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Can Insulin Resistance Serve as a Potential Biomarker for the Development of Clinically Significant Macular Oedema in Patients with Type 2 Diabetes Mellitus?

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Abstract

Objective: To study the prevalence of insulin resistance among diabetic patients. To analyze the association between insulin resistance and clinically significant macular edema (CSME) development.

Material and Methods: Single-centre, cross-sectional comparative study on a hospital-based population of diabetic patients. Patients were grouped based on the presence of CSME (group A) and the absence of CSME (group B). Simple logistic regression and multiple logistic regression analyses were performed to evaluate the association CSME with age, duration of diabetes, HbA1c, insulin resistance, body mass index, and lipid profile.

Results: The study cohort comprised 86 patients with type 2 DM, with a mean age of 60±7 years. We included 43 patients in each group A and B respectively. There were 37 patients (86%) in group A, who had diabetes ≥10 years. In group B, 23 patients (53%) had diabetes ≥10 years. The mean HbA1c was found to be 8.2±1.3 mmol/mol in group A and 7.6±0.85 mmol/mol in group B (p=0.01).

Increased insulin resistance was present in 74/86 (86 %) of diabetics. Elevated IR of ≥ 3.8 was found in 32/43 patients (74%) of group A and 17/43 (39%) of group B (p= 0.001). None of the patients in group A had normal insulin resistance. The odds ratio for the development of CSME in patients with increased HOMA-IR was found to be >4.

Conclusion: We observed positive association between insulin resistance and development of clinically significant macular edema. The odds for the development of macular edema was greater in uncontrolled diabetics with elevated insulin resistance.

Keywords: Insulin Resistance, Macular Edema, Type 2 Diabetes, clinically significant macular edema (CSME), HOMA-Insulin Resistance.

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INTRODUCTION

Macular edema is one of the leading causes of irreversible vision loss in diabetes mellitus (DM) patients. Diabetes-related retinopathy and macular edema can develop in patients having a deficiency of insulin (type 1 DM) or insulin resistance (IR) with subsequent beta cell dysfunction (type 2 DM).

The prevalence of diabetic macular edema (DME) depends upon the duration of diabetes, metabolic control, systolic blood pressure, glycosylated hemoglobin, presence of proteinuria, and possibly the degree of insulin resistance.[1] Insulin resistance can be defined as an impaired insulin sensitivity secondary to which a normal or elevated insulin levels produce an attenuated physiological response at the cellular level.[2]

The existing body of literature on diabetes-related angiopathy suggests that insulin resistance (IR) and compensatory hyperinsulinemia initiate a chain of occult angiopathic changes even before the manifestation of overt diabetic retinopathy.[2,3]

Insulin resistance with compensatory hyperinsulinemia is a pro-inflammatory state.[4] Studies have observed an independent association of IR with hypertension and ischemic heart disease.[4-6] Additionally, multiple prospective and retrospective studies have observed an increased prevalence of macular edema in patients under insulin therapy.[7]

Literature remains limited in comprehensive, quantitative, and comparative studies investigating the role of insulin resistance in the development of sight-threatening macular edema.[3,8,9] Understanding the clinical association between insulin resistance and sight-threatening maculopathy remains essential to ascertain the possible effects of insulin on the development and progression of maculopathy, to tailor treatment/management strategies and help identify the patient population at risk of developing vascular complications.

In this study, we have attempted to evaluate the role of IR by the homeostasis assessment model (HOMA) in diabetic patients who presented with and without clinically significant macular edema (CSME). The study's primary aim was to estimate prevalence of IR amongst diabetic patients with and without macular edema and analyze the association of IR with development of CSME.

MATERIAL AND METHODS

We performed a single-center, cross-sectional comparative study on the attending hospital-based population of diabetic patients, who were referred to the Ophthalmology department between August 2019 and August 2021. The study was conducted after clearance by the Institutional Review Board, informed consent was taken as per the recommendations provided by the Declaration of Helsinki 1975, as revised in 2000.

Our study population included all consecutive cases of type 2 diabetes referred to the ophthalmology department for retinopathy evaluation. The study included all patients above 35 years of age, consenting to enroll in the study, and willing to undergo HOMA assay for insulin resistance.

We excluded patients taking insulin treatment, those diagnosed with type 1 DM, those with proliferative diabetic retinopathy and those who had received any form of treatment for diabetic retinopathy/maculopathy in the past three months. All consecutive patients enrolled underwent retinal examination. The patients were divided into two groups based on the presence/absence of clinically significant macular edema. The enrolment of patients in the groups was stalled once the desired sample size of 43 cases in each group was achieved.

The demographic and clinical data were collected from patients satisfying our inclusion criteria. The demographic data included: Age, gender, duration of diabetes. The clinical data included metabolic parameters and findings of dilated fundus examination. We evaluated patients for baseline fasting and postprandial sugar levels, glycosylated hemoglobin, and blood pressure.

Dilated fundus examination using slit lamp biomicroscopy and indirect ophthalmoscopy was performed for all the eyes. The patient's perform was filled for the stage of background retinopathy, and the presence of clinically significant macular edema (CSME). Clinically significant macular edema was defined as per the ETDRS definition.[10]

Based on the clinical examination, the cases were grouped as group A (CSME present) and group B (no CSME). Even if the patient had CSME in one eye, he/she was labelled under group A. The groups were compared for baseline characteristics, metabolic control and severity of insulin resistance.

Insulin resistance was estimated using the homeostasis model assessment method for insulin resistance

index (HOMA-IR) by Mathews et al.[11]

The insulin resistance was calculated using the formula: HOMA-IR = (Fasting Plasma Insulin*Fasting Plasma Glucose)/22.5. The HOMA-IR was estimated for all patients. The HOMA-IR values were graded as normal <2.60, borderline high =2.60-3.70, high ≥3.80. For the purpose of analysis, the normal and borderline were considered under one heading of normal/marginally raised and HOMA-IR of ≥3.8 was considered raised.[12,13]

Statistical analysis

Sample was calculated using the formula: n= {(Za+Zß) ^{2}/ [In (1-e)] ^{2}} x {[1-p+1-p2]/p1 p2} where P1 =1/OR (OR=1.99), P2 =1.0 under null hypothesis. Coefficient difference (e) =0.3 was considered to be clinically significant. Type 1 error, α =15%, type 2 error, β =10% for setting power of study 80%. The sample size was calculated to be n =43 each group.

All of the data is presented as mean ± SD for continuous variables and proportions for categorical variables. Data analysis was done using STATA 11.2 (College Station TX USA). Descriptive statistics were expressed in the form of percentages and frequency. Chi square test was used to measure the association between the categorical variables.

For continuous variables: mean, standard deviation was calculated. The mean values were compared using Student's t-test. A p value of ≤0.05 was considered as statistically significant. The prevalence ratio and prevalence odds ratio were calculated for evaluation of relationship between predictor and outcome[14]. Simple logistic regression analyses were performed to estimate the magnitude of association CSME with age, duration of diabetes, HbA1c, insulin resistance, body mass index and lipid profile. Multiple logistic regression analyses were performed to estimate the magnitude of the association of CSME and insulin resistance.

RESULTS

The study cohort comprised 86 patients with type 2 DM, with a mean age of 60±7 years. The study population comprised 42 males and 44 females. There were 43 patients who had CSME (group A) and 43 patients who did not have macular edema (group B). The baseline demographic details and status of metabolic control are shown in Table 1 in both groups.

The mean duration of diabetes for the patients in the study cohort was 18±6 years in group A and 13.6±7.5 in group B (p= 0.008). There were 37 patients (86%) of patients in the group A population having diabetes ≥10 years whereas in the group B, 23 (53%) had a duration of diabetes ≥10 years. The mean duration of diabetes was found to be significantly higher in group A compared to Group B.

The mean HbA1c was found to be 8.2±1.3 mmol/mol in group A and 7.6±0.85 mmol/mol in group B (p= 0.01). Elevated levels of HbA1c (7.1-8.5) were found in 33(77%) patients in group A and 24 (56%) in group B. The prevalence odds ratio for development of CSME in diabetics with elevated HbA1c (>7) was estimated to be 2.4. (Table 1)

Table 1- shows the baseline demographic characteristics for the cohort and of groups A and B.

		TOTAL	GROUP A	GROUP B	
AGE		60.23±7.37	61.48±7.97	58.97±6.56	p= 0.1146 t= 1.59
DURATION		16±7	18±6	13.62±7.54	p= 0.0038 t= 2.98
HbA1c LEVELS		7.91±1.10	8.2±1.3	7.62±0.85	p= 0.0164 t= 2.44
LIPID PROFILE	**HDL**	43.93±11.27	40.80±11.40	47.07±10.35	p= 0.0091 t= 2.67
	LDL	141.04±26.63	136.60±21.40	145.53±30.58	p= 0.1204 t= 1.56
	TRIGLYCERIDES	194.67±64.24	211.80±80.70	177.59±35.34	p= 0.0127 t= 2.54
HOMA IR		3.45±0.91	3.80±0.80	3.10±0.88	p= 0.0002 t= 3.85
BMI		30.94±4.81	32.10±4.24	29.78±5.11	p= 0.0245 t= 2.29

The mean HOMA IR was 3.45±0.98 for the cohort, the mean HOMA-IR was estimated to be 3.80±0/80 in group A and 3.10±0.88 in group B (p= 0.0002). (Table 1)

The prevalence of increased insulin resistance was estimated to be present in 74/86 (86%) of diabetics. Elevated IR of ≥3.8 was found in 32/43 patients (74%) of group A and 17/43 (39%) of group B (p= 0.001). None of the patients in group A had normal insulin resistance (For the purpose of statistical analysis borderline and normal insulin resistance were clubbed under a common head. HbA1c >7 was suggestive of poor glycemic control, HbA1c ≤7 was representative of good glycemic control). The prevalence odds ratio for development of CSME in patients with increased HOMA-IR was found to be >4. (Table 2)

Table 2 represents the association between prevalence of CSME with regards to insulin resistance and glycemic control. The odds of incurring CSME were found to be >4 times in patients with increased insulin resistance. Similarly, the odds for incurring CSME in patients with poor metabolic control (HbA1c >7) were found to be >2.

HOMA IR	**HIGH (≥3.8)**	32	17	**PR= 2.1 POR=4.2**	**p= 0.0014**
	NORMAL / BORDERLINE (<3.8)	11	26		
HbA1c	**>7.0**	33	24	**PR= 1.67 POR= 2.4**	**p= 0.0427**
	≤7.0	10	19		

PR- Prevalence ratio, POR- Prevalence odds ratio

Multivariate analysis revealed a significant association between insulin resistance, BMI and lipid profile, and development of CSME. Insulin resistance was an independent predictor for development of CSME. The odds of developing CSME were found to be four times in patients showing increased insulin resistance. (Table 3)

Table 3 represents multivariate analysis for the associated risk factors of CSME, using logistic regression to control for confounders. Multivariate analysis revealed a significant association between Insulin resistance, BMI, lipid profile and development of CSME. Insulin resistance was found to be an independent predictor for CSME.

		GROUP A	GROUP B	
AGE		61.48±7.97	58.97±6.56	p= 0.781
DURATION		18±6	13.62±7.54	p= 0.155
HbA1c LEVELS		8.2±1.3	7.62±0.85	p= 0.092
LIPID PROFILE	**HDL**	40.80±11.40	47.07±10.35	**p= 0.004**
	LDL	136.60±21.40	145.53±30.58	**p= 0.013**
	TRIGLYCERIDES	211.80±80.70	177.59±35.34	**p= 0.047**
HOMA IR		3.80±0.80	3.10±0.88	**p= 0.008**
BMI		32.10±4.24	29.78±5.11	**p= 0.029**

When studying the effects of elevated insulin resistance amongst group A and B with respect to metabolic control, we observed that the prevalence odds ratio for developing CSME in patients with good glycemic control, i.e. Hba1C ≤7 was 2.2 (p=0.37), nonetheless the odds for the development of CSME in patients with HbA1c >7 (poor glycemic control) were found to be raised to 5.2 (p= 0.01), when insulin resistance was raised. (Table 4)

Table 4 shows the association of insulin resistance to prevalence of CSME in patients with poor (HbA1c>7) and good glycemic control (HbA1≤7). The odds for prevalence of CSME in patients with increased insulin resistance were estimated to be >5 times with poor glycemic control and >2 with good glycemic control.

	HOMA IR + (≥3.8)	29	14	PR=2.4 POR=5.2	0.01
	HOMA IR – (<3.8)	4	10		
	HOMA IR + (≥3.8)	3	3	PR=1.6 POR=2.2	0.37
	HOMA IR – (<3.8)	7	16		

DISCUSSION

Studies investigating risk factors for the development of CSME have confirmed a positive correlation between macular edema and numerous factors like Hba1c levels, lipid levels, body mass index (BMI), and elevated systolic blood pressure.[15] The aforementioned risk factors also constitute a part of the spectrum of metabolic syndrome. Insulin resistance and hyperinsulinemia surface to be the common link among the listed risk factors, the forerunners and key players for both diabetic retinopathy as well as metabolic syndrome.[16]

Insulin resistance and hyperinsulinemia have been shown to precede the development of vascular pathobiological changes. While on one hand, the addition of insulin regulates the glycemia-associated microvascular changes, nonetheless, it is wise not to overlook the possibility of indirect effects of insulin on angiopathy, wherein high insulin levels can foster vasoactive effect resulting in increased vessel permeability.[2]

In the present study, we attempted to evaluate the prevalence of insulin resistance and analyze its possible participatory role in the development of maculopathy.

We observed that more than 50 percent of the patients diagnosed with diabetes had poor glycemic control, with mean HbA1c being significantly higher for patients presenting with macular edema.

It is interesting to note, that even though the majority of the patients in our study cohort were having poor glycemic control, not all had developed CSME, despite the mean duration of diabetes being more than 10 years and mean HbA1c being more than 7.5 across our patient population. The above observations reflect the possible role of additional factors beyond a) duration of diabetes and b) HbA1c levels.

In tandem with the aforementioned factors, we realized that insulin resistance contributed significantly to the development of CSME. More than two third of the diabetic patients in our study had elevated insulin resistance levels. The proportion of patients with elevated insulin resistance was approximately double in patients presenting with CSME (group A) compared to their counterparts without CSME (group B). Additionally, the mean insulin resistance as measured by HOMA-IR was also found to be significantly greater in patients with CSME.

In a study similar to ours, Zapata et al evaluated the association of macular edema with insulin resistance,[6] where the authors compared insulin resistance to the pattern of macular edema. They observed a significantly

greater prevalence of cystoid patterns of macular edema in patients with insulin resistance, and the authors attributed this finding to the pro-inflammatory state, manifested by hyperinsulinemia secondary to insulin resistance. The authors conceded the relevance of increased insulin resistance in eyes with macular edema; however, they fell short to establish with perspicuity the association between other morphological forms of diabetic macular edema and insulin resistance.

To further add, in one of the initial studies on HOMA IR by CW Rowe et al, the authors identified a strong correlation between severity of DR and insulin resistance, where they suggested an association of maculopathy and retinopathy with insulin resistance.[17]

It has been argued time and again that insulin resistance is closely associated with endothelial dysfunction. In our opinion, it is not only cromulent but also pragmatic to consider insulin resistance as a participatory factor, for the development and evolution of CSME. To confidently deduce the effects of insulin resistance on the development of macular edema, it is important to take into consideration the following observations from our study.

Elevated levels of insulin resistance (HOMA-IR) were found in >90% of patients having CSME in our cohort. Multivariate analysis to control for the known confounders of our cohort, expressed HOMA-IR to be a significant/independent factor for those developing CSME. None of the patients having CSME had normal HOMA-IR levels. In patients with elevated HbA1C levels, the odds of developing CSME were found to be greater in patients with increased insulin resistance.

The higher prevalence of CSME in patients with elevated HOMA-IR in our study can be explained by the patho-physiological changes that follow insulin resistance.

Insulin resistance is associated with deranged expression of nitric oxide synthase (NOS) pathway and elevated endothelin 1 levels.

Additionally, compensatory hyperinsulinemia promotes the release of vasoconstrictor endothelin, decreases NOS, and promotes the release of Von Willebrand factor coupled with the increase in pro-coagulants.[18,19] The above conundrum can cascade into vasogenic and rheological bespoke attributing to relative retinal ischemia and increased vaso-endothelial growth factors (VEGF) levels-driven vaso-permeability.[2,20,21]

In our opinion, the interplay of IR-dependent vasoactive changes, along with endothelial dysfunction, vascular leakage, and hyperglycemia-related endothelial pericyte damage, collectively increase the risk of developing macular edema.

Our study does not intend to find a causal relationship between insulin resistance and maculopathy but rather explore the possibility of insulin resistance as a participatory tool in the development of CSME. Our study attempts to investigate an integral yet neglected pivotal factor of "insulin resistance", as it silently highlights the role of insulin resistance on maculopathy and demonstrates IR as a possible occult effector for the development of maculopathy. Since not all diabetic develop retinopathy , the patients may remain unaware of the potential risks.[22] With no available biomarker for prediction of retinopathy, presence of insulin resistance can assist in predicting patients at risk for developing sight threatening maculopathy.

Our study remains limited by the sample size, cross-sectional single-center design and lack of longitudinal follow up. The causal relationship between insulin resistance and CSME could not be assessed due to cross sectional design. As our study was not an OCT based study, we could not characterize macular edema as center involving and non-center involving and could have possibly overlooked subclinical macular edema cases.

An unattended dimension in our study was the possible confounding effects of oral hypoglycemic treatment on altering insulin resistance and on CSME. We excluded patients on insulin and did not account for the oral hypoglycemics which could have acted like insulin sensitizers. However, this does give us a future venue for prospective studies to evaluate the effect of insulin sensitizers in the management of CSME for patients with altered insulin resistance.

CONCLUSION

Elevated levels of insulin resistance were estimated to be present in more than three fourths of diabetic patients. The findings of our study indicate a positive association between insulin resistance and development of CSME. The odds for development of CSME were found to be greater in uncontrolled diabetics with elevated insulin resistance.

Insulin resistance should be estimated for all diabetic patients, patients with poor glycemic control and increased insulin resistance should be considered for retinal screening for diabetic macular edema at the earliest.

Ethics Statement and Conflict of Interest Disclosures

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

Ethics Consideration: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws.

Conflict of interest: No known conflict of interest correlated with this publication.

Availability of data and materials: The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.

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The use of generative AI and AI-assisted technologies: The authors did not use in this article generative AI and AI-assisted technologies.

REFERENCES

1. Jatoi A. Assessment of risk factors for the development of diabetic retinopathy in T2D. Medicina Moderna - Modern Medicine. 2024;31(2):149–150. DOI: 10.31689/rmm.2024.31.2.149
2. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. 2005 May;26(2):19-39.
3. Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, et al. Homa-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects. Diabetes Care. 2002;25(7):1135–41.
4. de Luca C, Olefsky JM. Inflammation and insulin resistance. *FEBS Lett*. 2008;582(1):97-105.
5. Reaven GM. Banting Lecture 1988. Role of insulin resistance in human disease. Nutrition. 1988;13:64-66.
6. Haffner SM, Howard G, Mayer E, Bergman RN, Savage PJ, Rewers M, et al. Insulin sensitivity and acute insulin response in African-Americans, non-Hispanic whites, and Hispanics with NIDDM: the Insulin Resistance Atherosclerosis Study. Diabetes. 1997;46(1):63-9.
7. Bressler P, Bailey SR, Matsuda M, De- Fronzo RA: Insulin resistance and coronary heart disease. Diabetologia. 1996;39:1345–1350.
8. Jangid A, Nainiwal SK, Porwal R. Comparative evaluation of the severity of diabetic macular oedema in patients with and without metabolic syndrome. Indian Journal of Clinical and Experimental Ophthalmology. 2020;6(3):369–73.
9. Zapata MA, Badal J, Fonollosa A, Boixadera A, Garcia-Arumi J. Insulin resistance and diabetic macular oedema in type 2 diabetes mellitus. British Journal of Ophthalmology. 2010;94(9):1230–1232.
10. 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;98:786–806.
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and ?-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia .1985; 28(7):412–9.
12. Singh Y, Garg MK, Tandon N, Marwaha RK. A study of insulin resistance by HOMA-IR and its cut-off value to identify metabolic syndrome in urban Indian adolescents. J Clin Res Pediatr Endocrinol. 2013;5(4):245-51.
13. Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, Gude F, García F, De Francisco A, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. BMC Endocr Disord. 2013;13:47.
14. Tamhane AR, Westfall AO, Burkholder GA, Cutter GR. Prevalence odds ratio versus prevalence ratio: choice comes with consequences. Stat Med. 2016;35(30):5730-5735.
15. Zhang J, Ma J, Zhou N, Zhang B, An J. Insulin use and risk of diabetic macular edema in diabetes mellitus: a systemic review and meta-analysis of observational studies. Med Sci Monit. 2015;21:929-36.
16. Mbata O, Abo El-Magd NF, El-Remessy AB. Obesity, metabolic syndrome and diabetic retinopathy: Beyond hyperglycemia. World J Diabetes. 2017 15;8(7):317-329.
17. Rowe CW, Haider AS, Viswanathan D, Jones M, Attia J, Wynne K, et al. Insulin resistance correlates with maculopathy and severity of retinopathy in young adults with Type 1 Diabetes Mellitus. Diabetes Res Clin Pract. 2017;131:154-160.
18. Rask-Madsen C, King GL. Mechanisms of Disease: endothelial dysfunction in insulin resistance and diabetes. Nat Clin Pract Endocrinol Metab. 2007;3(1):46-56.
19. Cersosimo E, DeFronzo RA. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. Diabetes Metab Res Rev. 2006;22(6):423-36.
20. Poulaki V, Qin W, Joussen AM, Hurlbut P, Wiegand SJ, Rudge J, et al. Acute intensive insulin therapy exacerbates diabetic blood-retinal barrier breakdown via hypoxia-inducible factor-1 alpha and VEGF. J Clin Invest. 2002;109(6):805-15.
21. Hernández C, Zapata MA, Losada E, Villarroel M, García-Ramírez M, García-Arumí J, et al. Effect of intensive insulin therapy on macular biometrics, plasma VEGF and its soluble receptor in newly diagnosed diabetic patients. Diabetes Metab Res Rev. 2010;26(5):386–92
22. Garg P, Khan M. Awareness of diabetic retinopathy among adult population attending rural health care center, Uttar Pradesh. Medicina Moderna - Modern Medicine. 2022;29(1):53–54. DOI: 10.31689/rmm.2021.29.1.53