

Original Article

Serum 25-hydroxyvitamin D levels and diabetic retinopathy: a systematic meta-analysis

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Received November 17, 2015; Accepted September 23, 2016; Epub December 1, 2016; Published December 15, 2016

Abstract: Vitamin D is a multifunctional pro-hormone, which is suggested to have protective effects against diabetes mellitus. Several studies showed a possible association between vitamin D deficiency and diabetic retinopathy (DR) in patients with diabetes. However, the results have been inconsistent. So, a systematic meta-analysis was performed to comprehensively assess the association between serum 25-hydroxyvitamin D [25(OH)D] levels and DR in patients with diabetes. In this study, multiple databases were searched until May 2015 to identify relevant studies. The search term was "vitamin D" and "diabetic retinopathy". We identified eleven studies on association between vitamin D deficiency and DR in patients with diabetes mellitus and five studies on association between vitamin D deficiency and DR in patients with T2DM. The data were accessed by software Review manager 5.2. A total of 6851 diabetic patients and 2189 T2DM patients were finally included into the meta-analysis. Meta-analysis showed that there were obviously decreased serum 25(OH)D levels in DR patients [95% confidence interval (CI) 0.92 to 2.51, $P < 0.00001$]. Vitamin D deficiency was also significantly associated with increased risk of DR in patients with T2DM [odds ratio (OR) 1.15, 95% CI 0.84-1.56, $P < 0.00001$]. Meta-analysis of three studies with adjusted estimates showed that vitamin D deficiency was independently associated with increased risk of DR in patients with type 2 diabetes (OR 2.68, 95% CI 1.67-4.30, $P < 0.0001$). We did not find evidence of publication bias. In conclusion, Vitamin D is involved in the development of DR in diabetic patients, and vitamin D deficiency is very likely to be associated with DR in type 2 diabetic patients. Further studies are needed to validate the association between vitamin D deficiency and DR.

Keywords: 25-hydroxyvitamin D, type 2 diabetes, diabetic retinopathy, meta-analysis

Introduction

Diabetic retinopathy (DR), which is among the most common diabetes complications [21, 22, 34], which affects more than 300 million individuals in the world with significant morbidity and mortality worldwide. Major risk factors for DR include a longer diabetes duration, age, smoking, poor glycemic control, and hypertension [10, 35], which have been strongly and consistently associated with DR across populations.

In parallel to the increase in the prevalence of diabetes mellitus, there has been a resurgence of vitamin D deficiency worldwide [1, 8, 25, 29], and much evidence have suggested that VDD is involved in the development of various diseases including diabetes [2, 3], cardiovascular

disease [4, 7, 23], cancer [24], and autoimmune diseases. Recent studies have shown that VD has inhibitory effects on inflammation and proliferation in endothelial cells, and angiogenesis [28, 31], which are involved in the development of DR. In addition, recent studies have also shown that Vitamin D receptor (VDR) is expressed in retina [5, 6, 9], and VD has direct inhibitory effects on the development of DR in experimental animal models. Albert et al. revealed that VD inhibits retinal neovascularization in a mouse oxygen-induced ischemic retinopathy model. Ren et al. revealed that VD has protective effects on DR by inhibiting vascular endothelial growth factor (VEGF) and transforming growth factor- β 1 (TGF- β 1) in the retinas of diabetic rats. In addition, some human genetic studies have shown that polymorphisms of VDR gene are associated with DR. These results

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Table 1. Characteristics of observational studies on 25-hydroxyvitamin D levels and Diabetic Retinopathy

Author	Year	Country	Age	Control (DM)			Case (BDR1, NPDR2, PDR3)		
				Number	Male	25(OH)D (ng/ml)	Number	Male	25(OH)D (ng/ml)
HULYA AKSOY [10]	2000	Turkey	57.3±7.37	20	12	29.8±10.50	46	23	30.9±12.48 1 35.3±13.30 2 29.0±14.20 3
Naoki Shimo [11]	2014	Japan	28.5±5.5	31	-	-	44	-	-
HARLEENKAUR [12]	2011	Australia	14.9±2.4	95	-	-	400	-	-
Hala Ahmadiéh [13]	2013	Lebanon	59±11	105	-	-	31	-	-
R. He [14]	2014	CHINA	59.03±11.67	625	317	18.86±7.12	895	456	17.44±6.19 15.36±4.81
Patricia A [15]	2014	American	62.7±11.1	1522	-	-	268	-	-
John F. Payne [16]	2012	Atlanta		82		24.3	41		23.6 2 21.1 3
Barbara J [17]	2014	Africa	55.2±13	84	39	38±11.3	66	26	25.1±14.8
Shokoufeh [18]	2014	Iran	54.8±9.4	153	27	10.3±9.4	72	15	9.0±7.0 10.1±6.8
Sarita Bajaj [19]	2014	India	52.85±8.26	104	-	23.10±6.12	54	-	19.25±7.86
Donghyun Jee [20]	2014	Korean	60.4±0.3	1738	954	18.7 (0.2)	375	204	18.3 (0.4)

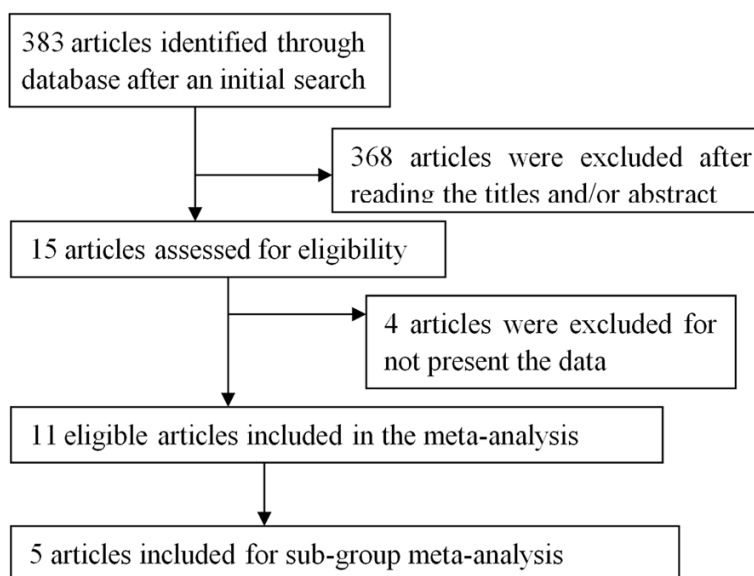


Figure 1. Flow chart of literature search and study selection.

suggest a role of VD in the pathogenesis of the development of DR.

Several studies reported a high prevalence of vitamin D deficiency in DR patients with diabetes. However, subsequent studies reported inconsistent results. As small sample size may have led to a weak or non-significant associations in those studies, the aim of this meta-analysis was to examine the association bet-

ween serum vitamin D and DR.

Methods

We generally followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. We searched literature published in PubMed, EBSCO, and Springer database until May 2015 to identify relevant studies that assessed the association between serum 25-hydroxyvitamin D and DR. Search terms included “vitamin D” and “diabetic retinopathy”.

Because there were no cohort studies, we could only select and analyze case-control and cross-sectional study which reported serum vitamin D levels of DR patients. Two authors (F.L. and K-X. W.) extracted data independently and disagreements were resolved by discussion. Information on each study is provided in **Table 1.**

In the meta-analysis graphical representation, the area of the black square indicates the weight contributed by each study. Heterogeneity

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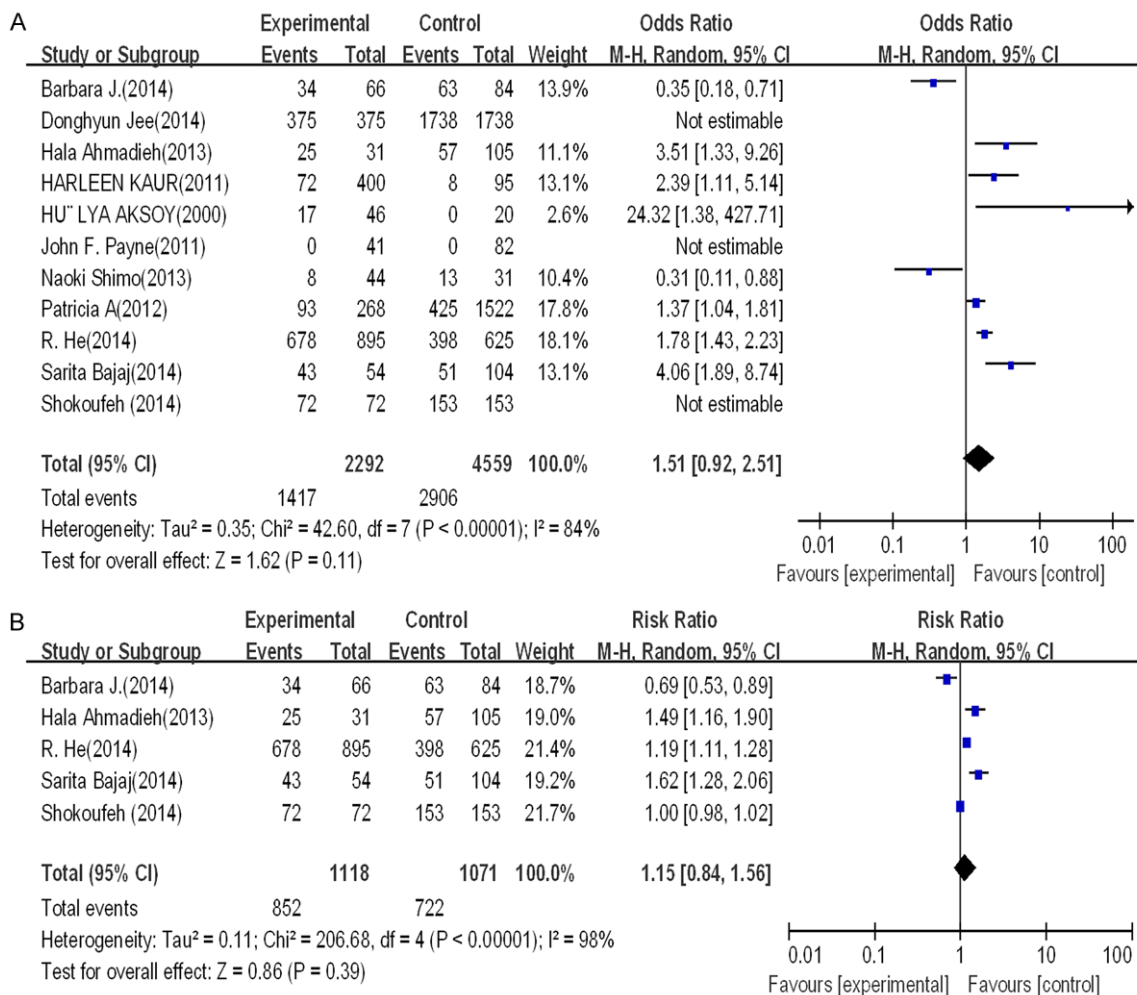


Figure 2. Meta-analysis of DM group and T2DM group. A: DM; B: T2DM.

was estimated by I^2 , substantial heterogeneity exists when I^2 exceeds 50%. A random effect model was used if heterogeneity was observed, while the fixed-effect model was applied in the absence of heterogeneity. All analyses were performed using Review Manager 5.2 software (Cochrane Collaboration, Oxford, England). A P value of less than 0.05 was considered to be statistically significant.

Results

Figure 1 presents a flow chart of the study selection process. We initially identified a total of 383 articles. After screening titles and abstracts, reviews and irrelevant articles, 15 relevant articles remained for full-text evaluation. Finally 11 studies were included in our study. Characteristics of the selected studies are presented in **Table 1**.

Meta-analysis of 25-hydroxyvitamin D and DR

In total, 6851 participants were included in this analysis. There was significant heterogeneity among the 11 studies ($I^2 = 84%$, $P < 0.00001$) and therefore a random effect model was used. The serum 25OHD levels of DM group was 1.51 ng/mL [95% confidence interval (CI): 0.92-2.51, $P < 0.0001$] lower than in control group (**Figure 2A**).

Meta-analysis of 25-hydroxyvitamin D and DR in patient with T2DM

A total of 2189 participants were included. Again a random effects model was used because of significant heterogeneity among the 5 studies ($I^2 = 98%$, $P < 0.00001$). The serum 25OHD levels of T2DM group were 1.15 ng/mL [95% confidence interval (CI): 0.84-1.56,

$P < 0.00001$] lower than the control group (Figure 2B).

Discussion

Recently, studies have evaluated the association between VD and the risk of DR [10, 32]. However, the results remain conflicting and inconsistent, and thus a systematic review and meta-analysis of association between the VD and DR were of great value. Our meta-analysis shows that patients with DR have a lower level of serum 25OHD.

If this association represents a causal link, complex mechanisms may be involved. Vitamin D affects on insulin secretion and insulin sensitivity [27]. It has immunosuppressive effect, anti-fibrotic properties and causes suppression in rennin-angiotensin system (RAS). A recent study suggested that vitamin D inhibited retinal neovascularization in a mouse model of c retinopathy and restrained endothelial cell proliferation in cell culture. Further rischaemie-search indicated that vitamin D had a protective effect on diabetic retinopathy via the inhibition of inflammation, vascular endothelial growth factor [33] and transforming growth factor- β 1 (TGF β 1) expression in retinal tissues. Some study VD can inhibit the oxidative stress among DM patients with DR [36]. Data from animal models support a causal role for vitamin D deficiency in proliferative retinopathy. Vitamin D deficiency may play a role in the pathogenesis of diabetic retinopathy. Masayuki Ouchi et al. represents Vitamin D-binding protein existed in vitreous from diabetic macular edema, which may play a role in the pathogenesis.

Some clinical trials have shown beneficial effects of vitamin D receptor (VDR) on DR [30]. Furthermore, the vitamin D receptor (VDR) is present in the human retina, and polymorphisms of VDR gene are related to retinopathy in patients with type 1 diabetes [26]. Data from Taverna MJ also support the association between VDR and low risk for severe diabetic retinopathy, especially in patients with long duration. Cyganek K et al. reported that VDR gene polymorphisms did not constitute a risk factor for type 2 diabetes patients in Polish. Zhelong Liu et al. did not find any association of the three polymorphisms (BsmI, Apal and TaqI) with an increased diabetic microvascular complications (DMI) risk in overall and subgroup

analysis by meta-analysis. However, due to complicated interactions of environmental factors and multiple genes, the precise role of VDR gene FokI polymorphism in DR remains elusive. Additional future studies should be performed to focus on the function of the VDR gene FokI polymorphism.

In the present meta-analysis, there existed a significant heterogeneity among the eleven studies. The sources of heterogeneity may come from ethnicity, gender, age, and so on, which was not performed on account of lack of information in these studies.

Conclusions

In conclusion, this meta-analysis had pooled all the available data related to the 25OHD and DR, and indicated that the 25OHD may be an increased susceptibility to DR. Therefore, more well-designed and large sample studies are warranted to confirm this conclusion, and to fully understand the mechanism of DR. Additionally, prospective cohort studies in combination with analyses of other gene and environment factors are also necessary to explore the true effect of the 25OHD on the risk of DR.

Disclosure of conflict of interest

None.

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References

- [1] Dong JY, Zhang WG, Chen JJ, Zhang ZL, Han SF, Qin LQ. Vitamin D Intake and Risk of Type 1 Diabetes: A Meta-Analysis of Observational Studies. *Nutrients* 2013; 5: 3551-3562.
- [2] Joergensen C, Hovind P, Schmedes A, Parving HH, Rossing P. Vitamin D levels, microvascular complications, and mortality in type 1 diabetes. *Diabetes Care* 2011; 34: 1081-1085.
- [3] Boucher BJ. Matrix metalloproteinase-10 and microvascular complications of type 1 diabetes: might vitamin D status be relevant?. *Diabetologia* 2014; 57: 1081.
- [4] Sheen YJ, Sheu WH. Risks of rapid decline renal function in patients with type 2 diabetes. *World J Diabetes* 2014; 5: 835-846.
- [5] Zhong X, Du Y, Lei Y, Liu N, Guo Y, Pan T. Effects of vitamin D receptor gene polymorphism and

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- clinical characteristics on risk of diabetic retinopathy in Han Chinese type 2 diabetes patients. *Gene* 2015; 566: 212-6.
- [6] Liu Z, Liu L, Chen X, He W, Yu X. Associations study of vitamin D receptor gene polymorphisms with diabetic microvascular complications: a meta-analysis. *Gene* 2014; 546: 6-10.
- [7] Alele JD, Luttrell LM, Hollis BW, Luttrell DK, Hunt KJ; VADT Study Group. Relationship between vitamin D status and incidence of vascular events in the Veterans Affairs Diabetes Trial. *Atherosclerosis* 2013; 228: 502-507.
- [8] Feng R, Li Y, Li G, Li Z, Zhang Y, Li Q, Sun C. Lower serum 25 (OH) D concentrations in type 1 diabetes: A meta-analysis. *Diabetes Res Clin Pract* 2015; 108: e71-5.
- [9] Ouchi M, West K, Crabb JW, Kinoshita S, Kamei M. Proteomic analysis of vitreous from diabetic macular edema. *Exp Eye Res* 2005; 81: 176-182.
- [10] Aksoy H, Akçay F, Kurtul N, Baykal O, Avci B. Serum 1,25 Dihydroxy Vitamin D (1,25(OH) 2D3), 25Hydroxy Vitamin D (25(OH)D) and Parathormone Levels in Diabetic Retinopathy. *Clin Biochem* 2000; 33: 47-51.
- [11] Shimo N, Yasuda T, Kaneto H, Katakami N, Kuroda A, Sakamoto F, Takahara M, Irie Y, Horikawa K, Miyashita K, Miyatsuka T, Yoshiuchi K, Kawamori D, Sakamoto K, Matsuoka TA, Kosugi K, Shimomura I, Matsuhisa M. Vitamin D deficiency is significantly associated with retinopathy in young Japanese type 1 diabetic patients. *Diabetes Res Clin Pract* 2014; 106: E41-E43.
- [12] Kaur H, Donaghue KC, Chan AK, Benitez-Aguirre P, Hing S, Lloyd M, Cusumano J, Pryke A, Craig ME. Vitamin D deficiency is associated with retinopathy in children and adolescents with type 1 diabetes. *Diabetes Care* 2011; 34: 1400-1402.
- [13] Ahmadiéh 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.
- [14] He R, Shen J, Liu F, Zeng H, Li L, Yu H, Lu H, Lu F, Wu Q, Jia W. Research: complications vitamin d deficiency increases the risk of retinopathy in chinese patients with type 2 diabetes. *Diabet Med* 2014; 31: 1657-1664.
- [15] Patrick PA, Visintainer PF, Shi Q, Weiss IA, Brand DA. Vitamin D and Retinopathy in Adults With Diabetes Mellitus. *Arch Ophthalmol* 2012; 130: 756-760.
- [16] Payne JF, Ray R, Watson DG, Delille C, Rimler E, Cleveland J, Lynn MJ, Tangpricha V, Srivastava SK. Vitamin D insufficiency in diabetic retinopathy. *Endocr Pract* 2012; 18: 185-93.
- [17] Klein BE. Overview of epidemiologic studies of diabetic retinopathy. *Ophthalmic Epidemiol* 2007; 14: 179-183.
- [18] Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen SJ, Dekker JM, Fletcher A, Grauslund J, Haffner S, Hamman RF, Ikram MK, Kayama T, Klein BE, Klein R, Krishnaiah S, Mayurasakorn K, O'Hare JP, Orchard TJ, Porta M, Rema M, Roy MS, Sharma T, Shaw J, Taylor H, Tielsch JM, Varma R, Wang JJ, Wang N, West S, Xu L, Yasuda M, Zhang X, Mitchell P, Wong TY; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012; 35: 556-564.
- [19] Jee D, Lee WK, Kang S. Prevalence and risk factors for diabetic retinopathy: the Korea National Health and Nutrition Examination Survey 2008-2011. *Invest Ophthalmol Vis Sci* 2013; 54: 6827-6833.
- [20] Mangge H, Weghuber D, Prassl R, Haara A, Schnedl W, Postolache TT, Fuchs D. The Role of Vitamin D in Atherosclerosis Inflammation Revisited: More a Bystander than a Player? *Curr Vasc Pharmacol* 2015; 13: 392-8.
- [21] Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. *Lancet Diabetes Endocrinol* 2014; 2: 76-89.
- [22] Payne JF, Ray R, Watson DG, Delille C, Rimler E, Cleveland J, Lynn MJ, Tangpricha V, Srivastava SK. Vitamin D insufficiency in diabetic retinopathy. *Endocr Pract* 2012; 18: 185-193.
- [23] Personne V, Partouche H, Souberbielle JC. [Vitamin D insufficiency and deficiency: epidemiology, measurement, prevention and treatment]. *Presse Med* 2013; 42: 1334-1342.
- [24] Györfy B, Vásárhelyi B, Krikovszky D, Madácsy L, Tordai A, Tulassay T, Szabó A. Gender-specific association of vitamin D receptor polymorphism combinations with type 1 diabetes mellitus. *Eur J Endocrinol* 2002; 147: 803-808.
- [25] Gagnon C, Lu ZX, Magliano DJ, Dunstan DW, Shaw JE, Zimmet PZ, Sikaris K, Grantham N, Ebeling PR, Daly RM. Serum 25-hydroxyvitamin D, calcium intake, and risk of type 2 diabetes after 5 years: results from a national, population-based prospective study (the Australian Diabetes, Obesity and Lifestyle study). *Diabetes Care* 2011; 34: 1133-8.
- [26] Pietschmann P, Scherthaner G, Woloszczuk W. Serum osteocalcin levels in diabetes mellitus: Analysis of the type of diabetes and microvascular complications. *Diabetologia* 1988; 31: 892-5.
- [27] Mitri J, Dawson-Hughes B, Hu FB, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic β cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: The Calcium and Vitamin D for Dia-

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- betes Mellitus (CaDDM) randomized controlled trial. *Am J Clin Nutr* 2011; 94: 486-94.
- [28] Robinson JG, Manson JE, Larson J, Liu S, Song Y, Howard BV, Phillips L, Shikany JM, Allison M, Curb JD, Johnson KC, Watts N. Lack of association between 25(OH) D levels and incident type 2 diabetes in older women. *Diabetes Care* 2011; 34: 628-34.
- [29] Chaychi L, Mackenzie T, Bilotta D, Lynch M, Cohen J, Comi R. Association of serum vitamin D level with diabetic polyneuropathy. *Med Practise Rev Feb* 2011; 2: 11-5.
- [30] Oikawa T, Hirotsani K, Ogasawara H, Katayama T, Nakamura O, Iwaguchi T, Hiragun A. Inhibition of angiogenesis by vitamin D3 analogues. *Eur J Pharmacol* 1990; 178: 247-250.
- [31] Suzuki A, Kotake M, Ono Y, Kato T, Oda N, Hayakawa N, Hashimoto S, Itoh M. Hypovitaminosis D in type 2 diabetes mellitus: Association with microvascular complications and type of treatment. *Endocr J* 2006; 53: 503-510.
- [32] Mantell DJ, Owens PE, Bundred NJ, Mawer EB, Canfield AE. 1 alpha, 25-dihydroxyvitamin D (3) inhibits angiogenesis in vitro and in vivo. *Circ Res* 2000; 87: 214-220.
- [33] Shokravi MT, Marcus DM, Alroy J, Egan K, Saornil MA, Albert DM. Vitamin D inhibits angiogenesis in transgenic murine retinoblastoma. *Invest Ophthalmol Vis Sci* 1995; 36: 83-87.
- [34] Yun YW, Shin MH, Lee YH, Rhee JA, Choi JS. Arterial stiffness is associated with diabetic retinopathy in Korean type 2 diabetic patients. *J Prev Med Public Health* 2011; 44: 260-266.
- [35] Hamden K, Carreau S, Jamoussi K, Miladi S, Lajmi S, Aloulou D, Ayadi F, Elfeki A. 1Alpha, 25 dihydroxyvitamin D3: therapeutic and preventive effects against oxidative stress, hepatic, pancreatic and renal injury in alloxan-induced diabetes in rats. *J Nutr Sci Vitaminol* 2009; 55: 215-222.
- [36] Al-Shabrawey M, Smith S. Prediction of diabetic retinopathy: role of oxidative stress and relevance of apoptotic biomarkers. *EPMA J* 2010; 1: 56-72.