Effect of Serum 25 Hydroxy Vitamin D Level on Macular Edema in Patients with Nonproliferative Diabetic Retinopathy*

Vitamin D Seviyesinin Nonproliferatif Diabetik Retinopatili Hastalardaki Diabetik Maküla Ödemine Etkisi

Ayşegül MAVİ YILDIZ[1], Dilek GÜVEN[2], Ali Atakhan YILDIZ[3], Mehmet DEMİR[4], Ali OLGUN[4]

ABSTRACT

Purpose: To assess the association of systemic parameters and macular edema in patients with non-proliferative diabetic retinopathy (NPDR) especially considering vitamin D which has anti-inflammatory, anti-angiogenic properties.

Material and Method: Patients referred from Diabetes Clinic with NPDR were recruited during summer time. They were grouped as macular edema (ME) negative (Group I) and ME positive (Group II). There were 20 patients in each group, none of them were taking multivitamin supplement. Detailed eye examination, optic coherence tomography and if needed flourescein angiography was applied. Serum Vitamin D, HbA1c, fasting blood glucose (FBG), body mass index (BMI) and duration of diabetes were recorded.

Results: No significant difference was found between the groups with respect to duration of diabetes, levels of vitamin D, HbA1c, FBG and sex distribution. Mean vitamin D levels were 19.56±10.56 ng/ml and 14.16±9.18 ng/ml in Group I and II respectively (p=0.092). Levels of vitamin D and HbA1c presented an average inverse relation considering all patients. In Group I, Vitamin D and HbA1c levels showed stronger inverse correlation whereas in Group II, Vitamin D and HbA1c levels do not show any correlation.

Conclusion: Previous studies showed lower vitamin D levels in diabetic patients compared with normal controls. In this preliminary study although not significant we found a trend of lower vitamin D levels in NPDR patients with ME. Average inverse relation between vitamin D and HbA1c in NPDR patients needs to be evaluated since diabetic control and serum vitamin D values may have an influence on each other.

Key Words: 25-hydroxyvitamin D, macular edema, diabetes mellitus, diabetic retinopathy, hemoglobin A1c.

ÖZ

Amaç: Başta anti-inflamatuar ve anti-anjiojenik etkileri bilinen vitamin D olmak üzere, sistemik parametreler ile non-proliferatif diabetik retinopati (NPDR) eşliğinde maküla ödemi arasındaki ilişkiyi araştırmak.

Gereç ve Yöntem: 2014 yaz sezonu boyunca Diabet Polikliniği'nce tarafımıza refere edilip NPDR tanısı alan hastalar çalışmaya dahil edildi. Hastalar maküla ödemi (MÖ) saptanmayan (Grup I) ve ME saptanan (Grup II) olarak iki gruba ayrıldı. Her grupta 20 hasta mevcuttu ve hiçbir hasta vitamin desteği almıyordu. Tüm hastalar rutin oftalmolojik muayene yanı sıra optik koherens tomografi ile değerlendirildi; gerek görülen hastalara fundus floresein anjiografi çekimi de yapıldı. Serum vitamin D, HbA1c, açlık kan glukozu (AKG), vücut kitle indeksi (VKİ) ve diabet süresi kaydedildi.

Bulgular: Gruplar arasında diabet süresi, vitamin D seviyesi, HbA1c, AKG ve cinsiyet dağılımı açısından anlamlı fark bulunmadı. Ortalama vitamin D seviyesi Grup I'de 19.56±10.56 ng/ml; Grup II'de 14.16±9.18 ng/ml saptandı (p=0.092). Tüm hastalarda vitamin D düzeyi ile HbA1c arasında orta düzeyde negatif yönde korelasyon saptandı. Grup I'de vitamin D ile HbA1c arasında güçlü negatif korelasyon saptanırken grup II'de anlamlı korelasyon saptanmadı.

Tartışma: Literatürde diabetik hastalarda vitamin D düzeylerinin sağlıklı kontrollere göre düşük saptandığı çalışmalar mevcuttur. Çalışmamızda istatistiksel olarak anlamlı düzeyde olmasa da vitamin D'nin NPDR'li hastalarda daha düşük olma eğiliminde olduğunu saptadık. Diabet kontrolü ile serum vitamin D düzeyinin birbirini etkileyebilmesi sebebiyle vitamin D ve HbA1c arasındaki orta düzeyli negatif korelasyonun tespiti için ileri araştırmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: 25-hidroksivitamin D, maküla ödemi, diabetes mellitus, diyabetik retinopati, hemoglobin A1c.

The abstract published in 14th EURETINA Congress e-poster presentations, London, September 11-14, 2014.

1- M.D. Bahcelievler Statae Hospital, Eye Clinic, Istanbul/TURKEY
MAVI YILDIZ A., dramavi85@hotmail.com
2- M. D. Associate Professor, Sisli Etfal Training and Research Hospital, Eye Clinic, Istanbul/TURKEY
GUVEN D., dkguven@hotmail.com
3- M. D. Associate Professor, Sisli Etfal Training and Research Hospital, Eye Clinic, Istanbul/TURKEY
DEMIR M., drdemirmehmet@yahoo.com
OLGUN A., draliolgun@yahoo.com

Geliş Tarihi - Received: 01.03.2015
Kabul Tarihi - Accepted: 03.06.2015
Ret-Vit 2016;24:49-51

Yazışma Adresi / Correspondence Adress: M.D. Aysegul MAVI YILDIZ
Bahcelievler Statae Hospital, Eye Clinic, Istanbul/TURKEY

Phone: +90 505 369 14 10
E-mail: dramavi85@hotmail.com

INTRODUCTION

Diabetes mellitus (DM) affects more than 300 million individuals globally, contributing to significant morbidity and mortality worldwide.[1] The number of children and adolescents with diabetes is increasing at rates never before seen, and the capacity of current therapeutic interventions to slow its progression in youth appears to be very limited

According to Turkish Diabetes, Hypertension, Obesity and Endocrine Diseases Prevalance Study-II (TURDEP-II) DM incidence is 13.7% among adults in 2010.(approximately 6.850.000 individuals)

A survey data in adults in US indicated that those with low vitamin D levels had an increased risk of HT, DM, obesity and high triglyceride levels, all metabolic manifestations associated with cardiovascular mortality.[2]

Vitamin D insufficiency has been implicated in the development of DM and also correlated with an elevated risk of cardiovascular disease, cancer and mortality.[3-5]

In patients with type 1 DM severe vitamin D deficiency independently predicted all-cause mortality.[6] Type 2 DM patients were shown to have lower 25 hydroxy vitamin D levels (25OH-D) than those without DM.[7]

There is an increasing evidence that vitamin D deficiency may play a role in the pathogenesis of diabetic retinopathy (DR). In diabetic patients lower 25OH-D levels have been associated with proliferative DR.[8-12]

Purpose of this study is to assess the association between systemic parameters and the presence of macular edema in Type 2 DM patients with non-proliferative DR especially considering 25OH-D which is known to have anti-inflammatory and anti-angiogenic properties.[13-15]

MATERIAL AND METHODS

Patients with Type 2 DM referred from Diabetes Clinic and having NPDR were recruited consecutively during summer time. They were grouped as macular edema (ME) negative (Group I) and ME positive (Group II). There were 20 patients in each group and none of the patients were taking multivitamin supplement. In addition to detailed eye examination, optic coherence tomography and if needed fluorescein angiography was applied. Serum Vitamin D, HbA1c, fasting blood glucose (FBG) levels, body mass indices (BMI) and duration of diabetes were recorded.

Ethical Considerations: The study was approved by the Ethics Committee of the Şişli Hamidiye Etfal Training and Research Hospital and was conducted according to the guidelines laid down in the Declaration of Helsinki.

Statistical Analysis: Using Kolmogorov Smirnov test in both groups quantitative variables were compatible with normal distribution so parametric tests; t test, ki square test and Pearson correlation test were used for statistical analysis. P value less than 0.05 is considered significant.

RESULTS

Mean age was significantly higher in Group II being 64.34 whereas 56.60 in Group I ($p<0.05$, Table) . Mean BMI of both groups pointed presence of obesity. Mean BMI was significantly higher in Group I being 33.36 whereas 30.1 in Group II. Mean HbA1c (%) was 8.81 in Group I and 8.55 in Group II. Duration of diabetes and age showed a positive correlation. No significant difference was found between the groups with respect to duration of diabetes, levels of vitamin D, HbA1c, FBG and sex distribution. Mean vitamin D levels were 19.56±10.56 ng/ml and 14.16±9.18 ng/ml in Group I and II respectively ($p=0.092$). Levels of vitamin D and HbA1c presented an average inverse relation considering all patients. In Group I, Vitamin D and HbA1c levels showed stronger inverse correlation whereas in Group II, Vitamin D and HbA1c levels do not show any correlation. In Group II age and BMI showed a positive correlation. In Group II age and HbA1c showed a negative correlation.

In Group I Vit D level was significantly higher in male patients. In Group II age was higher in female patients. In Group II BMI was higher in female patients.

DISCUSSION

Diabetic retinopathy is a very important and common complication caused by multiple biochemical abnormalities of the underlying diabetes mellitus. The central mechanism of altered blood-retina-barrier function is a change in the permeability characteristics of retinal endothelial cells caused by elevated levels of growth factors, cytokines, advanced glycation end products, inflammation, hyperglycemia and loss of pericytes.[16]

Table: *Patient demographics and levels of systemic parameters (Mean and standart deviation).*

	Group I (CSME-)	Group II (CSME+)	Significance
Age	56.60±8.04	64.35±10.94	p=0.015
Body mass index (kg/m^2)	33.36±4.70	30.21±5.01	p=0.048
Duration of DM (years)	10.21±5.30	11.99±10.09	p>0.05
Vitamin D level (ng/ml)	19.56±10.52	14.16±9.18	p=0.092
Fasting blood glucose level (mg/dl)	156.35±49.60	155.70±39.78	p>0.05
HbA1c (%)	8.81±1.94	8.55±1.67	p>0.05

CSME: Clinically Significant Macular Edema

Vitamin D is necessary for normal insulin secretion. Vitamin D receptors are present in pancreatic beta cells and vitamin D augmenst insulin secretion and insulin sensitivity. The administration of 1.25 hydroxy vitamin D increases insulin secretion and improves glucose tolerance.[8] Vitamin D may confer protection via inhibition of inflammation, down regulation of the renin angiotensin system, improved insulin secretion, and an antiproliferative effect on endothelial cells.[17]

The active form of vitamin D, catcitriol, was shown to inhibit retinal neovascularisation and reduced endothelial cell viability (which is thought to be involved in the pathogenesis of DR) and function in animal models 13 and adults with type II DM.[14] Vitamin D decreases the production of several proinflammatory cytokines, and exerts an anti inflammatory effect by decreasing the proliferation of helper T cells, cytotoxic cells, and natural killer cells.[15] As macular edema and neovascularisation in DR are driven by vascular endothelial growth factor (VEGF) production vitamin D could exert it's positive effect through calcitriol mediated reduction of VEGF. The inflammatory and angiogenic effects of vitamin D deficiency may contribute to early retinal vascular damage. In the present study NPDR patients with macular edema showed a trend of lower serum 25OH-D levels but there was no statistical significance.

Factors known to influence 25OH-D levels include race, vitamin D intake, sun exposure, adiposity, age and physical activity. Several conditions such as obesity and absorption, liver or kidney disorders pose an increased risk of developing vitamin D deficiency. Obesity has been shown to affect 25OH-D levels possibly through vitamin D sequestration in fat deposits.[5] This mechanism may explain presence of high BMI and low serum 25OH-D levels in our patients.

In the present study, mean age of the patients with macular edema were older than patients without macular edema presenting no correlation with the duration of diabetes.

Levels of vitamin D and HbA1c presented an average inverse relation considering all patients. In the study by Aksoy et al there was no significant correlation of serum 1.25 dihydroxy vitamin D(1.25 OH-D) with HbA1c or FBG in type 2 diabetic patients, indicating that diabetic control does not necessarily have an influence on serum 1.25 OH-D concentrations.[8] In another study low 25OH-D level was an independent predictor of HbA1c, DR and diabetic neuropathy in Type 2 DM patients.[12] 25 OH-D correlated negatively with age and with BMI but not with duration of DM. In the study by Joergensen, vitamin D level had a weak negative association with HbA1c in type 1 diabetic patients.[6] Average inverse relation between vitamin D and HbA1c in NPDR patients needs to be evaluated since diabetic control and serum vitamin D values may have an influence on each other.

Previous studies showed lower vitamin D levels in diabetic patients when compared with normal controls. We are not aware if there is any previous study considering correlation of level of vitamin D and presence of macular edema. In this preliminary study although not significant we found a trend of lower vitamin D levels in NPDR patients with macular edema.

Identification of early treatable predictors of DR may allow more aggressive management of those at high risk. In the management of DM, multifactorial intervention beyond glycemic control includes antihypertensive, lipid-lowering and anti aggregatory medications. Place of vitamin D supplementation for both prevention and treatment of diabetic retinopathy is yet to be determined.

REFERENCES/KAYNAKLAR

1. Sherwin R, Jastreboff AM. Year in diabetes 2012: the diabetes tsunami. J Clin Endocrinology and Metabolism, 2012;97:4293-301.
2. Martins D, Wolf M, Pan D et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2007;167:1159-65.
3. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis.Am J Clin Nutr. 2004;79:362-71.
4. Baz-Hecht M, Goldfine AB. The impact of vitamin D deficiency on diabetes and cardiovascular risk. Curr Opin Endocrinol Diabetes Obes. 2010;17:113-9.
5. Judd SE, Tangpricha V. Vitamin D deficiency and risk for cardiovascular disease.Am J Med Sci. 2009;338:40-4
6. Joergensen C, Hovind P, Schmedes A, et al. Vitamin D levels, microvascular complications, and mortality in type 1 diabetes.Diabetes Care. 2011;34:1081-5.
7. Payne JF, Ray R, Watson DG, et al. Vitamin D insufficiency in diabetic retinopathy. Endocr Pract. 2012;18:185-93.
8. Aksoy H, Akçay F, Kurtul N, et al. Serum 1,25 dihydroxy vitamin D (1,25(OH)2D3), 25 hydroxy vitamin D (25(OH)D) and parathormone levels in diabetic retinopathy. Clin Biochem. 2000;33:47-51.
9. Suzuki A, Kotake M, Ono Y et al. Hypovitaminosis D in type 2 diabetes mellitus: Association with microvascular complications and type of treatment. Endocr J. 2006;53:503-10.
10. Kaur H, Donaghue KC, Chan AK et al. Vitamin D deficiency is associated with retinopathy in children and adolescents with type 1 diabetes.Diabetes Care. 2011;34:1400-2.
11. Poon M, Craig ME, Kaur H et al. Vitamin D deficiency is not associated with changes in retinal geometric parameters in young people with type 1 diabetes. J Diabetes Res. 2013;2013:280691. doi: 10.1155/2013/280691.
12. Ahmadieh H, Azar ST, Lakkis N, Arabi A. Hypovitaminosis d in patients with type 2 diabetes mellitus: a relation to disease control and complications. ISRN Endocrinol. 2013;2013:641098.
13. Albert DM, Scheef EA, Wang S et al. Calcitriol is a potent inhibitor of retinal neovascularization. Invest Ophthalmol Vis Sci. 2007;48:2327-34.
14. Yiu YF, Chan YH, Yiu KH et al. Vitamin D deficiency is associated with depletion of circulating endothelial progenitor cells and endothelial dysfunction in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011;96:E830-5.
15. Palomer X, González-Clemente JM, Blanco-Vaca F, et al. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. Diabetes Obes Metab. 2008;10:185-97.
16. Klaassen I, Van Noorden CJ, Schlingemann RO. Molecular basis of the inner blood-retinal barrier and its breakdown in diabetic macular edema and other pathological conditions. Prog Retin Eye Res. 2013;34:19-48. doi: 10.1016/j.preteyeres.2013.02.001. Epub 2013 Feb 13.
17. Targher G, Bertolini L, Padovani R et al. Serum 25-hydroxyvitamin D3 concentrations and carotid artery intima-media thickness among type 2 diabetic patients.Clin Endocrinol (Oxf). 2006;65:593-7.