Vitamin D Deficiency in Sudanese patients with type 2 Diabetes Mellitus:with and without Diabetic Retinopathy.

Dalia Ibrahim WageaAllaBalla[1], Abdelmula M. Abdalla[2],ZeinabAbdelrahmanElbashir Elrayah[3],Altayeb Elazomi[4],Elrasheed I. Mohamed[4] , Salah Bahroun[5].
[1]Sharq Elniel College .Department of Clinical chemistry. Khartoum North,[2]Faculty of Medical Laboratory Science, Department of clinical chemistry, Elneelain University, Khartoum,Sudan, [3] Faculty of Medicine, Department of Internalmedicine, University of Khartoum,[4]Faculty of Medical Technology, Department of Medical Laboratories, University of Zawia, Libya, [5]National Medical Research Centre, Zawia, Libya.
Corresponding Author :Dalia Ibrahim WageaAlla
Email: *Daliawigealla@yahoo.com*
0024118132592

Abstract

Background

Vitamin D is reported as a possible risk factor for the development of diabetes in several epidemiologic studies. Vitamin D deficiency and diabetes mellitus are two common conditions and they are widely prevalent across all ages, races, geographical regions, and socioeconomic conditions. Diabetic retinopathy (DR) is a common cause of blindness; the association between vitamin D (VitD) and type 2 diabetes mellitus (T2DM) and its complications such as DR has been unclear.

Objectives:

To investigate the status of 25 OH vitamin D3, in Sudanese patients with type 2 diabetes mellitus with and without DRand assessing the relationship of 25 (OH) of vitamin D deficiency with diabetic retinopathy (DR).

Materials and Methods

Methods: A cross-sectional case–control study was conducted with 30 normal control (CN) participants and 60 patients with T2DM, of which 30 with diabetic retinopathy (DR) and 30 with No diabetic retinopathy (NDR) were collected in Jabir Abu Eliz Diabetes Center; Khartoum State, from February, 2015 to February, 2016.Subjects were evaluated for Clinical Data, fasting blood glucose, glycated

hemoglobin A1C (HbA1C), and 25 hydroxy vitamin D [25 (OH) D] levels.

Results

Mean± SD plasma Vitamin D levels were significantly lower in the NDR (20.40 ±11.12ng/ml) and DR(11.12± 6.45ng/ml), compared with the NC group(33.10± 4.428ng/ml).Significant differences were observed between the groups with diabetes, andthe mean levels of 25OH vitamin D in all diabetic groups were below the normal range. 25 OH vitamin D showed a gradually decreasing trend with diabetic retinopathy severity Mean serum concentration of 25 dihydroxy vitamin D 3 (25(OH) D3) was significantly different according to the degree of severity of retinopathy (p< 0.00). 25OH Vitamin D level was (27.00±8.12ng/ml), in mild nonproliferative diabetic retinopathy (mild NPDR), (13.50±3.32 ng/ml) in moderate nonproliferative diabetic retinopathy (moderate NPDR) and (4.00±2.10 ng/ml)severe proliferative diabetic retinopathy (severe PDR).

Vitamin D level did not seem to be related to patient's age (r=0.025,p= 0.408)but was correlated significantly to the duration of disease (r=0.345 p= 0.012) and HbA1c(r=0.288 P= 0.002).

Conclusion

It seems that vit D deficiency is accelerating factor for developing retinopathy on diabetic patients.

Keywords

Type 2 Diabetes mellitus-25(OH) vitamin-Diabetic retinopathy

Introduction

Diabetes mellitus is an important public health problem worldwide, and more than 75% of patients who have had diabetes mellitus for more than 20 years will have

some sort of retinopathy.[1]Today diabetes is the leading cause of blindness in the developed world. The pathogenesis of retinopathy has become better understood in recent years. Diabetic eye disease, caused by retinal vascular damage, is the leading cause of new blindness in adults aged 20 to 74 years is typically categorized as follows:

• Nonproliferative retinopathy—Microaneurysms and other retinal lesions.

• Proliferative retinopathy—Growth of abnormal blood vessels and fibrous tissue from optic nerve head or inner retinal surface.

• Macular edema—Fluid leakage from blood vessels that causes macular swelling[2,3].Development and progression of diabetic microangiopathy in terms of retinopathy are known to be closely related to poor metabolic control, elevated arterial blood pressure, and other risk factors[4,5].

Vitamin D stores are derived from either dietary intake or cutenous synthesis following ultraviolet irradiation [6, 7]. Vitamin D from either source undergoes 25-hydroxylation in the liver to form 25-hydroxyvitamin D (25-OHD). Serum 25-OHD concentrations are thought to accurately reflect vitamin D stores, because its half-life is approximately 3 weeks [6, 7].

Vitamin D deficiency is an important risk factor for glucose intolerance [8]. Studies have shown impaired insulin synthesis and secretion in animal models with vitamin D deficiency; diabetes onset can be delayed with1–25-OH vitamin D intake, and some specific studieshave reported that vitamin D deficiency contributes to the etiology and progression of type 2 diabetes [9, 10]. 25-OH vitamin D concentrations were found to be lower in patients with type 2 diabetes with impaired glucose tolerance than in controls [11].In addition to its osteocalcic effect, VitD has immunomodulatory, anti-inflammatory, antioxidant, antiangiogenic, andantiproliferative functions in many kinds of cell. All of them are mediated by vitamin D receptors (VDR), a member ofthe nuclear receptor super family, which is extensively ex-pressed in the retina.In a mouse model of ischemic retinopathy, 1, 25(OH) 2 D3inhibited retinal neovascularization,[12]while in cell culture, itinhibited endothelial cell proliferation[13].The antitumor activityof vitamin D compounds has been demonstrated against avariety of cancers, including retinoblastoma [14,15].

Materials & Methods

Study population: a cross sectional case control hospital base study was done in a patients who attendant the diabeticclinic inJabir Abu Eliz Diabetes Center were selected for this study during the period April 2015 to April 2016.

The study population comprised of 90 subjects, classified as: 30 patients with diabetic retinopathy (DR), 30 controls diabetic with no retinopathy(NDR) in addition to 30 age and gender matched normal control (NC).

Inclusion criteria:

Sudanese patients with type 2 diabetes mellitus who visited Jabir Abu Eliz center during the study period.

Exclusion criteria:

Patients with clinical history renal disease due to other etiology rather than diabetes, end stage renal disease, hypertension, cancer, autoimmune disorders, recentliver,disorder, patient in supplementation on vitamin D and pregnant women were excluded from this study

Data collection and Clinical examination:

An interview with a questionnaire to obtain the clinical and demographic data was used for each participant in this study. Clinical history and examination of the test group and the control group were done by a physician to help the classification of study group.For diagnosing diabetic retinopathy (DR), all participants underwent an ophthalmic examination by an experienced ophthalmologist. This examination consisted of funduscopy by slit-lamp with 90 D lenses and indirect ophthalmoscopy

Sample collection:

Blood samples were collected after an overnight fast. Plasma was separated and stored frozen at -20C.HbA1C was measured at the same time of collection by using a fluorescence immunoassay (FIA) by commercial kit (Boditech Med Incorporated 43 Republic of Korea) by using ichroma reader.

Glucose oxidase-peroxidase method was used to determined blood glucose using mindray BS 200 chemistry autoanalyzer**.**

Levels of vitamin D [25(OH) D3] was determined by ELISA Kit from EUROIMMUN 25 OH vitamin D ELISA kit based on competitive principle.

Quality control

Sample representing normal and pathological level of vitamin D, blood glucose, HbA1c were used for assessment of accuracy and precision of all the method used in analysis, and result ±2SD of the target value of the control sample were accepted.

Statistical analysis

SPSS software (version 20) was used for analysis of clinical variables. Descriptive statistics was used to analyze all variable studies such as the demographic characteristics. Data were summarizing as mean ± SD or present. Variables were compared between diabetic with retinopathy groups and control diabeticwithout retinopathy by t test p value of < 0.05 was considered significant. ANOVA test was used for comparison between the means of quantitative variables in the study group.

Result

Table (1) shows baseline characteristic of study group between patients and control group, which presented the: Gender (M/F), mean of : age in year, disease duration in years,BMI Kg/m2, Fasting blood glucose mg/dl, HbA1C % and vitamin D ng/ml in study group patients with diabetic retinopathy and control group. In the present study, male account 40% in group with diabetic retinopathy (DR) 40% in patients with nodiabetic retinopathy (NDR) and 53.3% in healthy control group (NC), while female account 60% in group with diabetic retinopathy (DR) 60% in group of no diabetic retinopathy (NDR) and 46.7% in healthy control group.Age(50.10±9.204 years)in DR,(42.77±8.31years) in NDR and(45.40±3.328 years)NC.BMI (26.330±3.6740Kg/m^2)inDR,(27.090±2.787 6Kg/m^2) in NDR and(25.793±2.98426Kg/m^2) in NC.Disease duration is (7.23 ± 4.747 years) in DR, (8.57±4.18years) in NDR. Fasting blood glucose (177.07 ± 66.71) in DR,(182.97± 39.13mg/l) and (93.57±7.573 mg/dl) NC.HbA1C% (9.56 ± 2.216%)in DR (8.530± 1.66%) in DNR and (5.100± 0.8710 %) in CN. Vitamin D (11.12± 6.45ng/ml) in DR,(20.40 ±11.12ng/ml) NDR and (33.10± 4.428ng/ml) NC.

Table (2) shows the comparison of parameters according to severity of retinopathy. Age was found to be (50.75±5.123 years) in mild NPDR, (44.50±9.854 years) in moderate N PDR and (51.65±9.332 years) in PDR, p value0.253.BMI was found to be (24.00±1.825 Kg/m^2) in mild NPDR, (24.233±4.1755 Kg/m^2) in moderate N PDR and (27.425±3.4197 Kg/m^2) in PDR p value0.064.Disease duration found to be (13.50±8.737 years) in mild NPDR, (6.83±1.722 years) in moderate N PDR and (6.10±3.447years) in PDR p value0.012. HbA1C found to be (7.725±0.7182%) in mild NPDR, (7.650±0.7287%) in moderate N PDR and (10.505±77.436) in PDR, p value= 0.002. FBS was found to be (173.00±30.746mg/dl) in mild NPDR, (176.17±49.414) in moderate N PDR and (178.15±77.436) in PDR p value0.0990.Mean plasma concentration of 25 dihydroxy vitamin D 3 (25(OH) D3) was significantly different according to the degree of severity of retinopathy (p< 0.00). In mild nonproliferative diabetic retinopathy (mild NPDR), the level was (27.00±8.12ng/ml),in moderatenonproliferative diabetic retinopathy (moderate NPDR) thelevel was (13.50±3.32 ng/ml) and in proliferative diabetic retinopathy (PDR) it was 4.00±2.10 ng/mlP.value =0.00

Table (3)There was no significant correlation between the Mean plasma concentration of 25 dihydroxy vitamin D 3 (25- OH D3) and the age (r= 0.025p< 0.408), but there was significant correlation between mean serum concentration of 25 dihydroxy vitamin D 3(25-OH D3)and duration of disease (r=0.345,p=0.012), and also with HbA1c(r=0.288,p= 0.002).

Discussion

Vitamin D deficiency is now recognized as a condition of increasing prevalence worldwide. Vitamin D has an established role in calcium and bone metabolism; however, more recently associations with vitamin D deficiency and risk of developing diabetes, diabetes complications, and cardiovascular disease have all been acknowledged [16].Serum 25-hydroxy-vitamin D3 (25(OH) D) is a better indicator of vitamin D sufficiency than the active hormone, that is, 1,25-dihydroxy-vitamin D3. Therefore, the serum concentration of 25(OH) D is widely accepted as a good indicator of the status of vitamin D in a given subject [17].

In the present study the mean plasma 25(OH)D3 levels were significantly lower in

both the diabetic groups (DNR and DR) compared with the CN group, this result is agree with the result ofG. B. Reddy et al. (2015). [18]

This study confirms the association of vitamin D deficiency with diabetic retinopathy in type 2 diabetes.Type 2 diabetic patients with retinopathy had lower serum 25(OH)D concentrations than diabetic patient without retinopathy. The same result was obtain from the Korean study that demonstrated that the risks of any DR and proliferative DR decreased in those with high blood 25-hydroxyvitamin D levels relative to those with the lowest blood 25-hydroxyvitamin D levels[19] , similar result has been replicate in Chinese population with type 2 diabetes[20]

Our study shows that the severity of retinopathy is increase with the increase in the 25 OH D3 deficiency Also, the first study carried out in the USA revealed an association of 25(OH) D concentrations with the severity of diabetic retinopathy [21] In the eye, vitamin D receptors are expressed extensively in the retina[22]. Therefore, vitamin D might prevent DR development and progression via its anti-inflammatory and antiangiogenic properties.In the present study, we showed that the increase in the HbA1c was negatively associated with serum 25-OHD concentrations in the subjects with type 2 diabetes mellitus, while the duration of diabetes was associated with serum 25- OHD levels. These results suggest that the control of blood glucose itself affects vitamin D metabolism. The progress of diabetic microangiopathy is known to be closely related to the control of blood glucose and the duration of diabetes. [23]

Conclusions

It seems that vit D deficiency is accelerating factor for developing retinopathy on diabetic patients.

Compared parameter	Control group	DNR	DR
Gender(M/F)	16/14(53.3%/46.7%)	12/18(40/60)	12/18(40/60)
Age	45.40 ±3.328	42.77±8.31	50.10±9.204
BMI	25.793±2.9842	27.090±2.7876	26.330±3.6740
Duration (year)	0.0±00	8.57± 4.18	7.23±4.747
FBG mg/dl	93.57±7.573	182.97± 39.13	177.07 ± 66.71
HbA1C	5.100±0.8710	8.530± 1.66	9.56±2.216
25 OH vit D ng/ml	33.10±4.428	20.40 ± 11.12	11.47±6.45

Table (1): comparison of Age, FBG, Disease duration, HbA1Cand serum 25 OH vitamin D level in the study group with their control

Parameters	Mild NPDR	Moderate PDR	PDR	P.value

Age	50.75±5.123	44.50±9.854	51.65±9.332	0.253
BMI	24.000±1.8257	24.233±4.1755	27.425±3.4197	.064
Disease duration	13.50±8.737	6.83±1.722	6.10±3.447	.012
HbA1c	7.725± 0.7182	7.650±0.7287	10.505±2.1152	.002
FBS	173.00±30.746	176.17±49.414	178.15±77.436	.990
25OH Vitamin D	27.00±8.12	13.50±3.32 ng/ml	4.00±2.10 ng/ml	0.00

Table (2) Comparison of parameter among mild non proliferative diabetic retinopathy, Moderate non proliferative diabetic retinopathy and proliferative diabetic retinopathy.

P value significant at the level of < 0.05

ANOVA test was used for comparison.

Table (3) Correlation between the serum 25OH D3 age, disease duration and HBA1C

r = Person correlation

p value significant at< 0.05

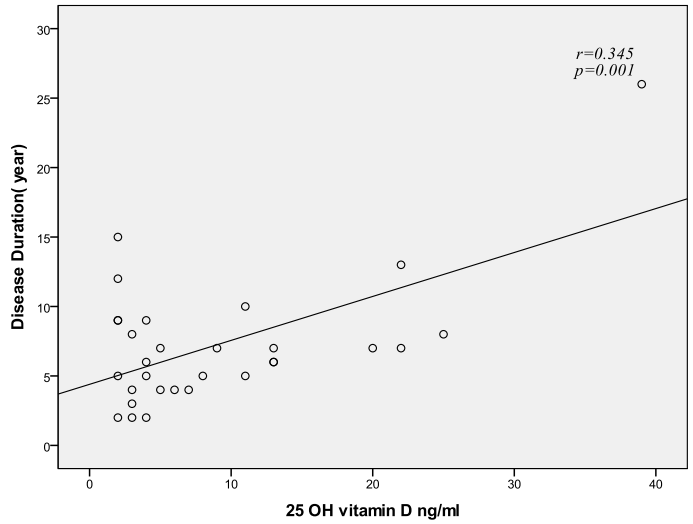

Figure 1 scatter plot shows the correlation between serum 25(OH) vitamin D level with disease duration in the study group.

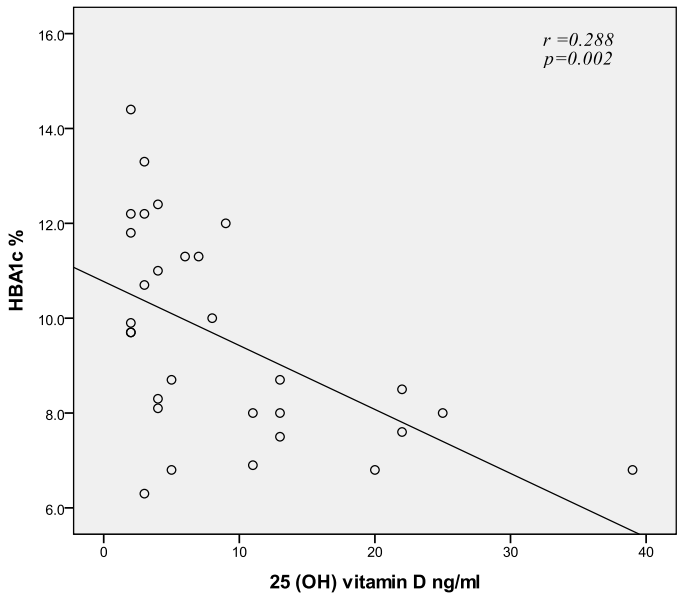

Figure 2 scatter plot shows the correlation between serum 25(OH) vitamin D level with HbA1C in the study group.

References

1.World Health Organization,Prevention of blindness from diabetes mellitus; Geneva: WHO2005.1-48

2. National Institute of Diabetes and Digestive and Kidney Diseases. Diabetes in America, 2nd ed. Bethesda, Md: National Institutes of Health; 1995. NIH publication 95-1468.

3. National Eye Institute. Facts about diabetic retinopathy. Available at: http://www.nei.nih.gov/health/ diabetic/ded>risk.htm. Accessed February 3, 2003.

4. Parving H-H, Mauer M, Ritz E. Diabetic nephropathy. In:Brenner BM, editor.Brenner& Rector's The Kidney. 8th ed. Bos-ton: WB Saunders; 2008. p. 1265–98.

5. The Diabetes Control and Complications Trial Research Group.The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med1993;329:977–86.

6.Thomas MK, Demay MB (2000) Vitamin D deficiency and disorders of vitamin D metabolism. EndocrinolMetabClin North Am 29: 611–627.

7. Reid IR (2003) Vitamin D and fracture prevention. In: New SA, Bonjour JP (eds) Nutritional Aspects of Bone Health. The Royal Society of Chemistry, Cambridge UK, 175–192

8. avidson MB, Duran P, Lee ML, Friedman TC. High-dose vitamin D supplementation in people with pre diabetes and hypovitaminosis D. Diabetes Care. 2013;36:260-6.

9.CangozS,ChangYY,ChempakaserilSJ,GuduruRC,HuynhLM,JohnJS,etal.Vitamin D and type 2 diabetes mellitus. J Clin Pharm Ther. 2013;38:81–4.7

10. Boucher BJ, Mannan N, Noonan K, Hales CN, Evans SJ. Glucose intolerance and impairment of insulin secretion in relation to vitamin D deficiency in east London Asians. Diabetologia. 1995;38:1239–45.

11. Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, Dryson E. Serum

25-hydroxy vitamin D3 levels decreased in impaired glucose tolerance and diabetes mellitus. Diabetes Res ClinPract. 1995;27:181–8

12.Albert DM, Scheef EA, Wang S, Mehraein F, DarjatmokoSR,Sorenson CM, et al. Calcitriol is a potent inhibitor of retinalNeovascularization.InvestOphthalmol Vis Sci2007;48:2327–34.

13. Kaur H, Donaghue KC, Chan AK, Benitez-Aguirre P, Hing S,
Lloyd M, et al. Vitamin D deficiency is associated with retinop-athy is children and adolescents with type 1 diabetes.DiabetesCare2011;34:1400–2.

14. Albert DM, Nickells RW, Gamm DM, Zimbric ML, SchlampCL,Lindstrom MJ, et al. Vitamin D analogs, a new treatment forretinoblastoma: the first Ellsworth Lecture.Ophthalmic Genet2002;23:137–56.

15. Shokravi MT, Marcus DM, Alroy J, Egan K, Saornil MA, AlbertDM. Vitamin D inhibits angiogenesis in transgenic murineretinoblastoma.InvestOphtalmol Vis Sci1995;36:83–7.

16. U Alam ,V Arul-Devah ,S Javed and RA. Malik;Vitamin D and Diabetic Complications: True or False Prophet? Diabetes Ther (2016) 7:11–26

17.D. Mauricio, T. Mandrup-Poulsen, and J. Nerup, “Vita-min D analogues in insulin-dependent diabetes mellitus andother autoimmune diseases: a therapeutic perspective,” Dia-betes/Metabolism Reviews vol.12,no.1,pp.57–68,1996.

18.Reddy, G BhanuprakashSc, M Sivaprasad MSc, T Shalini MD, A SatyanarayanaPhSc, M Seshacharyulu M D, N BalakrishnaPhViswanath, K M DD, ManishaSahay M (2015). Plasma vitamin D status in patients with type 2 diabetes with and without retinopathy. *Nutrition*, *31*(7-8), 959–963.

19. Jee D, Han K, Kim EC. Inverse association between high blood 25-hydroxyvitamin D levels and diabetic retinopathy in a representative Korean population. PLoS One. 2014;9:e115199

20. He R, Shen J, Liu F, et al. Vitamin D deficiency increases the risk of retinopathy in Chinese patients with type 2 diabetes. Diabet Med. 2014;31:1657–64

21. J. F. Payne, R. Ray, D. G. Watson et al., "Vitamin D insufficiency in diabetic retinopathy," Endocrine Practice, vol.18,no.2,pp. 185–193, 2012.

22.Taverna MJ, Selam J-L, Slama G 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. Journal of Clinical Endocrinology & Metabolism (2005) 90:4803–4808.

23. Suzuki, A., Kotake, M., Ono, Y., & Kato, T. Hypovitaminosis D in type 2 diabetes mellitus: Association with microvascular complications and type of treatment. *Endocrine* 5(2006). *3*(4), 503–10.