has been demonstrated with severity of diabetic retinopathy in T2DM patients in study of Suzuki et al. in Japaneses, by Ahmadieh H. et al. in Labanese, by He R. et al. in Chinese and by Payne J. F. et al. in American patients.[17,39-41]

Study reports of Patrick P. A. et al., Alam U et al., Engelene L. et al. did not demonstrate any association between retinopathy and vitamin D concentration.[16,22-23] However, our study reflects an association between retinopathy and vitamin D concentration.

The work of Albert D.M et al and Zittermann A. et al. showing inhibition of retinal neovessels by vitamin D and vitro study of retinoblastoma Wagner N. et al. showing reduction of growth and apoptosis of the retinoblastoma cells with vitamin D supplements, has prompted further research on vitamin D.[28-29, 42]

Conclusion:

There is an association between low levels of vitamin D and retinopathy in Type-II Diabetic Mellitus. Vitamin D has potential role in developing diabetic retinopathy as reflected by our study. Further research is required to confirm the role of vitamin D in developing diabetic retinopathy and it`s beneficial effect in controlling proliferative retinal disorders.

Conflict of interest: none

Funding source: none

Role and contribution of authors:

Mashhood uz Zafar Farooq, concept, study design and supervised the study and involved in data collection and writing manuscript.

Shama Mashhood, study design and manuscript writing and data interpretation.

Aisha Kaleem, data collection and manuscript writing, literature search.

Mir Amjad Ali, supervised, review of manuscript.

Muhammad Faisal Fahim, data handling, statistical analysis and write-up of results.

Abdul Rafiu Soomro, review of manuscript.

References:

1. Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular oedema. CurrDiab Rep. 2012 Aug;12(4):346–54.
2. Mumtaz SN, Fahim MF, Arslan M, Shaikh SA, Kazi U, Memon MS. Prevalence of diabetic retinopathy in Pakistan; A systematic review.Pak J Med Sci. 2018 Mar-Apr;34(2):493-500.
3. Ciulla TA, Amador AG, Zinman B. Diabetic Retinopathy and Diabetic Macular Edema Pathophysiology, screening, and novel therapies. Diabetes Care. 2003;26:2653–2664.
4. Shaikh MZ. Controlling diabetes mellitus: struggle continued. J Coll Physicians Surg Pak. 2010;20(4):223–224.
5. Manaviat MR, Rashidi M, Afkhami-Ardekani M, Shoja MR. Prevalence of dry eye syndrome and diabetic retinopathy in type 2 diabetic patients. BMC Ophthalmol. 2008;8:10.
6. Pidro A, Ahmedbegovic-Pjano M, Grisevic S,Sofic-Drino V, Gabric K and Biscevic A. Epidemiology of Diabetic Retinopathy at Eye Clinic Svjetlost Sarajevo: Two Years Retrospective Single Center Study.Mater Sociomed. 2019 Dec; 31(4): 290–293.
7. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35(3):556–564. doi:10.2337/dc11-1909.
8. Penman A, Hancock H, Papavasileiou E, James M, Idowu O, Riche DM, et al. Risk Factors for Proliferative Diabetic Retinopathy in African Americans with Type 2 Diabetes. Ophthalmic Epidemiol. 2016;23(2):88–93.
9. Xu J, Wei WB, Yuan MX, Yuan SY, Wan G, Zheng YY, et al. Prevalence and risk factors for diabetic retinopathy:the Beijing Communities Diabetes Study 6. Retina. 2012;32(2):322–329.
10. Chatziralli IP, Sergentanis TN, Keryttopoulos P, Vatkalis N, Agorastos A, Papazisis L. Risk factors associated with diabetic retinopathy in patients with diabetes mellitus type 2. BMC Res Notes. 2010;3:153.
11. Hu Y, Teng W, Liu L, Chen K, Liu L, Hua R, et al. Prevalence and risk factors of diabetes and diabetic retinopathy in Liaoning province, China: a population-based cross-sectional study. PLoSOne2015;10(3).
12. Raman R, Ganesan S, Pal SS. Prevalence and risk factors for diabetic retinopathy in rural India. SankaraNethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study III (SN-DREAMS III), report no 2. BMJ Open Diabetes Res Care. 2014;2:000005.
13. Anwar SB, Asif N,Naqvi SAH, and Malik S. Evaluation of multiple risk factors involved in the development of Diabetic Retinopathy. Pak J Med Sci. 2019 Jan-Feb; 35(1): 156–160.
14. Bonakdaran S., Shoeibi N. Is there any correlation between vitamin D insufficiency and diabetic retinopathy? International Journal of Ophthalmology. 2015;8(2):326–331.
15. Kaur H., Donaghue K. C., Chan A. K., et al. Vitamin D deficiency is associated with retinopathy in children and adolescents with type 1 diabetes. Diabetes Care. 2011;34(6):1400–1402.
16. Patrick P. A., Visintainer P. F., Shi Q., Weiss I. A., Brand D. A. Vitamin D and retinopathy in adults with diabetes mellitus. JAMA Ophtalmology. 2012;130(6):756–760.
17. He R., Shen J., Liu F., et al. Vitamin D deficiency increases the risk of retinopathy in Chinese patients with Type 2 diabetes. Diabetic Medicine. 2014;31(12):1657–1664.
18. Bener A,Eliaçık M, Cincik H, Ozturk M, DeFronzo RA, and Abdul-Ghani M. The Impact of Vitamin D Deficiency on Retinopathy and Hearing Loss among Type 2 Diabetic Patients. Biomed Res Int. 2018; 2018: 2714590.Published online 2018 Jul 9.
19. Van der Meer IM, Middelkoop BJ, Boeke AJ, Lips P. Prevalence of vitamin D deficiency among Turkish, Moroccan, Indian and sub-Sahara African populations in Europe and their countries of origin: an overview. Osteoporos Int. 2011;22:1009–1021. DOI: 10.1007/s00198-010-1279-1.
20. Nadri G, Saxena S, Mahdi AA, Kaur A, Ahmad MK, Garg P, and Meyer CH. Serum vitamin D is a biomolecular biomarker for proliferative diabetic retinopathy. Int J Retina Vitreous. 2019; 5: 31.Published online 2019 Nov 5. DOI: 10.1186/s40942-019-0181-z
21. Alam U, Fawwad A, Shaheen F, Tahir B, Basit A, Malik RA. Improvement in Neuropathy Specific Quality of Life in Patients with Diabetes after Vitamin D Supplementation. J Diabetes Res. 2017; 2017: 7928083. Published online 2017 Dec 28. doi: 10.1155/2017/7928083
22. Alam U, Amjad Y, Chan AWS, Asghar O, Petropoulos IN, and Malik RA. Vitamin D Deficiency Is Not Associated with Diabetic Retinopathy or Maculopathy.J Diabetes Res. 2016; 2016: 6156217.Published online 2016 Jan 14. DOI: 10.1155/2016/6156217
23. Engelen L., Schalkwijk C. G., Eussen S. J., et al. Low 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 levels are independently associated with macroalbuminuria, but not with retinopathy and macrovascular disease in type 1 diabetes: the EURODIAB prospective complications study. Cardiovascular Diabetology. 2015;14, article 67. DOI: 10.1186/s12933-015-0231-2.
24. Luo BA, Gao F, and Qin LL. The Association between Vitamin D Deficiency and Diabetic Retinopathy in Type 2 Diabetes: A Meta-Analysis of Observational Studies. Nutrients. 2017 Mar; 9(3): 307.Published online 2017 Mar 20. DOI: 10.3390/nu9030307
25. Mahmood K, Akhter ST, Talib A, Haider I. Vitamin D status in a population of healthy adults in Pakistan. Pak J Med Sci 2009;25(4):545-550.
26. Mathieu C., Gysemans C., Giulietti A., Bouillon R. Vitamin D and diabetes. Diabetologia. 2005;48:1247-1257. DOI: 10.1007/s00125-005-1802-7.
27. Ren Z., Li W., Zhao Q., Ma L., Zhu J. The impact of 1,25-dihydroxy vitamin D3 on the expressions of vascular endothelial growth factor and transforming growth factor-b1 in the retinas of rats with diabetes. Diabetes Res. Clin. Pract.

2012;98:474-480. DOI: 10.1016/j.diabres.2012.09.028.
28. Albert D.M., Scheef E.A., Wang S., Mehraein F., Darjatmoko S.R., Sorenson C.M., Sheibani N. Calcitriol is a potent inhibitor of retinal neovascularization. Investig. Ophthalmol. Vis. Sci. 2007;48:2327–2334. DOI: 10.1167/iovs.06-1210.
29. Zittermann A., Koerfer R. Protective and toxic effects of vitamin D on vascular calcification: Clinical implications. Mol. Asp. Med. 2008;29:423–432. DOI: 10.1016/j.mam.2008.04.002.
30. Jiao J, Li Y, Xu S, Wu J, Yue S, Liu L.Association of FokI, TaqI, BsmI and ApaI polymorphisms with diabetic retinopathy: a pooled analysis of case-control studies.Afr Health Sci. 2018 Dec;18(4):891-899. DOI: 10.4314/ahs.v18i4.7.
31. Zhang Y, Xia W, Lu P, Yuan H. The Association between VDR Gene Polymorphisms and Diabetic Retinopathy Susceptibility: A Systematic Review and Meta-Analysis.
32. BioMed Research International2016Nov;(3):1-10 •
33. Taverna MJ1, Selam JL, Slama G.J ClinEndocrinolMetab.Association between a protein polymorphism in the start codon of the vitamin D receptor gene and severe diabetic retinopathy in C-peptide-negative type 1 diabetes. 2005 Aug;90(8):4803-8. Epub 2005 May 17.
34. Hong YJ, Kang ES, Ji MJ, Choi HJ, Oh T, Koong S, and Jeon HJ. Association between Bsm1 Polymorphism in Vitamin D Receptor Gene and Diabetic Retinopathy of Type 2 Diabetes in Korean Population. EndocrinolMetab (Seoul). 2015 Dec; 30(4): 469–474.Published online 2015 Dec 31. DOI: 10.3803/EnM.2015.30.4.469
35. Fatma H and Abdul SN. Association of Vitamin D receptor gene Bsm I polymorphism with type 2 diabetes mellitus in Pakistani population.Afr Health Sci. 2019 Jun;19(2):2164-2171.DOI: 10.4314/ahs.v19i2.41
36. Nadri G, Saxena S, Mahdi AA, Kaur A, Ahmad MK, Garg P, Meyer CH. Serum vitamin D is a biomolecular biomarker for proliferative diabetic retinopathy.Int J Retina Vitreous. 2019; 5: 31. Published online 2019 Nov 5. DOI: 10.1186/s40942-019-0181-z
37. Michos E.D. Vitamin D deficiency and the risk of incident Type 2 diabetes. Future Cardiol 2009;5:15-18. DOI: 10.2217/14796678.5.1.15.
38. Cavalier E., Delanaye P., Souberbielle J.C., Radermecker R.P. Vitamin D and type 2 diabetes mellitus: where do we stand? Diabetes Metab. 2011;37:265–272. DOI: 10.1016/j.diabet.2011.01.001.
39. Danescu L.G., Levy S., Levy J. Vitamin D and diabetes mellitus. Endocrine2009;35:11-17. DOI: 10.1007/s12020-008-9115-5.
40. Suzuki A., Kotake M., Ono Y., et al. Hypovitaminosis D in type 2 diabetes mellitus: association with microvascular complications and type of treatment. Endocrine Journal. 2006;53(4):503–510. doi: 10.1507/endocrj.k06-001.
41. Payne J. F., Ray R., Watson D. G., et al. Vitamin D insufficiency in diabetic retinopathy. Endocrine Practice. 2012;18(2):185–193. doi: 10.4158/EP11147.OR.
42. Ahmadieh H., Azar S. T., Lakkis N., Arabi A. Hypovitaminosis D in patients with type 2 diabetes mellitus: a relation to disease control and complications. ISRN Endocrinology. 2013;2013:7. doi: 10.1155/2013/641098.641098.
43. Wagner N., Wagner K.-D., Schley G., Badiali L., Theres H., Scholz H. 1,25-Dihydroxyvitamin D3-induced apoptosis of retinoblastoma cells is associated with reciprocal changes of Bcl-2 and bax. Experimental Eye Research. 2003;77(1):1–9. doi: 10.1016/s0014-4835(03)00108-8