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Clinical examination and fundus photography in diabetic retinopathy screening

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Ethics Committee Approval
Adnan Menderes University Faculty of Medicine Ethics Committee approved the study [Protocol No: 2016/927].
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: An increasing number of patients and an ophthalmologist shortage in some areas necessitate reaching more patients in a shorter time to decrease the burden of devastating visual complications of diabetic retinopathy (DR). Screening and diagnosing DR using fundus photographs may save time and effort. In this study, we aimed to report the results of DR screening in a Turkish treatment-naive diabetes mellitus (DM) patient group by examining fundus photographs taken with ETDRS protocol and compare them with clinical examination and optical coherence tomography (OCT) findings.

Methods: Two hundred and ninety-two eyes of 150 DR treatment-naive DM patients were included in this cross-sectional study. Complete ophthalmic examination was performed by a single examiner. Fundus photograph acquisition according to ETDRS protocol and OCT were performed by an experienced technician. Fundus photographs were evaluated by the same examiner who was blinded to patient names, at the end of the study period.

Results: Two hundred and ninety-two eyes of 150 DR treatment-naive DM patients' findings were evaluated. According to stereoscopic fundus examination, 76 (26%) eyes showed no signs of DR, 76 (26%) eyes showed mild non-proliferative diabetic retinopathy (NPDR) signs, 44 eyes (15.1%) showed moderate NPDR signs, 78 eyes (26.7%) showed severe NPDR signs, and 18 eyes (6.2%) showed PDR signs. According to images acquired with the ETDRS protocol, 79 (27.1%) eyes showed no signs of DR, 81 (27.7%) eyes showed mild NPDR signs, 50 eyes (17.1%) showed moderate NPDR signs, 68 eyes (23.3%) showed severe NPDR signs, and 14 eyes (4.8%) showed PDR signs. Clinical examination and fundus photography showed substantial agreement in detecting DR severity (Kappa value: 0.78, $P<0.001$). Diabetic macular edema (DME) was present in 106 and 68 eyes according to OCT and ETDRS fundus photographs, respectively. These two methods showed moderate agreement in detecting DME (Kappa value: 0.57, $P<0.001$). ETDRS fundus photography is an effective method for screening DR severity in a Turkish DR population. When patients with no evident DR findings were excluded, we found a statistically significant negative correlation ($P<0.001$, Spearman Rho coefficient: -0.306) between central retinal thickness and best-corrected visual acuity, as expected.

Conclusion: For screening DR severity, ETDRS fundus photography is an effective method in a Turkish DR population.

Keywords: Diabetic retinopathy, Optical coherence tomography, Clinical examination, Fundus photography

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Introduction

Diabetes Mellitus (DM) is a chronic disease caused by ineffectiveness or deficiency of the insulin hormone [1]. Long-term hyperglycemia causes damage leading to loss of function and insufficiency [2]. Diabetic retinopathy (DR) is the leading cause of legal blindness all over the world [3]. DR prevalence is 34.6% in DM patients aged over 40 years, whereas sight-threatening DR prevalence is %10.2 in the same population [4, 5]. The most important risk factor for DR is the duration of the disease [6]. Once DR begins, glycemic control outweighs disease duration for predicting progression [7, 8]. Recommended first eye examination is the moment of diagnosis for type 1 and five years after the diagnosis for type 2 DM [9].

Despite advanced DR stages, patients can still have good visual acuity. The increasing number of patients necessitates reaching more patients in a shorter time. In this study, we aimed to compare clinical examination, optical coherence tomography (OCT), and fundus photography findings of treatment-naive DM patients. Also, OCT findings were evaluated with respect to DR stage and HbA1C levels.

Materials and methods

In this prospective study, treatment-naive 150 DM patients with DR were enrolled from the Endocrinology department.

Spearman correlation coefficient calculated from the diabetic retinopathy staging table in the "Nonmydriatic Ultrawide Field Retinal Imaging Compared with Dilated Standard 7-Field 35-mm Photography and Retinal Specialist Examination for Evaluation of Diabetic Retinopathy" study was used for power analysis at a tolerance rate of 7%, alpha value of 0.05 and statistical power of 0.80. Based on the results, at least 123 cases were needed.

Patients with DR treatment history, posterior segment pathologies other than DR, posterior segment surgery history, media opacity blocking fundus view were excluded from the study. Age, gender, duration of DM, a medication used for DM and duration of usage, HbA1C levels within the last three months of enrolment, and other systemic diseases were recorded. A complete ophthalmologic examination including best-corrected visual acuity (BCVA), intraocular pressure (IOP) anterior segment, and dilated fundus examination findings were recorded by one ophthalmologist. One technician performed OCT scans and took fundus photographs according to the ETDRS protocol. Dilated fundus findings were recorded using a +90D lens by one ophthalmologist. International clinical diabetic retinopathy disease severity scale (10) was used for grading DR. After dilated fundus examination, an experienced technician performed OCT scans and took fundus photographs with Kowa VX-20 (Kowa Company, Ltd, Aichi, Japan) according to the ETDRS protocol. Fundus photographs were evaluated at the end of the patient enrolment period by the same ophthalmologist blinded to the patient names. OCT scans were performed in a dusky room with Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA) macular cube 512x128 protocol. Scans with a signal strength of 7/10 or more were recorded for evaluation. Central retinal thickness (CRT) values were recorded from OCT scans. HbA1C levels were obtained from endocrinology records. DR grades decided with dilated fundus examination and fundus photographs were compared. Consistency between OCT and examination findings was analyzed.

Statistical analysis

For statistical analysis, Statistical Package for the Social Sciences 17 [SPSS] program was used. For the analysis of quantitative data, compatibility with normal distribution was examined with the Kolmogorov-Smirnov test; parametric methods were used in the analysis of variables with normal distribution, and non-parametric methods were used in the analysis of variables without normal distribution. The Mann-Whitney U test was used to compare independent binary groups. Spearman Rho test was used to examine the correlations of quantitative data with each other. In the comparison of categorical data, the Pearson Chi-square test was used. Quantitative data are expressed in the tables as mean (standard deviation). Categorical data are expressed in numbers (n) and percentages (%). The data were analyzed at a 95% confidence level and a *p*-value of less than 0.05 was considered significant. The agreement of DR stages between the methods was transferred to the crosstab. Kappa values were calculated and interpreted according to the Landis and Koch classification (0-0.20, slight, 0.21–0.40, fair, 0.41–0.60, moderate, 0.61–0.80, substantial, 0.81–1.00, almost perfect). For every patient included in the study, written informed consent was obtained. Adnan Menderes University Faculty of Medicine Ethics Committee approved the study [Protocol No: 2016/927]. This study was performed in line with the principles of the Declaration of Helsinki.

Results

Two hundred and ninety-two eyes of 150 patients (79 females (52.6%), 71 males (47. 4%)) were enrolled. Only one eye was included in eight patients. The mean age of the patients was 61.71(8.85) years. The mean duration of DM was 12.02(7.2) years and mean HbA1C levels within the last three months were %6.96 (1.27). Seventy-eight (%52) patients were using oral antidiabetic agents only, while 72 patients (48%) were on insulin. The mean best-corrected visual acuity (BCVA) of the whole patient group was 0.64 (0.30) and the mean intraocular pressure (IOP) measured with a pneumatic tonometer was 15.36 (2.90) mmHg (Table 1).

Table 1: Patient demographics according to DR severity and overall patient group

		Diabetic Retinopathy Severity					
		No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	Overall
Age	Mean	59.63	64.42	63.16	60.99	58.28	61.69
	SD	7.89	8.23	8.05	10.46	5.92	8.85
HbA1c	Mean	6.47	6.96	7.22	7.08	7.31	6.92
	SD	1.26	1.28	1.15	1.12	1.67	1.27
Visual Acuity	Mean	0.84	0.68	0.55	0.51	0.46	0.64
	SD	0.22	0.28	0.27	0.31	0.31	0.30
IOP	Mean	16.03	15.88	14.48	14.91	14.39	15.36
	SD	2.80	3.40	2.45	2.67	1.97	2.90
DM Duration	Mean	8.97	12.50	11.66	14.19	15.28	12.08
	SD	7.08	6.80	6.76	7.31	6.11	7.23
	N	76	76	44	78	18	292

DR: Diabetic retinopathy, NPDR: non-Proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, HbA1c: Hemoglobin A1c, IOP: Intraocular pressure, DM: Diabetes mellitus, SD: Standard deviation

According to stereoscopic fundus examination, 76 eyes (26%) showed no signs of DR, 76 eyes (26%) showed mild non-proliferative diabetic retinopathy (NPDR) signs, 44 eyes (%15.1)

showed moderate NPDR signs, 78 eyes (%26.7) showed severe NPDR signs and 18 eyes (6.2%) showed proliferative diabetic retinopathy (PDR) signs. According to images acquired with the ETDRS protocol, 79 eyes (27.1%) showed no signs of DR, 81 eyes (27.7%) showed mild NPDR signs, 50 eyes (17.1%) showed moderate NPDR signs, 68 eyes (23.3%) showed severe NPDR signs, and 14 eyes (4.8%) showed PDR signs. According to Field 2 image acquired with ETDRS protocol, 98 eyes (33.5%) showed no signs of DR, 84 eyes (28.8%) showed mild NPDR signs, 52 eyes (17.8%) showed moderate NPDR signs, 48 eyes (16.4%) showed severe NPDR signs, and 10 eyes (3.4%) showed PDR signs. Clinical examination and ETDRS fundus photographs showed a significant substantial agreement in detecting DR severity (Kappa value: 0.78 $P<0.001$) (Table 2).

Diabetic macular edema (DME) was diagnosed in 106 eyes with OCT, while 100 eyes had DME according to stereoscopic fundus examination. The sensitivity and specificity of detecting DME with stereoscopic fundus examination were 76.4% and 89.8%, respectively (Table 3). These two methods showed substantial agreement in detecting DME (Kappa value: 0.67; $P<0.001$). According to images acquired with the ETDRS protocol, 68 eyes were diagnosed with DME. When compared with the OCT data, these two methods showed a significant moderate agreement in detecting DME (Kappa value: 0.57, $P<0.001$).

Table 2: Cross-tabulation of diabetic retinopathy (DR) severity staging with clinical examination and ETDRS fundus photography

			Clinical Examination Stage					
			No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	Total
ETDRS Fundus Photography Stage	No DR	N	69	8	2	0	0	79
		%	90.8%	10.5%	4.5%	0.0%	0.0%	27.1%
	Mild NPDR	N	7	62	7	5	0	81
		%	9.2%	81.6%	15.9%	6.4%	0.0%	27.7%
	Moderate NPDR	N	0	6	34	8	2	50
		%	0.0%	7.9%	77.3%	10.3%	11.1%	17.2%
	Severe NPDR	N	0	0	1	65	2	68
		%	0.0%	0.0%	2.3%	83.3%	11.1%	23.3%
	PDR	N	0	0	0	0	14	14
		%	0.0%	0.0%	0.0%	0.0%	77.8%	4.7%
Total		N	76	76	44	78	18	
		%	100.0%	100.0%	100.0%	100.0%	100.0%	

DR: Diabetic retinopathy, NPDR: non-Proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, ETDRS: Early treatment diabetic retinopathy study

Table 3: OCT and clinical examination cross-tabulation for DME detection

			OCT		Total
			Normal	Edema	
Clinical Examination	Normal	N	167	25	192
		%	89.8%	23.6%	65.8%
	Edema	N	19	81	100
		%	10.2%	76.4%	34.2%
Total		N	186	106	292
		%	100.0%	100.0%	100.0%

OCT: Optical coherence tomography

Central retinal thickness (CRT) and BCVA had an insignificant negative correlation (Spearman Rho coefficient: -0.104) ($P=0.076$). When patients with no evident DR findings were excluded, a statistically significant negative correlation ($P<0.001$, Spearman Rho coefficient: -0.306) was found between CRT and BCVA.

The mean HbA1c levels of patients were 6.0% (5.7-6.7) in those with no apparent DR findings, 6.8% (6.1-7.47) in the mild NPDR, 7.1% (6.3-8.2) in the moderate NPDR, 7.05% (6.5-7.3) in the severe NPDR and 7.4% (5.82-8.1) in the PDR groups. HbA1c levels of the no apparent DR findings group were lower than those of all other groups (mild $P=0.013$, moderate $P<0.001$, severe $P<0.001$, and PDR $P=0.023$).

Median CRT of patients with no apparent DR findings was 253.5 µm (237.25-276), while they were 262 µm (239-331.75) in the mild NPDR, 280.5 µm (245.25-357) in the moderate NPDR, 258 µm (224-299.75) in the severe NPDR and 308.5 µm (250.5-384.5) in the PDR groups. As we compared median CRT of patients with respect to DR stages, we found a significant difference ($P=0.044$) between PDR and no apparent DR findings groups.

According to DR stages, the median BCVA of patients with mild, moderate, and severe NPDR, PDR and no apparent DR findings were 0.7 (0.5-0.9), 0.6 (0.32-0.70), 0.5 (0.2-0.8), 0.55 (0.1-0.72) and 1.0 (0.7-1.0), respectively. Patients with no apparent DR findings had better BCVA than patients with moderate NPDR ($P<0.001$), severe NPDR ($P<0.001$), and PDR ($P<0.001$). Also, patients with mild NPDR had better BCVA than those with severe NPDR ($P=0.01$).

A significantly low negative correlation was found between BCVA and HbA1C levels of patients (Spearman Rho: -0.159, $P=0.006$). BCVA was compared according to the drug used for DM regulation. BCVA of the patients in the insulin group was significantly lower than those in the OAD group ($P<0.001$). The HbA1C values of the group using insulin for DM regulation were higher than those using OAD, as expected ($P<0.001$). The CRT retinal thickness values of the insulin users were higher than those of OAD users ($P=0.036$).

Discussion

The number of patients with DM is increasing day by day. It is predicted that the prevalence will approach 600 million in 2035 and a potential diabetes epidemic could develop in Asia [11]. Diabetic retinopathy, which is the most common cause of vision loss and preventable blindness in the working-age group in developed countries, also increases among all causes of visual loss [12, 13]. Considering the incidence of DM and predictions, DR-related complications can lead to serious loss of labor and an increase in treatment costs in the working-age group [14]. Besides, as a result of DR, patients' quality of life can decrease. In the absence of other serious complications due to DM, the quality-of-life score was significantly lower in 148 patients with DR compared to the control group [15].

The UK National Institute of Clinical Excellence reported that the test to be used for DR screening should have a sensitivity of at least 80% and a specificity of at least 95% [16]. Defined by the ETDRS group, stereoscopic colored fundus photographs taken from seven areas is the gold standard photography method in DR screening [17]. This method has been reported to be useful in detecting areas of DME and small neovascularization [18]. This method is a little more time-consuming than wide-angle and very wide-angle fundus photography. However, the quality of wide-angle and very wide-angle fundus photographs taken without dilatation can be reduced in media opacities and small pupillary openings [19]. Very wide-angle fundus photography may be timesaving but may lead to misinterpretations due to reduced image quality. As a result, the patient may be diagnosed with a lower or higher stage than the fundus findings. Depending on this, unnecessary

treatment can be started or there may be a delay in receiving the necessary treatment.

In his study, Vujosevic et al. [20] compared the results of single and multiple digital colored non-mydriatic retinal images in DR screening with fundus photographs taken according to the ETDRS protocol. The Kappa agreement value was 0.56 for evaluating the DR severity of ETDRS fundus photographs and single retinal images. In our study, the kappa agreement value of the ETDRS fundus photograph taken from the fovea was 0.68 for DR staging. This value shows a statistically significant agreement. In our study, the reason for the higher agreement value can be explained by pupillary dilation.

OCT can provide detailed information about retinal thickness with high reproducibility. Browning et al. compared the relationship between retinal thickness and BCVA in 251 eyes with DME of 210 patients. According to the results, a moderate correlation was found between BCVA and OCT central retinal thickness. Although there was a moderate correlation in the discussion section, there was a significant variation in the BCVA of patients with similar or equal retinal thickness. Better BCVA was found in many eyes with relatively high retinal thickness, while lower BCVAs were detected in many eyes with near-normal retinal thickness [21]. Considering this data, it may not be correct to comment on BCVA with central retinal thickness only. In our study, there was no statistically significant correlation between central retinal thickness and BCVA (P=0.076, Spearman Rho coefficient: -0.104). However, in patients with DR findings at any stage, there was a statistically significant negative correlation between central retinal thickness and BCVA (P<0.001, Spearman Rho coefficient: -0,306). It should be kept in mind that other retinal pathologies might be present in DM patients, which may decrease BCVA levels, except for central retinal thickness increase.

In a study in which the effects of macular ischemia on BCVA were investigated by Sim et al. among DR patients, ischemia in the papillomacular retinal nerve fiber band had a strong relationship with low BCVA regardless of the foveal avascular zone and macular edema [22]. As seen in the study by Sim et al. [23], there is not always a significant relationship between central retinal thickness and BCVA, depending on other factors. In our study, in patients with DR findings at any stage, we found a significant but low negative correlation (P<0.001, Spearman Rho coefficient: -0.306) between central retinal thickness and BCVA. In our study, the correlation between BCVA and central retinal thickness may be low depending on the presence of patients with low BCVA due to ischemia. In the guideline published by AAO for DR in 2016, evaluation with FFA is recommended in presence of unexplained poor BCVA with fundus examination and OCT findings. It is predictable to increase the correlation between BCVA and central retinal thickness when excluding patients with ischemia with FFA.

In the study of Nunes et al. [24], the correlation between increased retinal thickness and BCVA in patients with CSME was evaluated in 62 eyes. The eyes included in the study were grouped according to the presence of retinal thickening in the central 500-µm area. In 19 eyes, there was no increase in retinal thickness in the central 500-µm area; there was no correlation between retinal thickness and BCVA in these eyes (R = 0.062). A moderate correlation was found between the BCVA and retinal thickness in 43 eyes with an increase in retinal thickness in the central 500-µm area (R = -0.459). In this study, it was reported that the correlation between retinal thickness and BCVA was found in 48.8% of patients even if there was an increase in retinal thickness in the central 500 µm area. In addition, there was no correlation between retinal thickness and HbA1C levels in this study. Although retinal thickness measurements with OCT provide useful information about macular edema, it is not a reliable marker alone in the evaluation of visual loss. In addition, the status of photoreceptor cells in the areas with macular edema is also effective on BCVA.

In a study conducted by Özdek et al. [25], 195 eyes of 110 DM patients were evaluated with OCT, FFA, and clinical examination. In this study, there was an increase in retinal thickness in 148 eyes with OCT; clinical examination revealed a retinal thickness increase in 112 eyes. Compliance of DME findings obtained from OCT with clinical examination was 77%. In our study, this ratio was 76.4%. In the study performed by Özdek et al., 36 eyes (24.3%) had retinal thickening in OCT while clinical examination did not reveal any. In our study, 25 of 106 eyes (23.6%) with retinal thickening in OCT were missed during fundus examination. Clinical examination is an effective method for detecting DME. However, in patients with suspected DME in clinical examination, evaluation should be performed with OCT.

Hyperglycemia is one of the most important risk factors for the development of DR and DME. In a meta-analysis of three broad population-based studies, a gradual relationship was found between the level of glycemia and the incidence of retinopathy [26]. Strict glycemic control (Hb1C <7%) has been reported to reduce the risk of DR development and progression in both type 1 and type 2 DM patients [27]. In our study, in 128 eyes of 66 patients with HbA1C values above 7%, PDR (9.4%) was found in 12 eyes and severe PODR (32.8%), in 42 eyes. PDR was detected in 6 eyes of 164 eyes of 84 patients with HbA1C value below 7% and severe PODR was found in 22 eyes (22%). According to the data obtained from our study, the DR severity phase of the patients increased with HbA1C levels. According to these data, our study also found that HbA1C levels are an important marker for DR development and progression.

Browning et al. compared the relationship between retinal thickness and severity of DR in 383 eyes of 383 patients. Patients with no apparent DR findings, mild NPDR, moderate NPDR, severe NPDR and PDR findings and those with retarded PDR findings had a central retinal thickness of 208(22), 198(25), 204(26), 224(38), and 205(27) µm, respectively. As the severity of DR increased, the likelihood of an increase in macular thickness was also reported to increase. While 15% of eyes with severe NPDR and PDR findings did not show edema in the clinical examination, macular thickening was detected by OCT. In our study, central retinal thickness measurements were 257(30), 290(81), 311(100), 271(82), and 335(115) µm for patients with mild NPDR, moderate NPDR, severe NPDR, and PDR, respectively [28]. In 5.2% of eyes with severe PODR and PDR findings, clinical examination revealed no signs of edema, but retinal thickening was detected with OCT.

In a multi-center prospective study conducted by Garcia-Serrano et al. in Spain, 8244 DM patients were compared in terms of indirect ophthalmoscope and DR screening results after pupil dilatation. The rate of participation in the screening program was 84.1% [29]. Among all, 91.3% of patients had undergone fundus examination at least once. 3.4% of patients were referred to a hospital for treatment. The total cost of the screening program was €53173 and the average cost per patient was 8.87 €. With the help of the screening program, it was predicted that vision loss was delayed for four years after the treatment of 93 patients who needed laser treatment [30]. Considering the possible loss of labor and treatment costs, it was concluded that the total cost of treatment and loss of labor force in two working patients were above the budget used for screening of 8244 patients in this study. Garcia Serrano et al. emphasized the need to create regular screening programs to prevent visual loss due to DR. With the awareness of individuals at risk, it is possible to achieve significant gains both in terms of community health, treatment costs, and labor loss.

Conclusions

In our study, clinical examination and fundus photographs taken according to the ETDRS protocol are suitable methods for detecting and evaluating DR severity. Dilated fundus examination is the method of choice for determining the severity of DR. The fundus photographs taken with the ETDRS protocol is another effective method for DR staging. In our study, these two methods showed significant agreement. Field 2 fundus photography in the ETDRS protocol showed moderate agreement with clinical examination. This method is also useful for detecting the severity of DR, although not as effective as the ETDRS protocol.

OCT is gaining value in the diagnosis of DME. Findings obtained by OCT detect minimal thickness increases that cannot be detected by fundus examination. It also provides quantitative data to compare with the previous findings during patient follow-up. The diagnosis of DME based on the clinical examination and OCT findings showed a statistically significant agreement. The clinical examination showed a sensitivity of 76.4%, specificity of 89.8%, and accuracy of 84.8% in detecting DME. The fundus examination performed after the pupil dilatation showed that an increase in OCT was detected in a significant portion of the cases with retinal thickness.

Considering the increasing number of DM patients, prompt diagnosis and initiation of treatment are of vital importance to prevent possible vision loss. Delays in treatment increase the number of patients in need of care as well as the risk of loss of workforce. In the diagnosis of DR and DME, there is a need for screening programs with high sensitivity and patient compliance, which can be applied quickly to the population at risk with high sensitivity and specificity.

The most prominent strength of our study is the evaluation of treatment-naive DM patients. Evaluation of fundus photographs and examination of patients were conducted by one ophthalmologist. Although the ophthalmologist was blinded to the patient data, an independent observer might have been a better option.

References

1. Satman İ, İmamoğlu Ş, Yılmaz C, Akalın S, Salman S, Dinççağ N. Turkey Endocrinology and Metabolism Association Diabetes Mellitus Complications, Diagnosis, Treatment and Monitoring Guide 2016. Ankara: 2016; Section 1: 15.
2. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2009;32(Suppl 1):S62-7.
3. Klein BE. Overview of epidemiologic studies of diabetic retinopathy. Ophthalmic Epidemiology. 2007;14:179-83.
4. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye and Vision. 2015;2:17.
5. Zhang X, Saaddine JB, Chou CF, et al. Prevalence of diabetic retinopathy in the United States, 2005-2008. JAMA 2010;304:649-56.
6. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol. 1984Apr;102(4):527-32.
7. Davis MD, Fisher MR, Gangnon RE, et al. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study report number 18. Invest Ophthalmol Vis Sci. 1998;39:233-52.
8. Kilpatrick ES, Rigby AS, Atkin SL, Frier BM. Does severe hypoglycaemia influence microvascular complications in Type 1 diabetes? An analysis of the Diabetes Control and Complications Trial database. Diabet Med. 2012;29:1195-8.
9. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol. 1984;102:520-6.
10. Wu L, Fernandez-Loaiza P, Sauma J, Hernandez-Bogantes E, Masis M. Classification of diabetic retinopathy and diabetic macular edema. World J Diabetes. 2013;4(6):290-4
11. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA. 2009;301(20):2129-40.
12. Congdon NG, Friedman DS, Lietman T. Important causes of visual impairment in the world today. JAMA .2003;290(15):2057-60.
13. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010;376(9735):124-36.
14. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care. 2013 Apr;36(4):1033-46.
15. Alcubierre N, Rubinat E, Traveset A, Martinez-Alonso M, Hernandez M, Jurjo C, Mauricio D. A prospective cross-sectional study on quality of life and treatment satisfaction in type 2 diabetic patients with retinopathy without other major late diabetic complications. Health Qual Life Outcomes. 2014 Aug 20;12:131.
16. National Institute for Clinical Excellence. Management of Type 2 Diabetes: Retinopathy—Screening and Early Management. London, UK: Inherited Clinical Guideline;2002.
17. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5 suppl):786-806.
18. Goh JK, Cheung CY, Sim SS, Tan PC, Tan GS, Wong TY. Retinal Imaging Techniques for Diabetic Retinopathy Screening. J Diabetes Sci Technol. 2016 Feb 1;10(2):282-94.
19. Rasmussen ML, Broe R, Frydkjaer-Olsen U, Olsen BS, Mortensen HB, Peto T, et al. Comparison between Early Treatment Diabetic Retinopathy Study 7-field retinal photos and non-mydriatic, mydriatic and mydriatic steered widefield scanning laser ophthalmoscopy for assessment of diabetic retinopathy. J Diabetes Complications. 2015 Jan-Feb;29(1):99-104.
20. Vujosevic S, Benetti E, Massignan F, Pilotto E, Varano M, Cavarzeran F, et al. Screening for diabetic retinopathy: 1 and 3 nonmydriatic 45-degree digital fundus photographs vs 7 standard early treatment diabetic retinopathy study fields. Am J Ophthalmol. 2009 Jul;148(1):111-8.
21. Browning DJ, Glassman AR, Aiello LP, et al. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. Ophthalmology. 2007;114:525-36.
22. Sim DA, Keane PA, Zarranz-Ventura J, Fung S, Powner MB, Plateau E, et al. The effects of macular ischemia on visual acuity in diabetic retinopathy. Invest Ophthalmol Vis Sci. 2013 Mar28; 54(3):2353-60.
23. Olsen TW, Adelman RA, Flaxel CJ, Folk JC, Pulido JS, Regillo CD, et al. Diabetic Retinopathy Preferred Practice Pattern. https://www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp-updated-2016 17.12.2016).
24. Nunes S, Pereira I, Santos A, Bernardes R, Cunha-Vaz J. Central retinal thickness measured with HD-OCT shows a weak correlation with visual acuity in eyes with CSME. Br J Ophthalmol. 2010 Sep;94(9):1201-4.
25. Özdek SC, Erdinç MA, Gürelik G, Aydin B, Bahçeci U, Hasanreisoğlu B. Optical coherence tomographic assessment of diabetic macular edema: comparison with fluorescein angiographic and clinical findings. Ophthalmologica. 2005;219:86–92.
26. Wong TY, Liew G, Tapp RJ, et al. Relation between fasting glucose and retinopathy for diagnosis of diabetes: three population-based cross-sectional studies. Lancet 2008;371:736-43.
27. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. JAMA. 2007;298(8):902–16.
28. Browning DJ, Fraser CM, Clark S. The relationship of macular thickness to clinically graded diabetic retinopathy severity in eyes without clinically detected diabetic macular edema. Ophthalmology. 2008 Mar 1; 15(3):533-9.
29. García-Serrano JL, Serrano-Laborda D, López-Pozas M, Cabello-Aparicio C, Castro-Rosales L. (The Granada Diabetic Retinopathy Study. Direct screening of 8,244 patients. I). Arch Soc Esp Oftalmol. 2007 Nov;82(11):681-9.
30. Javitt JC, Aiello LP. Cost-effectiveness of detecting and treating diabetic retinopathy. Ann Inter Med. 1996;124:164-9.

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