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Systemic Cellular Inflammatory Biomarkers in Diabetic Macular Edema

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Short title: Inflammatory Biomarkers in Diabetic Macular Edema

ABSTRACT:

Purpose: To assess the usefulness of cellular systemic inflammatory markers (leukocytes including lymphocytes; monocytes and neutrophils in addition to platelet count, mean platelet volume (MPV), and their ratios) as markers for developing diabetic macular edema (DME) in type 2 diabetes mellitus patients.

Methods: This study was a cohort comparative study and included 80 patients who were diagnosed with type two diabetes mellitus, the patients were divided into 2 groups; group A included 40 patients with type 2 DM without DME, group B included 40 patients with type 2 DM with DME and group C (control group) included age and sex-matched 40 nondiabetic patients. Spectral-domain OCT was done for diabetic patients to detect the presence of macular edema. Laboratory investigations included assessment of HbA_1C, Neutrophil, lymphocyte, monocyte, platelet counts, and MPV.

Results: HbA_1C was elevated in group B than group A and group C with statistically significant difference, in the same way it was higher in group B than other groups in MPV, M/L, P/L and MPV/L and NLR with statistically significant difference in all mentioned except NLR. There was a statistically significant difference between group A and group B in MPV, M/L, P/L and MPV/L, as well as a statistically significant difference between group A and group C in M/L and MPV/L.

Conclusion: Our study demonstrated that there was a strong relationship between DME and the inflammatory markers which was believed to have an essential role in its pathogenesis and could be used as promising markers for diagnosis.

Keywords: Diabetes mellitus, International Diabetes Federation, Diabetic retinopathy, DME

INTRODUCTION

Diabetes mellitus (DM) is a major cause of death worldwide and has been considered a major public health problem owing to its gradual increase in prevalence[1].

It has been demonstrated that DM prevalence among Egyptian adults represents about 15% that may be an underestimation. Therefore, it is necessary to thoroughly investigate the predisposing factors, treatment, prevention, and aftereffects of DM. In addition, awareness about its risk factors, methods of prevention has to gain much more popularity[2]**.** Diabetic retinopathy (DR) has been considered a major serious adverse event of DM and it is the most common etiology of new cases of visual loss among adults aged 20–74 years[3]**.**

Throughout the initial two decades of disease >60% of cases with type 1 DM have retinopathy. In cases with type 2 DM in which different ocular disorders were often develop, 1/3 of the cases of legal visual loss were owing to DR. In 2020, the number was estimated to be 103.12 million. The number of people affected by DR globally is predicted to reach 160.5 million by 2045, with nations with low-incomes suffering a disproportionate share of the burden[4]**.**

DME has been considered a major public health problem and comprises a major source of visual disability or loss in subjects with DR worldwide[5]**.** DME prevalence depends on the duration and type of diabetes. In type I diabetic patients, DME occurs within the first five years after diagnosis of DM with gradually increasing prevalence to 40% over 30 years[6]**.**

Nowadays, both DR and DME have been demonstrated to be associated with neurovascular degeneration **[8].** Of note, the actual cause of retinal neuroinflammation isn't totally understood. On the other hand, different nociceptive stimuli are comprised, which include hyperglycemia, glutamate, generation of free radicals, AGEs, and stress-level endothelial reticulum[9].

Essentially, DME pathogenesis is multifactorial. There are related anatomical and biochemical alterations that are correlated. DME is the result of microvascular alterations in DM leading to vascular incompetence and oedema. Hypoxic conditions trigger VEGF, causing more oedema[10].

The chronic hyperglycemic state in uncontrolled diabetes results in a microangiopathy and degenerative neuoretinopathy. Hyperglycemia activates deleterious intracellular metabolic pathways, including the hexosamine and polyol pathways, activation of protein kinase C, and results in increased glycosylation of proteins forming advanced glycosylation end products and formation of free radicals[11].

Hyperglycemia leads to upregulation of intercellular adhesion molecule 1 (ICAM-1), which mediates leukocyte adhesion to the vascular endothelium, resulting in vascular damage and capillary nonperfusion**[12].**

The inflammatory and vasogenic mediators, including vascular endothelial growth factor (VEGF) upregulation and inflammatory cytokines and chemokines, induce pathologic changes in the vascular endothelium triggering breakdown of the blood retinal barrier[13]. The vascular endothelial growth factor leads to capillary leakage, causing the accumulation of extracellular fluid in the macula[14].

Inflammation is an important parameter in major disorders and has been implicated in the pathogenesis of ocular diseases such as glaucoma, age-related macular degeneration (AMD), diabetic retinopathy, DRD and DME[15].

White blood cell (WBC) (including neutrophils, lymphocytes, and monocytes) and platelet counts, the mean platelet volume (MPV), and their ratios are useful indicators of systemic low-grade inflammation[16].

Leukocyte adhesion and the consequent leukocytosis are the early inflammatory responses in DME. In DR, endothelial cells upregulate ICAM-1 expression, leading to increased leukocyte adhesion, which ultimately ends in retinal vascular leaking[17].

Leukocytes may participate in microvascular injury by the generation of cytokines and superoxide via the respiratory burst, or by the induction of capillary occlusion, as a result causing local ischaemia downstream of the blockage. Leukocytes interact with, and bind to, ICAM-1 and VCAM on the surface of endothelial cells leading to adherence of the blood cells to the endothelial wall[18]. Leukocytes and platelet counts, the MPV, and their ratios are helpful indicators in terms of systemic low-grade inflammation[19].

Therefore, our study aimed to assess the value of cellular systemic inflammatory markers (such as leucocytes comprising lymphocytes; monocytes and neutrophils in addition to platelet count, MPV, and their ratios) as markers for developing DME in T2DM patients.

PATIENT AND METHOD

This study was a cohort comparative study conducted in Mansoura Ophthalmic Center, Mansoura University, Egypt, conducted between January 2022 and June 2023. This study enrolled 80 patients diagnosed with T2DM with high Hb A1c and received insulin therapy. The patients were divided into 2 groups; group A comprised 40 patients with type 2 DM without DME, and group B included 40 patients with T2DM with DME that were diagnosed according to ETDRS criteria for clinically significant macular oedema:

a) Retinal thickening at or within 500um from the center of the fovea.
b) Hard exudates at or within 500um from the center of the fovea with adjacent retinal thickening.
c) One or more disc areas of retinal thickening, any part of which is within one disc diameter of the center of the fovea.

A group C (control group) including age and sex-matched 40 non-diabetic patients were also included. Patients with any systemic inflammatory condition, infection, renal insufficiency, or inflammatory bowel disease, and patients with a history of previous ocular trauma or ocular surgery (vitreoretinal surgery or previous intravitreal injection) were excluded.

Method

Every patient was subjected to full history taking that included age, residency, medical history, surgical history,

social history, previous ocular trauma, or surgery. Ophthalmic examination was done comprising visual acuity (VA) UCVA and BCVA using landlot chart and was converted to the LogMAR for statistical analysis), Slit lamp (SL) examination to evaluate the anterior segment of the eye, Goldmann applanation tonometry to measure IOP, and SL biomicroscopy using +90 Volk lens to examine the fundus.

Optical coherence tomography was done for diabetic patients using spectral domain Topcon 3D 2000 OCT machine (Topcon, Inc., Paramus, NJ, 2. USA) to detect presence of macular edema. Peripheral blood samples were collected from the patients to assess HbA_1c, Neutrophil, lymphocyte, monocyte, platelet counts, and MPV. Different ratios were measured including NLR, monocyte/lymphocyte, platelet/lymphocyte, and MPV/lymphocyte ratios.

Ethical Consideration

The study protocol was approved by The International Research Board (IRB), faculty of medicine, Mansoura University and conducted in agreement with the tenets of the declaration of Helsinki. Verbal and written consent was obtained from each participant sharing in the study.

Statistical Analysis

Data was fed to the computer and analysed using IBM SPSS Corp. Released 2013, Version 22.0. Qualitative data were defined using number and percent. Quantitative data were described using median and mean, SD for parametric data following assessing normality by utilizing Kolmogrov-Smirnov test. Regarding all tests, significance was judged at the (0.05) level. We used Chi-Square test for comparison of 2 or more groups, One Way ANOVA test was utilized to compare more than 2 independent groups, Kruskal Wallis test to compare more than 2 independent groups, Mann Whitney U test to detect pair-wise comparison and Spearman's correlation to detect the strength and direction of a linear relationship between two non-normally distributed continuous or ordinal variables.

RESULTS

This study included 80 cases with type 2 DM from attendants to outpatient clinics of Mansoura Ophthalmic Center and 40 age and sex-matched subjects as a control group, table **(1)** demonstrates that there was no significant difference regarding age and gender between the 3 studied groups (P=0.853 and P=0.526 respectively). Regarding HbA_1c, it was elevated in group A than in group C with a statically significant difference (P<0.001), in the same way, it was higher in group B than in group A with a statistically significant difference (P<0.001),. Regarding visual acuity, UCVA and BCVA were worst in patients with DME (group B) in both right and left eyes with statistically significant difference between the three groups.

Regarding differential blood cell count, there were statistically significant differences between the 3 studied groups in WBCs, lymphocytes, platelets, and MPV (P=0.028, P<0.001, P=0.003, and P=0.037 respectively). Also, there were statistically significant differences between group A and group C in WBCs, lymphocytes, and platelet count in addition to a statistically significant difference between group A and group B in lymphocytes and platelet count (P<0.001, P=0.023 respectively). Regarding mean platelet volume (MPV), it was higher in the DME group (8.97±0.68) and reached a statistically significant difference between the 3 studied groups (P=0.037). details of differential blood count are shown in table (2).

As regard different ratios calculated from differential blood count, all ratios were high in group B and reaching statistically significant differences in M/L, P/L, and MPV/L (P=0.099, P=0.012, and P<0.001 respectively). There was a statistically significant difference between group A and group B in MPV, M/L, P/L, and MPV/L (P=0.013, P=0.0134, P=0.012, and P<0.001 respectively), as well as a statistically significant difference between group A and group C in M/L and MPV/L (P=0.016 and P<0.001 respectively). Details of different ratios are shown in table (3).

Table (1): Comparison of demographic characteristics, HBA1C, UCVA & BCVA between the studied groups.

	Diabetic Without macular edema (Group A) (N=40)	**Diabetic With macular edema (Group B) (N=40)**	**Control group (Group C) (N=40)**	**Test of significance**	**Within group significance**
Age/years mean±SD	59.28±7.25	58.55±6.15	58.45±7.89	F=0.159 P=0.853	**P1=0.606** **P2=0.950** **P3=0.650**
Sex N (%)				χ^2=1.28 P=0.526	**P1=0.496**
Male	25(62.5)	20(50)	22(55.0)		**P2=0.654**
Female	15(37.5)	20(50)	18(45.0)		**P3=0.368**
HbA1C	6.59±0.74	7.35±1.42	5.45±0.25	F=41.49 P<0.001*	**P1<0.001*** **P2<0.001*** **P3<0.001***
UCVA right	0.77(0.30-1.77)	1.0(0.3-2.3)	0.77(0.0-1.47)	KW=10.86 P=0.004*	**P1=0.166** **P2=0.001*** **P3=0.051**
UCVA left	0.77(0.3-1.47)	1.0(0.3-2.0)	1.0(0.05-2.3)	KW=6.10 P=0.047*	**P1=0.767** **P2=0.042*** **P3=0.025***
BCVA right	0.535(0.17-1.77)	0.885(0.170-2.3)	0.47(0.0-1.47)	KW=14.90 P=0.001*	**P1=0.610** **P2<0.001*** **P3=0.003***
BCVA left	0.60(0.17-1.47)	0.885(0.17-2.0)	0.77(0.0-2.3)	KW=10.88 P=0.004*	**P1=0.568** **P2=0.032*** **P3=0.001***

F: One Way ANOVA test, χ^2=Chi-Square test, P: difference between three studied groups, p1: difference between group A & group C, p2: difference between group B & group C, p3: difference between group A & group B

Table (2): Comparison of laboratory findings between the studied groups.

	Diabetic Without macular edema (Group A) (N=40)	Diabetic With macular edema (Group B) (N=40)	Control group (Group C) (N=40)	Test of significance	within group significance
WBCS	7.64±1.14	6.72±2.64	6.41±2.22	F=3.69 P=0.028*	**P1=0.01*** **P2=0.519** **P3=0.052**
Neutrophils	3155.75± 1141.23	3122.83±1583.66	3265.18±1977.78	F=0.086 P=0.917	**P1=0.761** **P2=0.692** **P3=0.927**
Lymphocytes	3980.85± 1210.43	3029.18±1403.88	2684.68±805.57	F=13.24 P<0.001*	**P1<0.001*** **P2=0.189** **P3<0.001***
Monocyte	402.80± 172.58	467.68±253.36	448.20±265.09	F=0.810 P=0.447	**P1=0.387** **P2=0.710** **P3=0.217**
Platelets	313.98± 89.50	267.35±99.17	245.48±82.26	F=5.97 P=0.003*	**P1=0.001*** **P2=0.282** **P3=0.023***
MPV	8.66± 0.48	8.97±0.68	8.74±0.48	**P=0.037*** **F=3.39**	**P1=0.509** **P2=0.067** **P3=0.013***

F:One Way ANOVA test, χ^2=Chi-Square test, P: difference between three studied groups, p1: difference between group A & group C, p2: difference between group B & group C, p3: difference between group A & group B

Table (3): Comparison of the studied ratios between studied groups with the following results

	Group A (N=40)	Group B (N=40)	Group C (N=40)	Test of significance	within group significance
M/L	0.113 (0.03-0.25)	0.157 (0.03-0.39)	0.153 (0.03-0.64)	KW=7.08 P=0.029*	**P1=0.016*** **P2=0.577** **P3=0.034***
P/L	0.074 (0.04-0.20)	0.093 (0.03-0.23)	0.09 (0.05-0.18)	KW=6.29 P=0.043*	**P1=0.08** **P2=0.722** **P3=0.012***
MPV/L	0.001 (0.001-0.004)	0.003 (0.0009-0.007)	0.003 (0.001-0.006)	KW=21.61 P<0.001*	**P1<0.001*** **P2=0.707** **P3<0.001***
NLR	1.01 (0.24-1.97)	1.095 (0.08-4.88)	0.908 (0.13-1.91)	KW=1.52 P=0.469	**P1=0.491** **P2=0.268** **P3=0.436**

KW: Kruskal Wallis test *statistically significant, P: difference between three studied groups, p1: difference between group A & group C, p2: difference between group B & group C, p3: difference between group A & group B

On mentioning the validity of CBC parameters in differentiating group A and group C a ROC curve was done and shows fair validity of both M/L and P/L as well as good validity of MPV/L.

Another ROC curve was done to determine the Validity of CBC parameters in differentiating group A and group B which revealed the following results, the highest accuracy detected was for both MPV and P/L (66.0%) followed by M/L (65.0%).

Additionally, another ROC curve was done to determine the Validity of CBC parameters in differentiating group B and group C which revealed the following results, the highest accuracy detected is for NLR (58.8) followed by both MPV and P/L (57.7). details of the validity of CBC parameters in differentiating between the 3 studied groups are shown in Tables 4,5 and 6.

Binary regression was used to detect the predictability of macular edema among diabetic patients and illustrated that HbA1c increase by 1gm/dl increases the risk of macular edema by 3.3 (AOR =3.3) and 95% C.I = 1.25-5.2 table (7).

Table (4): Validity of CBC parameters in differentiating group A and group C.

Test Result Variable(s)	**Area**	**P-value**	**Asymptotic** 95% **Confidence Interval**		**Cut off point**	Sensitivity %	specificity%	PPV%	PV%	**accuracy%**
			Lower Bound	Upper Bound						
MPV	.540	.538	.409	.671	8.45	65.0	40.0	52.0	53.3	**52.5**
M/L	.656	.016	.534	.778	0.1136	80	55.0	64	73.3	**67.5**
P/L	.614	.080	.487	.741	0.0723	75.0	47.5	58.8	65.5	**61.3**
MPV(L)	.779	.000	.677	.881	0.00227	97.5	55.0	66.7	84.6	**72.5**
NLR	**.545**	**0.491**	**.417**	**.672**	**0.9339**	**57.5**	**62.5**	**59.5**	**60.5**	**60.0**

Table (5): Validity of CBC parameters in differentiating group A and group B.

Test Result Variable(s)	**Area**	**P**	**Asymptotic 95% Confidence Interval**		**Cut Off Point**	**Sensitivity%**	**Specificity%**	**PPV%**	**NPV%**	**Accuracy %**
			Lower Bound	Upper Bound						
MPV	.613	.082	.486	.740	8.90	87.5	45.0	61.4	78.3	**66.3**
M/L	.638	.034	.514	.762	0.169	82.5	47.5	61.1	73.1	**65.0**
P/L	.662	.012	.536	.789	0.0861	70.0	55.0	62.5	65.1	**66.3**
MPV(L)	.741	.000	.632	.849	0.0027	70.0	65.0	61.9	62.2	**62.02**
NLR	**.551**	**.436**	**.423**	**.678**	**1.093**	**65.0**	**52.5**	**57.8**	**60.0**	**58.8**

Table (6): Validity of CBC parameters in differentiating group B and group C.

Test Result Variable(s)	**Area**	**P value**	**Asymptotic 95% Confidence Interval**		**Cut off point**	**Sensitivity %**	**Specificity %**	**PPV %**	**NPV %**	**Accuracy %**
			Lower Bound	**Upper Bound**						
MPV	.593	.153	.467	.719	9.0	70.0	45.0	56.0	**60.0**	**57.5**
M/L	.464	.577	.336	.592	0.221	80.0	22.5	50.8	**52.9**	**51.3**
P/L	.523	.722	.394	.652	0.0918	60.0	55.0	57.1	**57.9**	**57.5**
MPV(L)	.476	.707	.347	.604	0.00349	60.0	45.0	52.2	**51.5**	**51.9**
NLR	.572	.268	.445	.699	1.141	70.0	47.5	57.1	**61.3**	**58.8**

Table (7): binary logistic regression for prediction of macular oedema among DM cases

Predictors	**β**	**p value**	**AOR**	**95.0% C.I. for AOR**	
				Lower	**Upper**
M/L	7.942	.368	2813.891	.000	**8.964**
MPV.L	-506.400	.610	.000	.000	**.00**
WBC	-.578	.130	.561	.265	**1.186**
Lymphocyte	.000	.438	.999	.997	**1.001**
Platelets	.003	.630	1.003	.990	**1.017**
HBA1C	-9.307	.003	3.3	1.25	**5.2**
Constant	**60.037**	**.003**	**1.185**		

Overall% predicted=91.2%, AOR: Adjusted odds ratio

DISCUSSION

Diabetic macular edema (DME) is retinal thickening caused by the accumulation of intraretinal fluid in the macula in cases with DR leading to a marked impairment of visual field[20]. It has been demonstrated that systemic inflammatory markers, which include neutrophils, lymphocytes, and apolipoprotein A-1 play essential functions in disease pathophysiology which includes cardiovascular disease (CVD)[21] and cancers[22], as well as figures obviously in ocular disorders development which include retinal vein occlusion[23] and uveitis[24]. In addition, NLR could be considered as a valid predictor of DR[25], whereas WBCs have been recorded to be associated with retinal endothelial cell death and impairment of the blood-retina barrier (BRB)[26].

Thus, our study aimed to inspect the usefulness of cellular inflammatory markers (leucocytes including lymphocytes; monocytes and neutrophils in addition to platelet count, MPV, and their ratios) as markers for developing DME in T2DM cases.

The three studied groups (DME, non-DME, and control groups) displayed insignificant differences regarding both the age and female/male ratio (58.22±11.35, 61.92±6.82, and 63.54±5.68 years, and 21/19, 20/20, and 19/21, respectively, p=0.2 and 0.9)[27].

In relation to visual acuity, our study displayed that; UCVA and BCVA were worst in patients with DME with a significant difference among the three studied groups. Likewise, Ilhan and his colleagues have displayed that; BCVA was significantly reduced in DME compared to both diabetes without macular edema and those with the control group[28].

As regard HbA1c, the current study revealed that; it was elevated in group A than group C with statically significant difference (P<0.001), in the same way it was higher in group B compared to group A with significant difference (P<0.05). Likewise, Chou and his colleagues have demonstrated that; the HbA1C level (8 or over) showed a significant and positive association with macular thickness in OCT[29].

This came in agreement with Peng and his colleagues who revealed that higher glycosylated hemoglobin values were associated with increased central macular thickness (CMT) in cases without macular oedema, while glycosylated hemoglobin values has an inverse association with CMT among cases with macular oedema[30]. In contrast, Zhu and his colleagues displayed that; there was a non-significant increase in HbA1c value in the non-DME group compared to the DME group. As a result, even with the existence of prolonged hyperglycaemia, other factors could participate in DME development too[31].

With regard to lymphocyte and platelets, our study demonstrated that; there was statistically significant differences concerning both lymphocyte and platelets (P<0.001 and P=0.003 respectively). This was in agreement with Zhu and his colleagues who revealed that there was a significant reduction in lymphocyte percentage in the DME group compared to DME free one. Thus, they concluded that; Lymphocyte percentage could be utilized as an inflammatory marker for DME development in cases with extensive DR[32].

In contrast, Ilhan and his colleagues demonstrated that; the mean lymphocyte, and platelet counts were comparable

among the studied groups (DME, diabetes without macular edema and the control group)[33].

Concerning neutrophil, our study revealed that; there was no significant difference among the three studied group (P=0917). While, Ilhan and his colleagues have revealed that; the mean neutrophil counts of the DME and non- DME groups were similar and both were significantly higher than that of the controls[27]. Moreover, Zhu and his colleagues demonstrated that; the neutrophil percentage was significantly higher in the DME group than in the non-DME group[29].

In the context of MPV, our study displayed that there were significant differences among the studied groups regarding MPV being significantly elevated in cases with DME (P=0.039). Additionally, there was a statistically significant increase in MPV in DME compared to diabetic without macular edema (P=0.013). In accordance, Ilhan and his colleagues have revealed that; the mean MPV of the DME group was higher than those of the non-DME and control groups[27].

In terms of M/L ratio, our study demonstrated that there was statistically significant difference between the three studied groups being significantly increased in the DME (P=0.029). In agreement Vural & Hazar have illustrated that; in cases with DME the baseline MLR was significantly higher in cases with better visual outcomes[31].

As regards PLR, our study displayed that; there was statistically significant difference between the three studied groups being significantly increased in the DME (P=0.043).

In the context of NLR, our study demonstrated that it was higher in DME group than other two groups but didn't reach the significant level (P>0.05). In addition, our study revealed that NLR had the highest accuracy for differentiating between group A and group B (58.8). In the same line, Ilhan and his colleagues were in agreement with the current study who have displayed that; the mean NLR ratio of the DME and non-DME groups was higher than that of the controls, and the value of the DME group was higher than that of the non-DME group ($p<0.05$)[27].

Zhou and his colleagues have demonstrated that; there was a correlation between the number of HRF and NLR, in both univariate and multivariate linear regression analyses[32]. Likewise, Yalinbas Yeter and his colleagues have demonstrated that; logistic regression analysis demonstrated that NLR≥2 and monocyte/lymphocyte ratio ≥13.9 were significantly accompanied by DME prediction[33].

Such outcomes suggested a direct relationship between DME and inflammation. The systemic and local expressions of proinflammatory cytokines are elevated in the retina of DR cases[34]. Such proinflammatory molecules lead to structural and functional changes in the retina and negatively interfere with endothelial cells, pericytes, Müller cells, and microglia[35]. The detection of particular systemic inflammatory factors can be used for the early identification of DME[29].

CONCLUSION

There was a strong correlation between DME and the inflammatory markers which was believed to have an essential role in its pathogenesis and could be used as promising markers for diagnosis. HbA1c increase by 1% increases the risk of macular edema by 3.3. Lymphocyte percentage could be utilized as an inflammatory marker for DME development in cases with severe DR. All ratios used in this study were higher in DME group than other groups.

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Conflict of interest

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