Original Article

Retinal Nerve Fiber Layer and Macular Thickness in Patients with Type 2 Diabetes Mellitus without Retinopathy Using Optical Coherence Tomography: A Comparative Study

Samiksha Bhattarai[1], Poonam Lavaju[1], Badri Prasad Badhu[2], Sangeeta Shah[1], Santosh Chaudhary[1], Robin Maskey[1], Ashesh Koirala[1]

[1]B.P. Koirala Institute of Health Sciences, Dharan, Sunsari, Nepal

[2]Birat Medical College, Budhiganga-2, Morang, Nepal

ABSTRACT

Introduction: Diabetes leads to an alteration in retinal nerve fiber layer (RNFL) thickness and macular thickness which can easily be detected with optical coherence tomography (OCT).

Objectives: This study was done to compare the RNFL and macular thickness between diabetic patients without retinopathy and non-diabetic patients so that it would be useful in the early detection of retinal changes if present. The correlation between the RNFL and macular thickness with metabolic blood parameters of diabetic subjects was also studied.

Materials and methods: This is an observational, cross-sectional, hospital-based study including 120 subjects who were further divided into two groups. Group A consisted of 60 diabetic patients without retinopathy and group B consisted of 60 non-diabetic patients. The blood parameters were recorded and the RNFL thickness and macular thickness were compared between the two groups after evaluation by OCT.

Results: The average central macular thickness was found to be more in group A but was statistically insignificant (p=0.29). Macular thickness in the superior quadrant was significantly higher among group A when compared with group B (p=0.01). Whereas RNFL thickness difference between the two groups was statistically insignificant (p=0.53). Blood urea showed significant positive correlation (r=0.269) with central macular thickness (p=0.03).

Conclusion: Our study showed that diabetic patients without retinopathy could have increased macular thickness in the superior quadrant when compared with normal people whereas RNFL thickness may not alter. The blood urea levels of the diabetic patients can provide us clues regarding possible retinal changes.

Key words: Diabetes, Optical coherence tomography, Retinal nerve fiber layer.

Financial Interest : Nil
Conflict of Interest : Nil

Received : 19.08.2022
Accepted : 21.11.2022

Corresponding Author
Dr. Samiksha Bhattarai
Lecturer, Department of Ophthalmology,
B.P. Koirala Institute of Health Sciences,
Dharan, Sunsari, Nepal.
E-mail: saumri.6112@gmail.com

Access this article online
Website: www.nepjol.info/index.php/NEPJOPH
DOI: https://doi.org/10.3126/nepjoph.v15i1.47629

ISSN: 2072-6805, **E-ISSN:** 2091-0320

INTRODUCTION

Diabetes Mellitus is an enormous and increasing clinical and public health problem. According to a global report on diabetes by World Health Organization (WHO), the prevalence of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population (WHO, 2016). Diabetes mellitus is one of the most prevalent health diseases worldwide with an incidence of 6.9%. The number of people with diabetes is estimated to rise from 171 million in 2000 to 366 million in 2030 (Wild et al., 2004).

Diabetic retinopathy is a devastating complication of diabetes and leading cause of blindness among adults of working age around the world (Neupane and Kalestrup, 2013). It is the most frequent cause of new cases of blindness among adults aged 20 –74 years (Cheung et al, 2010). Twenty years after onset of diabetes, almost all patients with type 1 diabetes and over 60% of patients with type 2 diabetes will have some form of retinopathy (Watkins, 2003). In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 1.6% of patients with type 2 diabetes were legally blind among which one-third of the cases of legal blindness was due to diabetic retinopathy (Fong et al, 2003).

It is important to detect the early signs of diabetic retinopathy to facilitate timely monitoring and prevent ocular morbidity. The introduction of optical coherence tomography (OCT) has enabled clinicians to reliably detect and measure small changes in retinal layers (Chan et al., 2006). With the help of OCT people with diabetes in their preclinical stages can be screened out. OCT has been documented to be more sensitive than a clinical examination in assessing diabetic macular edema and is a quantitative tool for documenting changes in macular thickening (Yang et al., 2001). Studies have suggested that macular thickness is increased and RNFL thickness decreased when compared between normal and diabetic without retinopathy eyes (Sugimoto et al., 2005). On reviewing the literature there was litlle information regarding this comparative study among the Nepalese population. Thus, the purpose of this study was to detect RNFL and macular thickness in patients with type 2 diabetes mellitus without retinopathy and to compare it with non-diabetic eyes.

MATERIALS AND METHODS

A hospital-based observational, cross-sectional study was conducted at the Ophthalmology Department of B. P. Koirala Institute of health sciences, Dharan, Nepal for a duration of one year. Ethical clearance was obtained from the Institutional Ethical Review Board of B.P. Koirala Institute of Health Sciences, Dharan, Nepal (IRC/1347/018). A written informed consent was obtained from all the patients involved in the study.

The study considered a 95% confidence interval and 80% power to estimate the sample size. Mean ± standard deviation (SD) of retinal thickness was taken as a parameter from the study conducted by Sugimoto et al. (2005) to calculate the sample size (n). It was calculated using

$$n = \frac{2(Z_{\alpha/2}+Z_{1-\beta})2\delta^2}{d^2}$$

in which ($Z_{\alpha/2}$ =1.96, $Z_{1-\beta}$ = 0.84 , d is the difference between two means and σ is combined

population standard deviation of two groups). Calculated sample size was 54.4 then 10% for non-response was added and final sample size was 60 (in each group).

A total of 120 patients of age ≥ 40 years were taken and were divided into two groups using the non-probability purposive sampling method. The patients were categorized as Group A (patients with diabetes mellitus without diabetic retinopathy) and Group B (patients with normal fundus findings and no comorbidities) attending eye outpatient department or referred from the department of internal medicine. Patients with co-existing ocular morbidity (e.g., Age-related macular disorder, high myopia, uveitis, glaucoma) and any ocular pathologies obscuring the fundus evaluation, having a history of intraocular surgery (other than cataract surgery) or laser therapy and ocular trauma were excluded. A detailed history regarding diabetes, hypertension, neurological and other systemic illnesses were taken. General physical, systemic, and detailed ocular examination were done as per the proforma. Visual acuity was taken with the help of standard Snellen's chart and refraction to determine best corrected visual acuity (BCVA) in both the eyes. In both these groups, BCVA was 6/12 or better. Detailed anterior segment examination was done under slit lamp biomicroscope. Fundoscopy evaluation was done after full dilatation with tropicamide 1% with help of +90 D lens (Volk). The findings of media clarity, optic disc margins, cup:disc ratio, arterioles:venules ratio, neuroretinal rim, foveolar reflex, and peripheral retina were noted down. Macular and retinal nerve fiber layer thickness in superior, inferior, nasal, and temporal quadrants of both the groups were measured with the help of RTVue XR-100 Avanti, Optovue, Fremont, CA, USA; Software v2014.2; Spectral-Domain OCT. The mean data of both eyes were calculated and compared between two groups. Metabolic blood parameters (Fasting blood sugar, postprandial, blood urea, serum creatinine, HbA1c level, and serum lipid profile) of diabetic patients were also recorded. Blood sugar level was categorized on the basis of American Diabetes association (ADA) criteria (ADA, 2010). The normal range of blood urea nitrogen taken was 5 to 20 mg/dl and serum creatinine was 0.6- 1.2 mg/dl (Hoston, 1990). Similarly, Adult treatment panel III (ATP III) guidelines were followed for classification of lipid profile (Cleeman et al., 2001). Correlation between average central macular thickness and RNFL thickness with metabolic blood parameters and lipid profile were also studied. The two groups were compared to find out the difference in the variables. The data were entered into Microsoft Excel Sheet computer software. Statistical Analysis was performed using SPSS Statistics for Windows (version 11.5). The Student's t-test was used to compare mean differences among the two groups. Pearson correlation coefficient was used to analyze the correlation of macular and RNFL thickness with different metabolic blood parameters. A p value less than 0.05 was considered statistically significant.

RESULTS

The study included a total of 120 patients in which the maximum number of participants belonged to age group 51-60 years in both the groups i.e.25(42%) in group A and 33(55%) in group B, second highest group was 40-50 years of age as it comprised of 19(32%) and 20(33%)

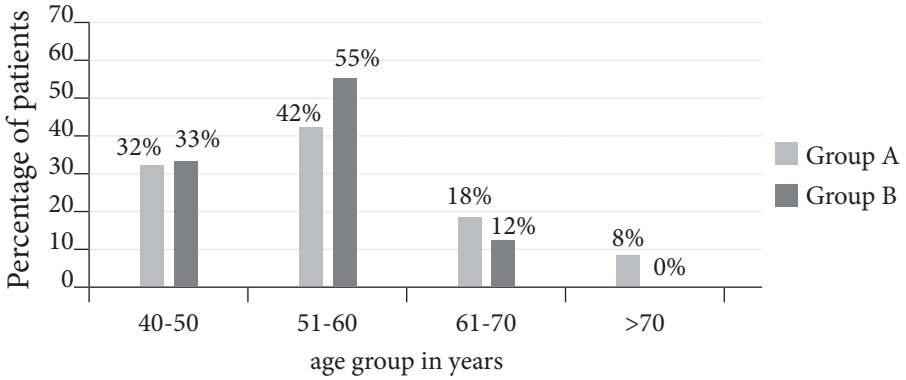

Figure 1: Distribution of patients based on age

in group A and B respectively. Whereas, 11(18%) and 7(12%) in group A and B were in age group 61-70 and only 5(8%) of group A belonged to age above 70 years as shown in (figure 1). Among 120 patients, 36(60%) were male and 24(40%) were female in group A and 35 (58%) male and 25 (42%) female in group B.

Majority of the patients in both groups (156 eyes) had visual acuity of 6/6 followed by 6/9 (52 eyes) with least numbers having visual acuity of 6/12 (32 eyes).

Among 60 diabetic patients, the maximum duration of the disease was 17 years (204 months) and the minimum was 2 days (0.06 months) with a median of 12 months. Among them 49(82%) were under treatment whereas 11(18%) cases were under lifestyle modification only.

In this study, majority 36 (60%) of diabetic patients had good control of fasting blood sugar, 15 (25%) were in prediabetic stage and 9 (15%) had higher fasting blood sugar. Whereas, 28 (47%) patients had their post prandial blood sugar in pre-diabetes range, 20 (33%) in normal and 12 (20%) in diabetic range. Also, 24 patients (40%) had normal Hba1c level , 21(35%) were in pre-diabetes stage and 15 (25%) had Hba1c in diabetic range. It was also found that 31 (52%) patients had blood urea level more than or equal to 20 mg/dl and 29 (48%) had less than 20 mg/dl. Whereas, 52 (87%) patients had creatinine value less than 1.2 mg/dl and remaining 8(13%) had more than 1.2 mg/dl.

In this study, 38 (63%) patients had high cholesterol level with the remaining 22(37%) within normal range. Out of 60 patients,47(78%) had their LDL level in optimal level, 9(15%) in borderline high and remaining 4 (7%) in high scale. Likewise, 54 (90%) patients had triglyceride in normal range whereas 5(8%) had mild hypertriglyceridemia and 1 (2%) had moderate hypertriglyceridemia. However, 52(87%) patients had high HDL and the remaining 8(13%) had normal level.

Mean RNFL thickness of superior, inferior, nasal, and temporal quadrants of Group A was 123.72 ± 10.74, 124.32 ± 8.94, 88.68 ± 5.51 and 93.28 ± 9.45 respectively and 123.53 ±7.54, 121.29 ±8.49, 90.37 ± 7.31 and 92.30 ±7.81 respectively in Group B . Difference between two groups was not statistically significant (Table 1).

Table 1: Retinal nerve fiber layer thickness of all quadrants in group A and group B.

Parameters (µm)	Group A Mean ± SD	Group B Mean ± SD	p value
Superior quadrant	123.72 ± 10.74	123.53 ± 7.54	0.94
Inferior quadrant	124.32 ± 8.94	121.29 ± 8.49	0.09
Nasal quadrant	88.68 ± 5.51	90.37 ± 7.31	0.20
Temporal quadrant	93.28 ± 9.45	92.30 ± 7.81	0.54

Group A had average RNFL thickness of 107.50 ± 5.77 µm, whereas Group B had thickness of 106.89 ±4.82 µm and the difference was statistically insignificant (p = 0.53).

Mean macular thickness in superior quadrant was 318.33 ± 11.2 in Group A and 312.07 ± 12.1 in Group B and the difference was found to be significant (p value = 0.01) whereas inferior, nasal, and temporal quadrants showed no significant change (Table 2).

Average central macular thickness of Group A was found to be higher (245.22 ± 20.51 µm) when compared with Group B (241.80 ± 14.69 µm) but was statistically insignificant (p value = 0.29).

Fasting and postprandial blood sugar showed negative correlation with average central macular thickness but was statistically insignificant. Serum creatinine level revealed insignificant correlation whereas blood urea level showed significant positive correlation (r = 0.269, p = 0.03) with average central macular thickness (Table 3, Figure 2).

Table 2: Macular thickness (µm) of all quadrants in Group A and Group B.

Parameters (µm)	Group A Mean ± SD	Group B Mean ± SD	p value
Macular thickness superior	318.33 ± 11.2	312.07 ± 12.1	0.01*
Macular thickness inferior	315.38 ± 8.54	314.68 ± 9.98	0.65
Macular thickness temporal	310.21 ± 7.87	308.3 ± 9.88	0.26
Macular thickness nasal	311.3 ± 13.25	311.35 ± 16.55	0.98

*statistically significant

Table 3: Correlation of metabolic blood parameters with average central macular thickness.

Metabolic blood parameters	Average central macular thickness	
	Correlation coefficient (r)	p value
Fasting blood sugar	-0.149	0.25
Postprandial	-0.148	0.25
Urea	0.269	0.03*
Creatinine	0.238	0.06
HbA1c	-0.075	0.56

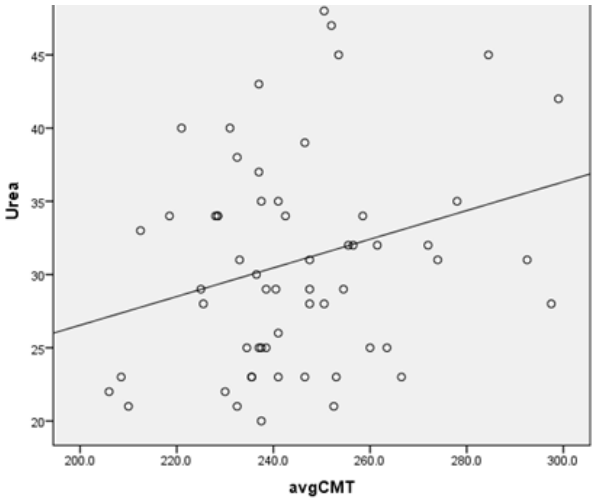

Figure 2: Scatter plot between average central macular thickness and urea.

There was no significant correlation between average central macular thickness and lipid profile (Table 4). Likewise, average RNFL thickness did not show any significant correlation with metabolic blood profile and lipid profile (Table 5 and 6 respectively).

Table 4: Correlation between average central macular thicknesses with lipid profile.

Lipid profile	Average central macular thickness	
	Correlation coefficient (r)	P value
Cholesterol	-0.120	0.36
Triglyceride	-0.145	0.26
High density lipoprotein	0.067	0.6
Low density lipoprotein	-0.058	0.66

Table 5: Correlation between Average RNFL and metabolic blood parameters.

Metabolic blood parameters	Average RNFL thickness	
	Correlation coefficient (r)	P value
Fasting blood sugar	0.011	0.93
Postprandial	-0.041	0.75
Urea	-0.255	0.06
Creatinine	0.214	0.1
HbA1c	0.198	0.12

Table 6: Correlation between average RNFL thickness and lipid profile.

Lipid Profile	Average RNFL thickness	
	Correlation coefficient (r)	p value
Cholesterol	-0.105	0.42
Triglyceride	0.102	0.43
High density lipoprotein	-0.120	0.36
Low density lipoprotein	-0.046	0.73

DISCUSSION

Early detection of diabetes-related changes in the macula and retinal nerve fiber layer before it is clinically evident can be beneficial to patients. In our study, it was seen that the mean thickness of central macula among diabetic patients without retinopathy was higher when compared with that of normal eyes of the same age group. However, the difference observed between the two groups was not statistically significant (p value of 0.25). This finding was supported by other studies that also have shown no significant change in macular thickness among diabetic and normal people (Demir et al, 2013; Srinivasan et al, 2016). The macular thickness in all four quadrants was compared in our study, and it showed a significant difference in the superior quadrant (318.33±11.2 μm in the diabetic group and 312.07 ± 12.1 μm in non-diabetic group with a p value of 0.01). Likewise, a study by Sugimoto et al (2005) also showed a significant increase in macular thickness in the superior quadrant in the diabetic eye (p value of 0.03). Ramappa and Thomas (2016) concluded that there was increased central macular thickness in diabetic cases (267.86 ± 17.39 μm) than in normal people (249.76 ± 28.94 μm).

This increase in thickness in the superior quadrant only has also been justified by a study performed by Kern and Engerman (1995) in an animal model which had shown to have twice the number of microaneurysms and cellular

capillaries in the superior compared to the inferior retina suggesting superior quadrant being more susceptible to early damage.

In our study, average RNFL thickness revealed no significant change between the two groups (p value of 0.53). However, RNFL was clinically thinner in the nasal quadrant among diabetic people when compared with healthy subjects, which was statistically insignificant (p value of 0.2).

In a study by Oshitari et al (2009) the mean, superior, and inferior RNFL thicknesses were calculated in diabetic patients with no diabetic retinopathy (NDR) group and compared with the corresponding sectors of the normal participants (control) group and were found to be thinner in NDR group but were statistically insignificant.

Similarly, the study conducted by Ramappa and Thomas (2016) showed that RNFL thickness (average and of inferior, superior, and nasal quadrants) between the normal subjects and the NDR group was insignificant. However, the thickness in temporal RNFL was significantly increased in NDR, non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) groups when compared with normal people (p value of <0.01).

In a study conducted by Dhasmana et al (2016) RNFL thinning was observed in supero-temporal (p value of 0.001) and upper nasal sectors (p value of 0.031) around the optic disc in eyes with diabetic retinopathy (DR). Increased apoptosis, glial cell reactivity, microglial, and altered glutamate mechanism are some neurodegenerative changes that have been proposed to occur in DR and which may have led to this thinning of RNFL (Barber, 2003).

As stated by Saxena et al (2017), serum levels of urea and creatinine are surrogate markers for disruption of retinal photoreceptor external limiting membrane and inner segment ellipsoid zone on spectral-domain optical coherence tomography in diabetic retinopathy.

In addition to this, Singh et al (2018) also concluded that higher levels of blood urea is significantly associated with diffuse retinal thickening (p value=0.006). Srivastav et al (2015) revealed a positive correlation between increased levels of serum urea and creatinine with retinal nerve fiber layer thinning.

Our study also showed that blood urea has a significant positive correlation with mean central macular thickness suggesting that the measurement of urea level in diabetic patients should be done regularly.

It would have been better if the patients with increased macular thickness were followed up and evaluated to see the pattern of changes leading to retinopathy at a later stage.

CONCLUSION

Diabetes mellitus can alter macular thickness before demonstrable clinical signs which can be detected by OCT as shown in our study. Therefore, OCT should be included as a standard investigation in all diabetic patients with no retinopathy for early detection of possible structural changes and further management. Along with this, various metabolic blood parameters should be tested regularly as they may warn us of potential changes in the retina of diabetic cases.

REFERENCES

American Diabetes Association (2010). Diagnosis and classification of diabetes mellitus. Diabetes Care; 33(1): S62-S69. https://doi.org/10.2337/dc10-S062

Barber AJ (2003). A new view of diabetic retinopathy: A neurodegenerative disease of the eye. Prog Neuropsychopharmacol Biol Psychiatry;27(2):283-90. https://doi.org/10.1016/S0278-5846(03)00023-X

Chan A, Duker JS, Ko TH, Fujimoto JG, Schuman JS (2006). Normal macular thickness measurements in healthy eyes using stratus optical coherence tomography. Arch Ophthalmol;124(2) :193–198. https://doi.org/10.1001/archopht.124.2.193

Cheung N, Mitchel P, Wong TY (2010). Diabetic retinopathy. Lancet; 376(9735) : 124-136. https://doi.org/10.1016/S0140-6736(09)62124-3

Cleeman JI, Grundy SM, Becker D, Clark LT, Cooper RS, Denke MA et al (2001) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Executive Summary of Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA; 285(19): 2486-2497.https://doi.org/10.1001/jama.285.19.2486

Demir M, Dirim B, Acar Z, Yilmaz M, Sendul YD (2013). Central macular thickness in patients with type 2 diabetes mellitus without clinical retinopathy. J Ophthalmol; 3:767931. https://doi.org/10.1155/2013/767931.

Dhasmana R, Sah S, Gupta N (2016). Study of retinal nerve fiber layer thickness in patients with diabetes mellitus using Fourier domain optical coherence tomography. J Clin Diagn Res; 10(7): NC05–NC09. https://doi.org/10.7860/JCDR/2016/19097.8107

Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD et al (2003). Diabetic retinopathy. Diabetes Care;26(1): S99-S102. https://doi.org/10.2337/diacare.26.2007.s99

Hosten AO (1990) BUN and creatinine. In: Walker HK, Hall WD, Hurst JW, editors (1990). Clinical Methods: The History, Physical, and Laboratory Examinations.(3rd ed.). Boston: Butterworths. Chapter 193. https://www.ncbi.nlm.nih.gov/books/NBK305/

Kern TS, Engerman RL (1995). Vascular lesions in diabetes are distributed non-uniformly within retina. Exp Eye Res; 60(5):545-549. https://doi.org/ 10.1016/s0014-4835(05)80069-7

Neupane D, Kallestrup P (2013). Non-communicable diseases in Nepal: Challenges and opportunities. J Nepal Health Res Counc;11(24) :225–228. PMID: 24362618.

Oshitari T, Hanawa K, Adachi-Usami E (2009). Changes of macular and RNFL thicknesses measured by Stratus OCT in patients with early stage diabetes. Eye (Lond);23(4) :884–889. https://doi.org/10.1038/eye.2008.119

Ramappa R, Thomas RK (2016). Changes of macular and retinal nerve fiber layer thickness measured by optical coherence tomography in iabetic patients with and without diabetic retinopathy. Int J Sci Study;3(12) : 27–33. https://doi.org/10.17354/ijss/2016/117

Saxena S, Ruia S, Prasad S, Jain A, Mishra N, Natu SM et al (2017). Increased serum levels of urea and creatinine are surrogate markers for disruption of retinal photoreceptor external limiting membrane and inner segment ellipsoid zone in type 2 diabetes mellitus. Retina;37(2): 344-349. https:// doi.org/10.1097/IAE.0000000000001163.

Singh L, Mullick R, Ahmed L, Garg P, Lal BB (2018). Diabetic macular edema and its association to systemic risk factors in urban north Indian population. J Clin Ophthalmol;2(2) :86-91. https://doi.org/10.35841/clinical-ophthalmology.2.2.86-91

Srinivasan S, Pritchard N, Sampson GP, Edwards K, Vagenas D, Russell AW et al (2016). Retinal thickness profile of individuals with diabetes. Ophthalmic Physiol Opt;36(2): 158-166. https://doi.org/10.1111/opo.12263.

Srivastav K, Saxena S, Mahdi AA, Kruzliak P, Khanna VK (2015). Increased serum urea and creatinine levels correlate with decreased retinal nerve fiber layer thickness in diabetic retinopathy. Biomarkers;20(6-7): 470-473. https://doi.org/10.3109/1354750X.2015.1094142.

Sugimoto M, Sasoh M, Ido M, Wakitani Y, Takahashi C, Uji Y (2005). Detection of early diabetic change with optical coherence tomography in type 2 diabetes mellitus patients without retinopathy. Ophthalmologica; 219(6):379–385. https://doi.org/10.1159/000088382.

Watkins JP(2003). Retinopathy. BMJ. 326(7395): 924-6. https://doi.org/10.1136/bmj.326.7395.924.

Wild S, Roglic G, Green A, Sicree R, King H (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care; 27(5): 1047-53. https://doi.org/10.2337/diacare.27.5.1047. PMID: 15111519.

World Health Organisation (2016). Global report on diabetes.www.who.int/diabetes/global-report.

Yang CS, Cheng CY, Lee FL, Hsu WM, Liu JH (2001). Quantitative assessment of retinal thickness in diabetic patients with and without clinically significant macular edema using optical coherence tomography. Acta Ophthalmol Scand;79(3):266–270. https://doi.org/10.1034/j.1600-0420.2001.790311.