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The Correlation between Changes in Biochemical Parameters and Central Macular Thickness in Patients with Non-Proliferative Diabetic Retinopathy

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ABSTRACT

This study aimed at evaluating the correlation between changes in Hemoglobin A1c (HbA1c) and fasting serum lipids, and Central Macular Thickness (CMT) in patients with Non-Proliferative Diabetic Retinopathy (NPDR).

In the current research, both eyes of 68 patients with mild or moderate NPDR, without clinically significant macular edema, were studied. Levels of fasting serum lipids, HbAlc, and CMT were measured during the first visit and at the end of the follow-up period (3 months). For statistical analysis, CMTs of each eye were studied and the correlation of changes was investigated. Additionally, the direction of changes in CMT for each eye was determined, and whether the changes in both eyes were symmetrical was investigated.

Out of 68 patients, 24 were male and 44 were female. The mean CMT of all eyes was 290.05 ± 48.90 µm during the first visit and 286.80 ± 37.57 µm on the 3rd month follow-up. The mean HbAlc was 8.71 ± 1.82% at first visit to the hospital and the mean HbAlc was 8.39 ± 1.65% at the final visit. Although the changes in HbA1c and CMT during the follow-up period were statistically insignificant, the correlation of these 2 values was statistically significant (p=0.01). However, amongst l3 patients, the CMTs were asymmetrically changed in each eye during the follow-up period.

To the best of the author's knowledge, this was the first study, which indicated a significant correlation in changes of CMT and HbA1c, even amongst patients with low-grade diabetic retinopathy. Demonstration of asymmetric changes in CMT of each treatment-naive eye of the same patient, during changes in systemic conditions, was another important finding of this study.

KEY WORDS

HbA1c; Macular Edema; Central Macular Thickness; Non-Proliferative Diabetic Retinopathy

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INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic syndrome characterized by hyperglycemia due to insulin resistance. Long-standing DM influences many organs and tissues, leading to several complications, such as Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME) [1, 2]. The pathogenesis of DME remains unclear as complex processes, with various contributing factors, seem to be involved. Increasing diabetes duration with chronic

hyperglycemia, advanced glycation end-products, such as levels of glycosylated hemoglobin (HbA1c), free oxygen radicals, protein kinase C, hypercholesterolemia, and blood pressure play important roles in such progressive metabolic diseases [3-5]. Hemoglobin A1c is the index of average glycemic control over the previous 2 to 3 months and indicates the level of diabetic control; therefore, increased HbA1c concentration is the most important risk factor for the development of DM complications, mainly DME [6]. Several conflicting reports regarding the effect of serum lipid profile on macular edema have been published, a number of which did not show any statistical correlation between serum lipid parameters and CMT, while others showed that high serum lipid levels indicate a risk of hard exudate and macular edema development [3-6]. The purpose of the current study was to evaluate and compare the correlation between changes in HbA1c, fasting serum lipids, and Central Macular Thickness (CMT) in patients with low-grade DR. Additionally, the researchers aimed at examining whether the changes in CMT of each eye were symmetrical under the changing systemic conditions of the same subject.

MATERIALS AND METHODS

The current study was carried out at the Ulucanlar Eye Education and Research Hospital. All procedures were designed in accordance with ethical standards and principles of the Declaration of Helsinki for human subjects. The Medical Ethics Committee of Diskapi Training and Research Hospital reviewed and approved the study protocol and informed consent forms were obtained from all participants. Both eyes of 68 patients with type 2 DM and mild or moderate Non-Proliferative DR (NPDR) and without Clinical Significant Macular Edema (CSME), according to the criteria of the International Clinical Diabetic Retinopathy Disease Severity Scale [7] and Early Treatment Diabetic Retinopathy Study (ETDRS), were studied in the current research [8]. The presence of type 2 DM in each patient was confirmed by an internal medicine consultant. For systemic evaluation, presence of other systemic diseases associated with type 2 DM, including hypertension, diabetic nephropathy, and diabetic neuropathy, and types of diabetic treatment and history of other medications, such as antihypertensive, were recorded for each patient. Patients with a history of other retinal diseases, glaucoma, uveitis, ocular trauma, and any type of ocular surgery, eyes with proliferative DR, laser photocoagulation or intravitreal injections were excluded from the current study. All patients had undergone detailed ophthalmic evaluation including Visual Acuity (VA) and intraocular pressure measurement, detailed slit lamp, and dilated fundus examinations. All measurements and evaluations were performed on the patients' first visit and at the 3rd month follow-up. None of the patients had ocular risk factors, such as cataract extraction, trauma, inflammation, and topical treatment, which may affect CMT during this period. To evaluate the correlation between changes in biochemical parameters, including fasting serum lipids, levels of High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Triglyceride (TG), and plasma HbA1c were recorded for each subject through peripheral blood sampling. Samples were evaluated with standard methods, including a Roche Modular-P 800 device (Roche Diagnostic, GmbH, Germany) for fasting serum lipids. Low-Density Lipoprotein levels were calculated with available lipid data, using the Friedewald formula. Hemoglobin A1c was measured by high-performance liquid chromatography-ultraviolet detection [9].

Central Macular Thickness was measured on the same day of serum parameters evaluation. Spectral Domain Optical Coherence Tomography (SD-OCT) (Spectralis; Heidelberg Engineering, Heidelberg, Germany), volume scans of 20x20 degree, consisting of 49 horizontal high-resolution line sections and including scanning laser ophthalmoscopy en face and fundus auto-fluorescence images of the macula were obtained with HRA2 (Heidelberg Retina Angiograph-Optical Coherence Tomography, Heidelberg Engineering, Heidelberg, Germany). The morphology of central retinas, such as macular cystic changes or diffuse macular thickening, was evaluated by the same observer. Central Macular Thickness was measured from the same area each time with the aid of an eye tracker system, and to obtain high quality images without pupil dilation, motion artifacts were eliminated by the SD-OCT device. To evaluate changes in CMT during the follow-up period, differences in macular thickness in the same location of the fovea were calculated with the progression mode of the SD-OCT devices, during each observation period. The direction of CMT changes for each eye was determined by different analysis systems in OCT. Statistical analyses of data were performed using the Statistical Package for the Social Sciences software (SPSS Inc., Chicago, IL, USA), version 24. The normality of variables was assessed by the Kolmogorov-Smirnov test and the variables were evaluated with statistical methods. The Wilcoxon test was used for comparison of each parameter, measured during different examination periods, as variables did not have a normal distribution. In order to evaluate the correlations between non-normally distributed variables, the correlation coefficients and their significance were

calculated using the Spearman's correlation test. Mann-Whitney U test was used to evaluate the significance of correlations between non-normally distributed numerical variables of different groups. To evaluate the correlation between changes of HbAlc, the CMT chi-square test was performed. The P values of < 0.05 were considered significant.

RESULTS

Amongst 68 patients, 24 (35.30%) were male and 44 (64.70%) were female. The number of female subjects was significantly more than male subjects (P = 0.03). The mean age was 57.5 years (range of 38 to 80 years). The mean age in the female group was 60 years (range of 39 to 74 years), while it was 53 years (range of 38 to 80 years) in male patients. The difference was statistically insignificant (P = 0.10). Hypertension was observed in 28 (41.2%) out of 68 cases, being the most frequent systemic disease associated with DM in the current study. There was also no significant difference between genders regarding the presence of hypertension (p=0.14). Any other complications of DM, such as polyneuropathy, nephropathy, history of dialyses, diabetic foot or any other systemic disease, were not present in any of the patients. A total of 43 patients were under insulin treatment, while 23 were receiving oral anti-diabetic medication, 1 patient was under combined treatment of oral anti-diabetic medications and insulin injection, and only 1 patient did not require any systemic treatment for DM. The summary of demographic data, presence of hypertension, and treatment protocol of diabetes mellitus, according to gender, is presented in Table 1.

The mean HbAlc was 8.71 ± 1.82% when the patients were first presented to the hospital, while it changed to 8.39 ± 1.65% on the 3rd month follow-up. The mean HbAlc was significantly higher than the recommended upper limits of patients with diabetes, according to the American Diabetes Association (ADA) recommendations [10]. In 22 patients, the HbA1c level was increased, while it was decreased in 39 patients, and in only 7 subjects, the HbA1c level remained the same. Both during the initial visit and on the 3rd month, HbA1c levels were normally distributed, as evaluated by the Kolmogrov-Smirnov test, and there was an insignificant decrease during the 3rd month follow-up visit (P = 0.06). Furthermore, the difference between fasting serum lipid measurements was not statistically significant (p values were 0.25, 0.62, and 0.09 when comparing HDL, LDL, and TG levels, respectively). All of these serum parameters were also normally distributed during each period. When the patients were first presented, the mean CMT of all eye examinations was 290.05 ± 48.90 µm, while it became 286.80 ± 37.57 µm on the 3rd month follow-up. The difference between CMT during the 2 observation periods was statistically insignificant (P = 0.11), although a slight decrease was observed on the 3rd month follow-up visit. In contrast to serum parameters, CMTs were not normally distributed during both observation periods. The mean value ± Standard Deviation (SD) of HbA1c, serum lipids, and CMT during the first and final visit are presented in Table 2.

Table 1. Summary of Demographic Data, Presence of Hypertension, and Treatment Protocol of Patients with Diabetes Mellitus According to Gender

Variables	Male	Female	P value*
Demographic data			
Sample size, n	24	44	0.027
Mean age, Y	53	60	0.103
Hypertension, n	7	21	0.137
Treatment protocol			
Insulin, n	13	30	0.316
Oral anti-diabetic medication, n	10	13	0.628
Insulin + Oral anti-diabetic medication, n	0	1	

n = number; Y = years. *P Value for all Treatment Groups according to the MANN-Whitney U Test.

A total of 41 patients out of 68 patients had parallel changes in HbAlc and CMT. Both the HbAlc and CMT were increased in 16 patients, and in 25 patients, they decreased during the follow-up period. On the other hand, in 20 (29.41%) patients, HbAlc changes were discorrelated with CMTs, in which 14 patients' HbAlc levels were decreased while the CMTs were increased, and in 6 patients HbA1c were increased while the CMTs were decreased. The overall changes in HbA1c and CMT during the follow-up period were significantly correlated, according to Yates continuity correction of chi-square test (P = 0.01). However, none of the serum lipid changes were correlated with the CMT changes (P values were 0.09, 0.15, and 0.70 when comparing HDL, LDL, and TG, respectively). Analyses of the correlation of differences in CMT with HbA1c, HDL, LDL, and TG are provided in Table 3.

Table 2. The Mean Value ± Standard Deviation of Hemoglobin A1c, Serum Lipids, and Central Macular Thickness During the First and Final Visit

Variables	First visit	Last visit	P value*
Hemoglobin A1c (%)	8.71 ± 1.8	8.39 ± 1.6	0.062
Serum lipids			
HDL (mmol/L)	48.3 ± 11.8	49.5 ± 15.9	0.254
LDL (mmol/L)	119.1 ± 44.4	118.6 ± 54.7	0.623
TG (mmol/L)	165.3 ± 89	159.5 ± 94	0.094
CMT (µm)	290.5 ± 48.90	286.8 ± 37.57	0.107

HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; TG = Triglyceride; CMT = Central Macular Thickness; % = Percentage; mmol/L = Millimoles per Litre; µm = Micrometer; SD = Standard Deviation. *P Value for all Treatment Groups according to Wilcoxon Test.

Table 3. Analyses of the Correlation of Differences in Central Macular Thickness with Hemoglobin A1c, High-Density Lipoprotein, Low-Density Lipoprotein, and Triglyceride

Variables	Central macular thickness		P value*
	Increased (n)	Decreased (n)	
Hemoglobin A1c			0.013
Increased (n)	6 (27.3 %)	16 (72.7 %)	
Decreased (n)	25 (64.1 %)	14 (35.9 %)	
High-density lipoprotein			0.092
Increased (n)	20 (64.5 %)	11 (35.5 %)	
Decreased (n)	10 (38.5 %)	16 (61.5 %)	
Low-density lipoprotein			0.154
Increased (n)	12 (41.4 %)	17 (58.6%)	
Decreased (n)	19 (63.3 %)	11 (36.7 %)	
Triglyceride			0.701
Increased (n)	13 (46.4 %)	15 (53.6 %)	
Decreased (n)	18 (54.5 %)	15 (45.5 %)	

CMT = Central Macular Thickness; HbA1c = Hemoglobin A1c; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; TG=Triglyceride; n = Number; % = Percentage.*P Value for all Treatment Groups according to Chi-Square Test.

A total of 55 subjects (80.88%) had CMT changes, which had the same direction in both eyes of the same patient. In 28 subjects, CMTs of both eyes were decreased while it was increased in both eyes of 27 subjects. During the follow-up period, in 13 subjects (19.11%), CMTs were asymmetrically changed, amongst which in 3 subjects CMTs were increased in one eye while it remained the same in the other eye. Similarly, in 3 subjects, CMT was decreased in one eye while its level did not change on the other side, and in 7 subjects, CMT was increased in one eye while it was decreased in the other eye.

DISCUSSION

In the current study, a correlation was found between macular thickness and both HbA1c and fasting serum lipids, as an indirect evidence of metabolic control. Type 2 DM is a complex disease and the risk of developing DR was found to be associated with several factors, such as diabetes duration, cardiovascular disease, and blood pressure [2, 5, 6]. Thapa et al. [6] found that concurrent hypertension was observed in 55.76% and abnormal lipid profile in 52.56% of their subjects. In the current study, results similar to that of Thapa et al. [6] were found. In the mentioned study, hypertension was observed in 58.82% of patients, being the most frequent systemic-associated factor in patients with diabetes. In clinical practice, decision to initiate treatment is based on retinal findings in biomicroscopy and SD-OCT changes rather than VA. The findings of Pieramici et al. [11] reaffirm the discordance between retinal thickness and VA, which had been widely accepted and demonstrated previously. In accordance with previous studies, the current evaluation also focused on the anatomic correlation with both fasting blood lipids and HbAlc rather than VA. Thapa et al. [6] observed that poor glycemic control (HbA1c > 7%) was found in 73.97% of newly diagnosed proliferative DR among patients with type 2 DM. Even though the current study only evaluated NPDR, high HbA1c (HbA1c > 7%) was seen in 79.4% of the subjects during both visits, which was very similar to the results of Thapa et al. This finding indicates that uncontrolled blood sugar is very common in patients with DR of any stage. According to several studies, reduction of HbAlc values decreases the risk of development or progression of any stage of DR

among patients with type 2 DM [6, 12-14]. In addition, Benarous et al. [13] reported that HbA1c had a positive correlation with DR stage, which was 7.3% in patient without DR, 8.0% in eyes with DR, 8.1% in eyes with DME, and increased up to 8.3% in eyes with CSME. Various studies have indicated that a higher HbA1c level is associated with the occurrence of DME [14, 15]. Jew et al. [5] published his work on the correlation between HbA1c and DME, in which the HbA1c was 7.8% in eyes without DME while it was 10.3% in eyes with DME. Such studies suggest a significant correlation between HbA1c and different stages of DR, yet the range of systemic and local conditions between mild NPDR and severe proliferative DR is very large. Additionally, DME is an important outcome and can occur at any stage of DR, being a major cause of visual impairment and blindness. Several SD-OCT images on DME, such as diffuse retinal thickening, serous retinal detachment, tractional retinal detachment due to posterior hyaloid traction, and cystoid macular edema, have been described, with all of these patterns generally co-existing with one another [16-18]. To evaluate the real effect of systemic factors on CMT and exclude local factors, the current study did not include patients with vitreomacular/vitreopapillary traction. To enhance homogeneity and validity of the study group, only the treatment-naive eyes with mild and moderate NPDR, which did not need laser photocoagulation or intravitreal anti-Vascular Endothelial Growth Factor (anti-VEGF) injection, were evaluated.

In the current study, the mean HbA1c was 8.71% and CMT was 290.05 µm at initial visit, while the mean HbA1c was decreased to 8.39% and CMT was decreased to 286.8 µm in eyes with NPDR. A total of 60.29% of patients had parallel changes in HbA1c and CMT, which was statistically correlated. Ozturk et al. [19] found similar results, where the serum HbAlc values were found to correlate with change in CMT during the anti-VGF treatment. The mean HbAlc was 8.25 ± 1.74% (range of 5.7% to 12.7%) in their sample, which was very similar to that of the current study, while the mean CMT was 468 µm (range of 255 to 964 µm) in their study, which was higher than the current subjects. This may be because patients with advanced DR, who needed anti-VGF treatment, were enrolled in their study. Suwal et al. [2] showed that each of the serum lipid associations with DME were not statistically significant and serum lipid profiles, including total cholesterol, HDL, LDL, and TG, had no effect on CMT. Similarly, Benarous et al. [13], found that serum lipid levels were not correlated with the development of DME or increased macular thickness. On the other hand, Sasaki et al. (20) observed that total cholesterol, HDL, and TG levels were not significantly associated with CMT; however, LDL was positively associated with CMT. The current study did not evaluate subjects with DME and each of the subjects had low-grade DR compared with the studies of Suwal et al. [2] and Benarous et al. [13]. No one developed DME during the follow-up period in the current study. In this study, while there was an absence of association with any type of fasting serum lipids and CMT changes, a significant correlation was observed between HbAlc and CMT changes during the observation period. This result showed that blood sugar level may be an essential determining factor for CMT. Altintas et al. [20] reported that the mean CMT of both eyes with NPDR was 297.12 µm, as evaluated by SD-OCT. The CMT of each eye was not symmetrical in most of the patients, being 304.40 µm in the worse eye and 273.28 µm in the better eye. In the current study, l3 patients' CMTs were asymmetrically changed in each eye of the same patient. This means that under different systemic conditions, while changing the HbA1c and fasting serum lipids level in the follow-up period in the same subjects, each retina could behave differently. Therefore, other local factors may influence each macula differently in the same subject. There is an upregulation of growth factors and cytokines, including angiopoietins, tumor necrosis factor, interleukins, and matrix metalloproteinases that contribute to the breakdown of the blood retinal barrier with consequent vascular leakage, finally being responsible for DME. Therefore, due to several variabilities in each patient, and even in each eye in the same patient, different responses to the same type of therapy could be indicated. To the best of the author's knowledge, the current study was the first that revealed a significant correlation in changes of CMT and HbA1c, and even a slight alteration in HbA1c in eyes with treatment naive NPDR. Demonstration of asymmetric changes in CMT for both eyes of the same patient under changing systemic conditions is another important outcome of the current research. The limitation of this study was the short follow up period, and further studies are required to evaluate local factors that cause asymmetric involvement of each macula in the same patient.

DISCLOSURE

No funding or sponsorship was received for this study. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

REFERENCES

1. Martinell M, Dorkhan M, Stalhammar J, Storm P, Groop L, Gustavsson C. Prevalence and risk factors for diabetic retinopathy at diagnosis (DRAD) in patients recently diagnosed with type 2 diabetes (T2D) or latent autoimmune diabetes in the adult (LADA). J Diabetes Complications. 2016;30(8):1456-61. DOI: 10.1016/j.jdiacomp.2016.08.009 PMID: 27593902
2. Suwal B, Shrestha JK, Joshi SN, Sharma AK. Diabetic retinopathy with or without clinically significant macular edema: The influencing factors. Nepal J Ophthalmol. 2016;7(2):142-7.
3. Matthews DR, Stratton IM, Aldington SJ, Holman RR, Kohner EM, Group UKPDS. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. Arch Ophthalmol. 2004;122(11):1631-40. DOI: 10.1001/archopht.122.11.1631 PMID: 15534123
4. Tajunisah I, Nabilah H, Reddy SC. Prevalence and risk factors for diabetic retinopathy--a study of 217 patients from University of Malaya Medical Centre. Med J Malaysia. 2006;61(4):451-6. PMID: 17243523
5. Jew OM, Peyman M, Chen TC, Visvaraja S. Risk factors for clinically significant macular edema in a multi-ethnics population with type 2 diabetes. Int J Ophthalmol. 2012;5(4):499-504. DOI: 10.3980/j.issn.2222-3959.2012.04.18 PMID: 22937513
6. Thapa R, Bajimaya S, Sharma S, Rai BB, Paudyal G. Systemic association of newly diagnosed proliferative diabetic retinopathy among type 2 diabetes patients presented at a tertiary eye hospital of Nepal. Nepal J Ophthalmol. 2015;7(1):26-32. DOI: 10.3126/nepjoph.v7i1.13163 PMID: 26695602
7. Wilkinson CP, Ferris FL, 3rd, Klein RE, Lee PP, Agardh CD, Davis M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110(9):1677-82. DOI: 10.1016/S0161-6420(03) 00475-5 PMID: 13129861
8. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985;103(12):1796-806. PMID: 2866759
9. Abraham EC, Huff TA, Cope ND, Wilson JB, Jr., Bransome ED, Jr., Huisman TH. Determination of the glycosylated hemoglobins (HB AI) with a new microcolumn procedure. Suitability of the technique for assessing the clinical management of diabetes mellitus. Diabetes. 1978;27(9):931-7. PMID: 689304
10. American Diabetes A. Executive summary: Standards of medical care in diabetes--2014. Diabetes Care. 2014;37 Suppl 1(Supplement_1):S5-13. DOI: 10.2337/dc14-S005 PMID: 24357214
11. Pieramici DJ, Wang PW, Ding B, Gune S. Visual and Anatomic Outcomes in Patients with Diabetic Macular Edema with Limited Initial Anatomic Response to Ranibizumab in RIDE and RISE. Ophthalmology. 2016;123(6):1345-50. DOI: 10.1016/j.ophtha.2016.02.007 PMID: 26992841
12. Canadian Ophthalmological Society Diabetic Retinopathy Clinical Practice Guideline Expert C, Hooper P, Boucher MC, Cruess A, Dawson KG, Delpero W, et al. Canadian Ophthalmological Society Evidence-based Clinical Practice Guidelines for the Management of Diabetic Retinopathy - executive summary. Can J Ophthalmol. 2012;47(2):91-6. DOI: 10.1016/j.jcjo. 2012.01.022 PMID: 22560411
13. Benarous R, Sasongko MB, Qureshi S, Fenwick E, Dirani M, Wong TY, et al. Differential association of serum lipids with diabetic retinopathy and diabetic macular edema. Invest Ophthalmol Vis Sci. 2011;52(10):7464-9. DOI: 10.1167/iovs.11-7598 PMID: 21862642
14. Unsal E, Eltutar K, Zirtiloglu S, Dincer N, Ozdogan Erkul S, Gungel H. Choroidal thickness in patients with diabetic retinopathy. Clin Ophthalmol. 2014;8:637-42. DOI: 10.2147/OPTH.S59395 PMID: 24707168
15. Cetin EN, Bulgu Y, Ozdemir S, Topsakal S, Akin F, Aybek H, et al. Association of serum lipid levels with diabetic retinopathy. Int J Ophthalmol. 2013;6(3):346-9. DOI: 10.3980/j.issn.2222-3959.2013.03.17 PMID: 238265 31
16. Bandello F, Midena E, Menchini U, Lanzetta P. Recommendations for the appropriate management of diabetic macular edema: Light on DME survey and consensus document by an expert panel. Eur J Ophthalmol. 2016;26(3):252-61. DOI: 10.5301/ejo.5000736 PMID: 26776698
17. Kim BY, Smith SD, Kaiser PK. Optical coherence tomographic patterns of diabetic macular edema. Am J Ophthalmol. 2006;142(3):405-12. DOI: 10.1016/j.ajo.2006.04.023 PMID: 16935584
18. Browning DJ, Altaweel MM, Bressler NM, Bressler SB, Scott IU, Diabetic Retinopathy Clinical Research N. Diabetic macular edema: what is focal and what is diffuse? Am J Ophthalmol. 2008;146(5):649-55, 55 e1-6. DOI: 10.1016/j.ajo.2008.07.013 PMID: 18774122
19. Ozturk BT, Kerimoglu H, Adam M, Gunduz K, Okudan S. Glucose regulation influences treatment outcome in ranibizumab treatment for diabetic macular edema. J

Diabetes Complications. 2011;25(5):298-302. DOI: 10.1016/j.jdiacomp.2010.09.006 PMID: 21075650

20. Kocak Altintas A, Citirik M, Gulpamuk B. Relationship of Serum HbA1c and Fasting Serum Lipids with Central Macular Thickness in Patients with Type 2 Diabetes Mellitus. J Clin Res Ophthalmol. 2016;3(1):23-6. DOI: 10.17352/2455-1414.00003