

Systemic predictors of diabetic macular edema in patients visiting tertiary hospital

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Abstract:

Objective: To evaluate the systemic predictors of diabetic macular edema in patients of tertiary care hospital of Rawalpindi.

Material and Methods: A cross sectional study of 8 months was performed on 191 diabetic patients at Retina Department of Holy Family Hospital, Rawalpindi. The research performas were filled from all participants of the study to kept them on proper follow ups at the clinic which contained the variables for demographics of the patients, their diabetic type, diabetic age, treatment modality, consumption of alcohol or smoking, also systemic i.e. blood pressure, results of renal function test, hemoglobin A1c (HbA1c) level, lipid profile of serum, urine albumin level of 24hrs, and neuropathy existence were also noted and entered in the data. The ophthalmological examination of every patient was also performed and noted on performa, The patients with age above 18 years and diagnosed to have diabetes were included, while patients with other ocular complication such as vitreomacular traction, epiretinal membrane, etc.) and opacity at media which effect the reliability of OCT imaging like dense cataract, uveitis, etc or those who have insufficient data for the study were excluded from the study. All the collected data was entered to SPSS 22.0 for the statistical analysis.

Results: The DME was detected in 83 (43.45%) patients and DR was found in 108 (56.5%) of the 191 study participants. The frequency of DME was found significantly greater in those patients who had HbA1c value of 7.0% or greater ($p=0.029$). The diabetic type had found no effect on DME while duration was significantly found longer in DME patients, mostly in the patient who had the diabetes history of previously one or two decade ($p 0.001$). The comparison of normo-albuminuric, micro-albuminuric, and macro-albuminuric patients were also done for DME and found statistically significant difference, the p-value was found 0.001.

Conclusion: Duration of diabetes, baselines of patients like creatinine levels, lipoprotein levels and level of albuminuria has statistically significant associations of Diabetic macular edema. Proper observation of the underlying conditions in diabetic patient on periodic intervals can help prevent the vision threatening condition of DME.

Keywords: Systemic predictors, diabetic macular edema (DME), diabetic retinopathy

Introduction:

Diabetic Macular edema (DME) is a serious complication of Diabetic retinopathy. Diabetes is now a global epidemic affecting millions of people from both the developing and developed world.¹ There has been increasing emphasis on complications and aftermaths of diabetes as it is capable of affecting virtually any organ of the body. Among all the other complications of dia-

betes, the one affecting the quality of life to a greater extent is the diabetic retinopathy (DR).²

In a 28 years review (1980-2008) the overall prevalence of Diabetic retinopathy was reported to be 34.6%. Individually, proliferative diabetic retinopathy was affecting 17-million people, Diabetic Macular edema (DME) was affecting 21-million patients with diabetes and 28-million

Received

Date: 2nd February 2020

Accepted

Date: 15th September 2020

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had reported Vision threatening diabetic retinopathy (VTDR).³ The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014.⁴ In 2019, the global prevalence of diabetes was reported to be 9.3% which is estimated to be rising to 10.2% in 2030 and projected to be 10.9% till 2045.⁵ This is an established Public Health issue now.

In Pakistan, the prevalence of DR has increased from 15.3% in 2007 to a startling value of 56.9% in diabetic population.⁶ In a Second national survey on prevention of blindness (2004) the prevalence of DR was reported to be <0.5% while in a systematic review published in 2018 the pooled prevalence was risen to 28.78%.⁷

Clinically significant diabetic macular edema (DME) is the most common complication seen in South-Asian patients with diabetic retinopathy.⁸⁻⁹ The Cochrane review of diabetic macular edema has shown the prevalence rates in range from 19% to 65%.¹⁰ Type-1 diabetic patients have shown diabetic macular edema prevalence between 4.2%-7.9% while type-II had shown it to be 1.4%-12.8% in different population based studies.¹¹⁻¹⁴

Life long management of diabetes can help the patient to prevent themselves from quality of life affecting complications. This requires in depth understanding of the factors that results in such disabilities. High prevalence of diabetic macular edema in South-Asian population demands understanding of risk factors for the vision threatening complication. To the best of our knowledge, current literature in Pakistan is deficient of systemic risk factors for diabetic macular edema specifically. This study aims to find out the systemic predictors of diabetic macular edema (DME) in patients of Diabetic Retinopathy.

Material and Methods:

A cross sectional study of 8-months duration (from April 2019 to November 2019) was performed on 191 diabetic patients at retina department of Holy Family Hospital, Rawalpindi. The sample size was calculated by using WHO sample size calculator by keeping population

proportion with specified absolute precision taking confidence level 95%, anticipated population proportion 40%¹⁵ and 7% required precision. The research performas were filled from all participants of the study to kept them on proper follow ups at the clinic which contained the variables for demographics of the patients, their diabetic type, diabetic age, treatment modality, consumption of alcohol or smoking, also systemic i.e. blood pressure, results of renal function test, hemoglobin A1c (HbA1c) level, lipid profile of serum, urine albumin level of 24hrs, and neuropathy existence were also noted and entered in the data. The ophthalmological examination of every patient was performed and noted on performa, which contained the best corrected visual acuity, complete slit lamp examination, measurement of intraocular pressure (IOP), and fundoscopy after dilation. For the analysis of central macular thickness OCT was performed and fluorescein angiography was also done for each participant. The association between the systemic findings with risk of diabetic macular edema was study thoroughly.

The patients with age above 18 years and diagnosed to have diabetes (type 1 or 2) by endocrinologist and refer to eye department for the screening of diabetic macular edema and diabetic retinopathy, who visited to the retina department of the hospital during the study period were included to the study.

The patients who were with any other ocular complication such as vitreomacular traction, epiretinal membrane, etc.) and opacity at media which effect the reliability of OCT imaging like dense cataract, uveitis, etc or those who have insufficient data for the study were excluded from the study.

The ophthalmological examination of the patients contained, best corrected visual acuity (BCVA) after correction of refractive error. The slit examination of every patient was performed for the anterior segment of the eye and also dilated fundoscopy was done. The Goldmann applanation tonometer was used to measure the IOP of each patient while Spectralis HRA-OCT

Table 1: Best corrected VA and IOP in patients with and without DME

| Variable | With DME | Without DME | p-value |
|--------------------|------------|-------------|---------|
| BCVA mean (logMAR) | 0.61±0.63 | 0.51±0.21 | 0.001 |
| IOP mmHg | 15.10±2.51 | 16.10±2.73 | 0.614 |

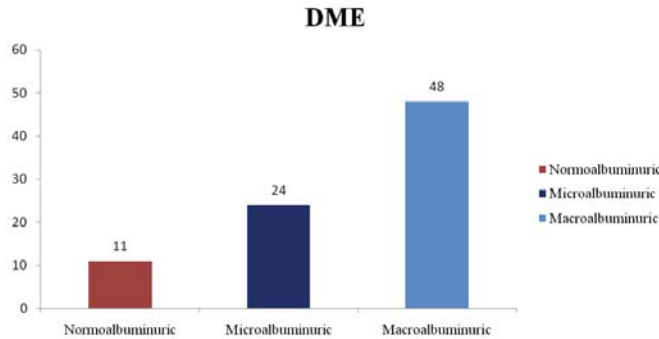


Figure 1: Frequency of DME in Normo-albuminuric, Micro-albuminuric, and Macro-albuminuric patients

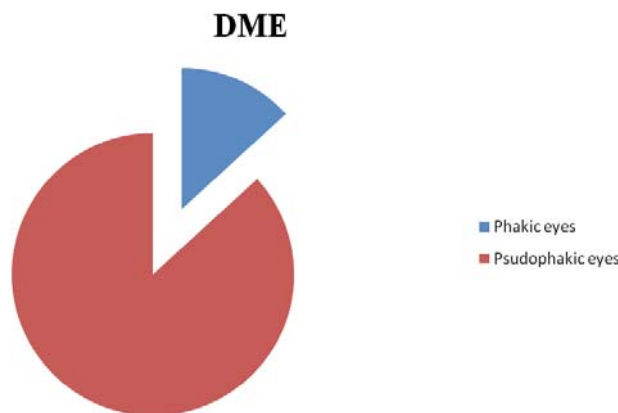


Figure 2: The frequency of DME in phakic and pseudophakic eyes

II was used for the OCT and Heidelberg retinal angiography (HRA). Six OCT shots were lined up by the radial line scan and each other at an angle of 30° after obtaining a fixation point for the patient. Evaluation of the eye were done for clinical significant macular edema (CSME) as per the definition Early Treatment Diabetic Retinopathy Study (ETDRS) and with central macular thickness (CMT) which was taken the main thickness at the point of intersection of 6 radial scans by OCT ≥ 250 μm attributed to DME.¹⁶

All the collected data was entered to SPSS 22.0

for the statistical analysis, the mean, standard deviation and percentages were calculated for the descriptive data. The univariate analysis was performed by applying the Chi-square test, Fisher’s exact test and t-test. The p-value 0.05 was considered as statistically significant.

Results:

A total of 191 patients were included in the study who were fulfilling the criteria. Out of these 191 individuals, 107 (56.02%) were male while 84 (43.97%) were females. The mean age of the study participants was 57.65±10.92 years.

The DME was detected in 83 (43.45%) patients and DR was found in 108 (56.5%) of the study participants. Furthermore the classification of diabetes showed that 14 (16.84%) patients were reported with DME have had type1 diabetes while 69 (83.13%) were found with type 2 diabetes (p=0.591). Out of these 83 patients 23 received focal or grid laser treatment, 12 were previous intravitreal anti-vascular endothelial growth factor (VEGF) or steroid treatments and 9 received previously both focal laser and anti VEGF and steroid treatment.

When the laboratory characteristics were assessed with demographics of the patients so it found that males were more prevalent than female the p-value was 0.031. Same, the male participants were found more high values of HbA1c level as compare to females i.e. the male were found with 8.32±2.33% and in female it was reported as 7.93% and p=0.056. The DME and HbA1c were assessed and there is no direct correlation was found between them. The frequency of DME was found significantly greater in those patients who had HbA1c value of 7.0% or greater (p=0.029). The diabetic type had found no effect on DME while duration was significantly found longer in DME patients, mostly in the patient who had the diabetes history of previously one or two decade (p 0.001). The antihyperlipidemic drug users were also found significant effect on DME reduction (p =0.040) and the density of lipoprotein cholesterol (HDL-C) was noted high in them (p=0.38). The mean serum creatine with DME was reported 1.21±0.79 mg/

dL and in without DME it was found 0.91 ± 0.59 mg/dL which shows statistically significant difference in between them ($p=0.022$).

The comparison of normo-albuminuric, micro-albuminuric, and macro-albuminuric patients were also done for DME and found statistically significant difference, the p-value was found 0.001 as shown in graph 1 below.

The peripheral neuropathy was also found significantly frequent in the DME patients and their p-value was 0.005.

The frequency of DME was reported high in those patients who were with severe NPDR to proliferative diabetic retinopathy (PDR) such as 140 (73.29%) patients were found while the patients who were with mild to moderate non proliferative diabetic retinopathy (NPDR) reported only 51 (26.70%) of the patients and p-value reported less than 0.001.

The frequency of DME in phakic and pseudophakic eyes are assessed and describe figure 2 below. The DME found in total of 83 patients in which 11 (13.2%) were phakic eyes and 72 (86.7%) were pseudophakic which shows significant statistical difference and the p-value was less than 0.001.

The analysis of possible effect of cataract surgery on DME and the evaluation of only phakic patients showed that significant affect was noted due to duration of diabetes, neuropathy, nephropathy and use of antihyperlipidemic drugs in same ways as their p-values are reported. While gender, creatine level and HDL-C level in phakic patients have not any statistically significant effect on diabetic macular edema.

Discussion:

This cross sectional study was done on 191 patients who were visiting tertiary eye care hospital with established Diabetic retinopathy. There were a total of 107 males and the mean age of participants was 57.65 ± 10.92 . Systemic predictors for diabetic macular edema were assessed in the current study.

The proportion of diabetic macular edema was 43.4% ($n=83$) in current study. This is alarming as such a small sample has a large proportion of patients with Diabetic Macular edema. This can even worse if done on a large scale. This is in contrast to different population based studies where the prevalence of DME was ranging from 4.2% to 7.9%.^{15,17} The increased proportion of DME in current study can also be because the patient's sample has been taken from a tertiary eye care hospital where most of the presented patients have already facing the underlying condition of diabetes as well as diabetic retinopathy since a long time. The clue to this can be taken from the truth that patients with increased duration of diabetes were found statistically significant with the presence of diabetic macular edema ($p<0.05$).

Different studies have shown that type of diabetes have an association with the occurrence of diabetic macular edema, where patients with type 2 diabetes have more risk of developing DME as compared to the other type of diabetic patients¹⁸. But this study has shown that there is no statistically significant association between type of diabetes and diabetic macular edema development ($p>0.05$).

Only 9 patients in the current had undergone both modalities i.e. anti-VEGF and Laser treatment (Grid and focal) for diabetic macular edema treatment, whereas, 12 patients have given anti-VEGF alone and 23 received laser treatment alone, respectively. Different comparative studies have shown that anti-VEGF is the most trustworthy, promising and significant treatment for DME than laser.¹⁹⁻²¹

Presence of peripheral neuropathy, severe NPDR and pseudophakia was significantly associated with the development of diabetic macular edema in the current study. This could be because cataracts are developed in the diabetic patients at an increasing pace than a same aged normal individual.²² One of the common complications of diabetes is cataract. Similarly, issues like Non-Proliferative Diabetic retinopathy and peripheral neuropathy are different phases of

DR and underlying factors for causing Diabetic Macular edema (DME). There occurrence goes line in line with one another. This is in agreement with Zachary T in a review 23. David J et al also had shown the same pathophysiology of DME.²³

Association of diabetic macular edema with baselines of the patient showed that serum creatinine levels and levels of albuminuria (micro & macro) was significantly affecting patients with DR. This is in agreement with a chinese study where urinary albumic excretion (UAE) was significantly associated with diabetic macular edema development.²⁴ A comparative study by Nam Kyun Koo et al showed a non-significant association between creatinine levels and diabetic macular edema.²⁵

Levels of Hb1ac are directly associated with the gender where males have high levels of it as compared to females. It may be because males are less likely to have good diabetic control and keep health as priority due to earning and family needs as there priority. This is in contrast to Muhammad A. Siddique et al where males were more positive and devoted to their condition and caring towards their medication regimen as compared to females.²⁶

Conclusion:

The proportion of diabetic macular edema was 43.4% (n=83) in current study. Duration of diabetes, baselines of patients like creatinine levels, lipoprotein levels and level of albuminuria were statistically significant associations of Diabetic macular edema. Proper observation of the underlying conditions in diabetic patient on periodic intervals can help prevent the vision threatening condition of diabetic macular edema.

Conflict of interest: None

Funding source: None

Role and contribution of authors:

Dr. Abdullah Naeem Syed, collected the data, references and did the initial writeup.

Dr. Muhammad Safdar, collected the data and helpd in introduction writing

Dr. Shahid Abbas, critically review the article and made the final changes in the article.

References:

1. Wong T, sun J, Kawasaki R, Ruamviboonsuk P. Guidelines on Diabetic Eye Care: The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings. *Journal of Ophthalmology* [Internet]. 2018 [cited 5 January 2020];125(10):1608-22.
2. Sivaprasad S, Gupta B, Crosby-Nwaobi R, Evans J. Prevalence of Diabetic Retinopathy in Various Ethnic Groups: A Worldwide Perspective. *Survey of Ophthalmology*. 2012;57(4):347-370.
3. WY. Yau J, Kawasaki R, Lamoureux E. Global Prevalence and Major Risk Factors of Diabetic Retinopathy. *Diabetes care* [Internet]. 2012 [cited 6 October 2020];35(3):556-64. Available from: <https://doi.org/10.2337/dc11-1909>.
4. Sarwar N, Gao P, Shesasai S, Gobin R. Diabetes Mellitus, Fasting Blood Glucose Concentration, and Risk of Vascular Disease: A Collaborative Meta-Analysis of 102 Prospective Studies. *Journal of Vascular Surgery*. 2011;53(2):548-549.
5. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*. 2019;157:107843.
6. Khan A. PREVALENCE OF DIABETIC RETINOPATHY IN PAKISTANI SUBJECTS A PILOT STUDY. *Journal of Pakistan Medical Association*. 1991;41(3).
7. Mumtaz S, Fahim M, Arslan M, Shaikh S, Kazi U, Memon M. Prevalence of diabetic retinopathy in Pakistan: A systematic review. *Pakistan Journal of Medical Sciences*. 2018;34(2).
8. Acan D, Calan M, Er D, Arkan T, Kocak N, Bayraktar F et al. The prevalence and systemic risk factors of diabetic macular edema: a cross-sectional study from Turkey. *BMC Ophthalmology*. 2018;18(1).
9. Otani T, Kishi S, Maruyama Y. Patterns of diabetic macular edema with optical coherence tomography. *American Journal of Ophthalmology*. 1999;127(6):688-693.
10. Virgili G, Menchini F, Murro V, Peluso E, Rosa F, Casazza G. Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. *Cochrane Database Syst Rev*. 2011;7:CD008e081.
11. Bertelsen G, Peto T, Lindekleiv H, Schirmer H, Solbu MD, Toft I, Sjølie AK, Njølstad I. Tromsø eye study: prevalence and risk factors of diabetic retinopathy. *Acta Ophthalmol*. 2013;91:716-21.
12. Knudsen LL, Lervang HH, Lundbye-Christensen S, Gorst-Rasmussen A. The north Jutland county diabetic retinopathy study: population characteristics. *Br J Ophthalmol*. 2006;90:1404-9.
13. Zheng Y, Lamoureux EL, Lavanya R, Wu R, Ikram MK, Wang JJ, Mitchell P, Cheung N, Aung T, Saw SM, Wong TY. Prevalence and risk factors of diabetic retinopathy in migrant Indians in an urbanized society in Asia: the Singapore Indian eye study. *Ophthalmology*. 2012;119:2119-24.
14. Al Ghamdi AH, Rabiou M, Hajar S, Yorston D, Kuper H, Polack S. Rapid assessment of avoidable blindness and diabetic retinopathy in Taif, Saudi Arabia. *Br J Ophthalmol*. 2012;96:1168-72.
15. Bursell S, Fonda S, Lewis D, Horton M. Prevalence of diabetic retinopathy and diabetic macular edema in a primary care-based teleophthalmology program for American Indians and Alaskan Natives. *PLOS ONE*. 2018;13(6):e0198551.

16. Cohen S, W. Gardner T. Diabetic Retinopathy and Diabetic Macular Edema. *DevOphthalmol*. 2017;55:137-46.
17. Lee R, Wong T, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye and Vision*. 2015;2(1).
18. Romero-Aroca P. Managing diabetic macular edema: The leading cause of diabetes blindness. *World Journal of Diabetes*. 2011;2(6):98.
19. Venderbeek B. Comparing the Changing Trends in the Treatment of Diabetic Macular Edema. *Retina*. 2016;35(7):40-42.
20. Anwar H, Khalil I, Ikram S, et al. Comparison of laser and anti VEGF therapy in treatment of diabetic macular edema. *AdvOphthalmol Vis Syst*. 2020;10(1):8-11. DOI: 10.15406/aovs.2020.10.00373
21. Jawadi M, Zarei- Ghanavati S. Cataracts in Diabetic Patients: A Review Article. *Journal of Ophthalmic and vision research*. 2008;3(1):52-65.
22. Bloomgarden Z. Diabetic Retinopathy and Diabetic Neuropathy. *Diabetes Care*. 2007;30(3):760-765.
23. Stewart M, Browning D, Lee C. Diabetic macular edema: Evidence-based management. *Indian Journal of Ophthalmology*. 2018;66(12):1736.
24. Liu Z. Association of urinary albumin excretion with central foveal thickness and intravitrealconbercept treatment frequency in patients with diabetic macular edema. *International Journal of Ophthalmology*. 2019;12(10):1598-1604.
25. Koo N, Jin H, Kim K, Kim Y. Relationship between the Morphology of Diabetic Macular Edema and Renal Dysfunction in Diabetes. *Korean Journal of Ophthalmology*. 2013;27(2):98.
26. Siddiqui M, Khan M, Carline T. Gender Differences in Living with Diabetes Mellitus. *Materia Socio Medica*. 2013;25(2):140.