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CORRELATION BETWEEN THE LEVELS OF SERUM TSG-14, ALBP, AND EGLN1 AND THE SEVERITY OF DIABETIC MACULAR EDEMA

KORELACIJA IZMEĐU NIVOA SERUMSKIH TSG-14, ALBP I EGLN1 I TEŽINE DIJABETIČNOG MAKULARNOG EDEMA

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Summary

Background: To investigate the relationships among serum TNF-stimulated gene 14 (TSG-14), adipocyte lipid binding protein (ALBP), and Egl nine homolog 1 (EGLN1) levels and the severity of diabetic macular oedema (DME).A total of 314 patients with DME who were admitted to our hospital from March 2022 to March 2025 were selected (DME group). The patients were divided into mild, moderate, and severe groups based on their severity. Additionally, 314 patients with simple T2DM who were admitted to our hospital during the same period were selected (T2DM group). The levels of serum TSG-14, ALBP, and EGLN1 were measured by ELISA. Logistic regression was used to identify determinants of severe DME, and receiver operating characteristic (ROC) curves were constructed to evaluate the blood levels of TSG-14, ALBP, and EGLN1 in patients with severe DME.
Results: There were significant differences in diabetes duration, fasting blood glucose, glycosylated haemoglobin, and homocysteine levels between the T2DM and DME groups (all $P<0.05$). Compared with those in the T2DM group, the levels of serum TSG-14, ALBP, and EGLN1 in the DME group were considerably larger (all $P < 0.05$). Serum TSG-14, ALBP, and EGLN1 levels in the moderate and severe groups were significantly higher (all $P<0.05$) than those in the mild group; serum TSG-14, ALBP, and EGLN1 levels in the severe group were significantly higher (all $P<0.05$) than those in the moderate group. According

Kratak sadržaj

Uvod: Cilj je bio da se ispita odnos između nivoa TNF-stimulisanim genom 14 (TSG-14), adipocitnog lipid-vezivnog proteina (ALBP) i homolog proteina Egl-9 (EGLN1) u serumu i težine dijabetičnog makularnog edema (DME).
Metode: U studiju je uključeno ukupno 314 pacijenata sa DME hospitalizovanih u našoj ustanovi u periodu od marta 2022. do marta 2025. godine (DME grupa). Pacijenti su, prema težini bolesti, podeljeni u blagu, umerenu i tešku grupu. Takođe je uključeno 314 pacijenata sa nekomplikovanim dijabetes melitusom tip 2 (T2DM grupa), hospitalizovanih u istom periodu. Nivoi TSG-14, ALBP i EGLN1 u serumu određeni su metodom ELISA. Za identifikaciju faktora povezanih sa teškim DME korišćena je logistička analiza, dok su ROC krive konstruisane radi procene dijagnostičke vrednosti koncentracija TSG-14, ALBP i EGLN1 u krvi kod pacijenata sa teškim DME.
Rezultati: Uočene su značajne razlike u trajanju dijabetesa, nivou glikemije natašte, glikozilovanog hemoglobina i homocisteina između T2DM i DME grupe (sve $P<0,05$). U poređenju sa T2DM grupom, nivoi TSG-14, ALBP i EGLN1 u serumu bili su značajno viši u DME grupi (sve $P<0,05$). Nivoi TSG-14, ALBP i EGLN1 u umerenoj i teškoj grupi bili su značajno viši (sve $P<0,05$) nego u blagoj grupi, dok su u teškoj grupi bili značajno viši (sve $P<0,05$) nego u umerenoj grupi. Logistička analiza je pokazala da su EGLN1, ALBP i TSG-14 faktori rizika za teški DME (sve $P<0,05$). Rezultati ROC analize pokazali su da

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to logistic analysis, EGLN1, ALBP, and TSG-14 were risk factors for severe DME (all P<0.05). When evaluating patients with severe DME, ROC curve analysis showed that the AUCs for serum TSG-14, ALBP, and EGLN1 alone and in combination were 0.781, 0.805, 0.817, and 0.950, respectively. The combined evaluation AUC was higher than in the individual evaluations (Z=2.699, 2.714, and 2.717, all P<0.05).

Conclusion: The levels of TSG-14, ALBP, and EGLN1 in the serum of DME patients were dramatically raised. These three signs are related to the severity of the condition. The combination detection approach has certain clinical utility for evaluating patients with severe DME.

Keywords: diabetic macular oedema, TNF-stimulated gene 14 (TSG-14), adipocyte lipid binding protein (ALBP), Egl nine homolog 1 (EGLN1)

su AUC vrednosti za TSG-14, ALBP i EGLN1 pojedinačno, kao i u kombinaciji, iznosile 0,781; 0,805; 0,817 i 0,950. Kombinovana procena imala je višu AUC vrednost u odnosu na pojedinačne procene (Z=2,699; 2,714; 2,717; sve P<0,05).

Zaključak: Nivoi TSG-14, ALBP i EGLN1 u serumu pacijenata sa DME značajno su povišeni i povezani su sa težinom bolesti. Kombinovani pristup određivanju ovih biomarkera ima određeni klinički značaj u proceni pacijenata sa teškim DME.

Ključne reči: dijabetični makularni edem, TNF-stimulisani gen 14 (TSG-14), adipocitni lipid-vezivni protein (ALBP), homolog proteina Egl-9 (EGLN1)

Introduction

In addition to presenting its own physiological abnormalities, diabetes can also cause serious complications that significantly affect health. Diabetic retinopathy (DR) is a prevalent condition (1, 2). Diabetic macular oedema (DME) is a condition that develops based on DR and is one of the reasons for visual impairment in patients with type 2 diabetes mellitus (T2DM) (3, 4). DME can increase the amount of extracellular fluid produced by highly permeable retinal capillaries, leading to thickening of the macula and causing vision loss. Approximately one quarter of patients with T2DM progress to DME within 10 years of their initial diagnosis, and the treatment methods for patients with different disease severities also vary (5, 6). Therefore, in clinical practice, it is necessary to identify indicators of DME severity to improve patients' quality of life and provide a reference for clinicians to formulate targeted treatment strategies. TNF-stimulated gene 14 (TSG-14) is released locally by cells such as vascular endothelial and smooth muscle cells. It is related to insulin resistance. Studies have shown that in T2DM patients, elevated blood sugar leads to the destruction of vascular endothelial cells and the aggregation of inflammatory cells, thereby increasing serum TSG-14 levels, which are associated with the progression of DR (7). Fatty acid-binding protein 4 (ALBP) is predominantly expressed in adipose tissue and macrophages, functioning as an intracellular lipid chaperone, participating in regulating glycolipid metabolism and inflammatory responses. When its level increases, it can contribute to the progression of various complications, such as dry eye (8). Prolyl hydroxylase 2 (EGLN1) is an enzyme that degrades hypoxia-inducible factor-1α (HIF-1α) and is aberrantly produced in human retinal vascular endothelial cells in response to elevated glucose levels (9).

At present, there are few reports on TSG-14, ALBP, and EGLN1 in DME. Therefore, this study aimed to explore the correlation between the levels of serum TSG-14, ALBP, and EGLN1 and the severity of DME.

Materials and Methods

General information

A total of 314 patients with DME (314 eyes) who were admitted to our hospital from March 2022 to March 2025 were selected (DME group). Inclusion criteria: (1) met the criteria for DME; (2) aged ≥18 years; (3) had a clear history of T2DM; and (4) had complete clinical data. Exclusion criteria: (1) other types of diabetes; (2) previous ocular trauma or surgical history; (3) other ocular diseases (glaucoma, retinal vein occlusion); (4) diseases of the thyroid or adrenal glands; (5) immune system damage; (6) malignant tumours; (7) relevant treatment before admission (antivascular endothelial growth factor); (8) impaired function of important organs; and (9) pregnancy or lactation.

The T2DM group consisted of an additional 314 individuals with uncomplicated T2DM who were hospitalized at our hospital during the same time period. Inclusion criteria: (1) met the criteria for T2DM; (2) had no fundus lesions; (3) were aged ≥18 years; and (4) had complete clinical data. The exclusion criteria were the same as those of the DME group.

All participants signed the informed consent form. The ethics committee of our hospital granted approval for this study (approval number: PKSH-22-089).

Detection of serum TSG-14, ALBP and EGLN1 levels

All enrolled patients had their elbow venous blood samples collected in the fasting state early the next morning. The blood samples were left at room temperature for 30 minutes, then centrifuged at 3,500 r/min for 15 minutes (with a centrifugal radius of 10 cm) to separate the upper serum, which was aliquoted for storage at -80 °C for testing. The serum TSG-14 level was measured using the R&D Systems Human TSG-14 Quantikine ELISA Kit (catalogue number DPT300), which employs a double-antibody sandwich ELISA method. The detection range is 15.6–1000 pg/mL, with within-batch differences of <5% and between-batch differences of <7%. The serum ALBP level was detected using the Cusabio Human ALBP ELISA Kit (catalogue number CSB-EL011878HU), using the competitive ELISA method. The detection range is 0.156–10 ng/ml, with a sensitivity of 0.058 ng/mL. The serum EGLN1 level was measured using the Cloud-Clone Human EGLN1/EGLN1 ELISA Kit (catalogue number SEA922Hu) by the double-antibody sandwich ELISA method. The detection range is 15.6–1000 pg/ml, with a sensitivity of 9.38 pg/mL.

All detection steps were carried out according to the instructions for the reagents. Each sample was set up with two wells for repetition, and the average value was taken as the final result. At the same time, clinical data such as the patient's age, gender, BMI, smoking history, drinking history, hypertension status, diabetes duration, systolic blood pressure, diastolic blood pressure, fasting blood glucose, glycosylated haemoglobin, homocysteine, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum creatinine, and urea nitrogen were collected for subsequent correlation analysis (10–12).

Judgment of DME severity

Patients with DME were grouped according to relevant references. When there was a certain degree of thickening or hard exudation in the posterior pole of the retina and the distance from the macula was relatively far, it was classified as mild oedema (mild group, 124 cases, 124 eyes); when there was thickening of the retina or hard exudation close to the macula, it was classified as moderate oedema (moderate group, 108 cases, 108 eyes). When there was significant retinal thickening and hard exudation involving the macula, it was classified as severe oedema (severe group, 82 cases, 82 eyes).

Observation indicators

(1) A comparison was conducted between the general data of the T2DM group and the DME group; (2) serum levels of TSG-14, ALBP, and EGLN1 were compared between the T2DM and DME groups; (3) serum levels of TSG-14, ALBP, and EGLN1 were compared among patients with varying disease severities; (4) factors influencing severe DME were analysed; and (5) the significance of serum TSG-14, ALBP, and EGLN1 in patients with severe DME was evaluated.

Statistical analysis

The data were analysed using SPSS 25.0. The quantitative data are reported as $\bar{x}\pm s$, and independent sample t-tests were performed for comparisons between two groups. The count data are presented as n (%) and were analysed using χ^2 testing. SNK-q tests were used for pairwise comparisons, whereas one-way ANOVA was used for comparisons across multiple groups. Logistic regression was performed to identify influencing factors of severe DME, and ROC curves were developed to evaluate the diagnostic utility of serum TSG-14, ALBP, and EGLN1 in patients with severe DME. A difference was deemed statistically significant if P was less than 0.05.

Results

Comparison of general data between the T2DM group and the DME group

Significant differences were observed in diabetes duration, fasting blood glucose, glycosylated haemoglobin, and homocysteine levels between the T2DM and DME groups (all $P<0.05$). In contrast, no changes were detected in other general data (all $P>0.05$), as shown in *Table I*.

Compared with patients with simple type 2 diabetes, patients with diabetic macular oedema have a longer duration of diabetes and poorer glycaemic control, manifested by significantly elevated fasting blood glucose and glycated haemoglobin levels. Additionally, homocysteine levels in DME patients are significantly higher than those in T2DM patients, indicating more pronounced endothelial dysfunction and an inflammatory state. These differences reflect the pathophysiological characteristics of diabetic macular oedema as a serious complication of diabetes, namely the exacerbation of microvascular damage and inflammatory response caused by the long-term high glucose environment.

Table I Comparison of general data between the T2MD GROUP and the DME group.

Item	T2DM group (n=314)	DME group (n=314)	X^2/t	P
Age ($\bar{x}$±s, years)	51.28±6.57	51.67±6.77	0.523	0.606
Male/Female (Cases)	168/146	178/136	0.325	0.574
BMI ($\bar{x}$±s, kg/m^2)	23.51±3.19	23.60±3.25	0.253	0.806
Smoking history (Cases,%)	164 (52.2)	172 (54.8)	0.208	0.654
Drinking history (Cases,%)	170 (54.1)	180 (57.3)	0.326	0.573
Hypertension (Cases,%)	108(34.4)	112(35.7)	0.082	0.768
Course of diabetes ($\bar{x}$±s, a)	6.34±1.46	8.19±2.04	9.390	<0.001
Systolic blood pressure ($\bar{x}$±s, mmHg)	130.68±21.68	131.29±22.49	0.248	0.800
Diastolic blood pressure ($\bar{x}$±s, mmHg)	82.37±7.59	83.26±8.64	0.976	0.334
Fasting blood glucose ($\bar{x}$±s, mmol/L)	7.26±1.29	8.99±1.30	11.649	<0.001
Glycated haemoglobin ($\bar{x}$±s,%)	6.35±1.15	7.82±1.24	11.934	<0.001
Homocysteine ($\bar{x}$±s, μmol/L)	21.45±3.49	35.39±4.42	30.817	<0.001
TG ($\bar{x}$±s, mmol/L)	2.29±0.34	2.34±0.37	1.365	<0.001
TC ($\bar{x}$±s, mmol/L)	5.97±0.60	6.01±0.72	1.696	<0.001
LDL-C ($\bar{x}$±s, mmol/L)	3.59±0.48	3.64±0.55	0.914	<0.001
HDL-C ($\bar{x}$±s, mmol/L)	1.37±0.29	1.35±0.34	0.612	<0.001
Blood creatinine ($\bar{x}$±s, μmol/L)	81.01±6.46	81.60±6.52	0.806	<0.001
Urea nitrogen ($\bar{x}$±s, mmol/L)	4.59±0.49	4.64±0.54	0.915	<0.001

Table II Comparison of serum TSG-14, ALBP, and EGLN1 levels between the T2DM group and DME group $\bar{x}$±s.

Group	Example	TSG-14 (mg/L)	ALBP (ng/mL)	EGLN1 (ng/mL)
T2DM group	314	15.65±2.60	14.65±3.08	143.28±21.01
DME group	314	32.14±4.32	29.99±4.67	302.32±26.27
T		40.215	34.619	59.245
P		<0.001	<0.001	<0.001

Comparison of serum TSG-14, ALBP, and EGLN1 levels between the T2DM group and the DME group

Compared with those in the T2DM group, the serum levels of TSG-14, ALBP, and EGLN1 in the DME group were significantly greater (all P<0.05), as shown in *Table II*.

Compared with patients with simple type 2 diabetes, the serum levels of TSG-14, ALBP, and EGLN1 in patients with diabetic macular oedema were significantly higher, suggesting that these biomarkers may be closely associated with the onset and progression of diabetic macular oedema. This difference reflects the special pathological and physiological process of DME as a serious complication of diabetes, which may be related to enhanced inflammatory response, vascular dysfunction, and tissue hypoxia, among other factors.

Comparison of serum TSG-14, ALBP, and EGLN1 levels in patients with different severities of DME

Compared with those in the mild group, the serum levels of TSG-14, ALBP, and EGLN1 in the moderate and severe groups were significantly greater (all P<0.05); compared with those in the moderate group, the serum levels of TSG-14, ALBP, and EGLN1 in the severe group were also significantly greater (all P<0.05), as shown in *Table III*.

Table III Comparison of serum TSG-14, ALBP, and EGLN1 levels in DME patients with different disease severity $\bar{x}\pm s$.

Group	n	TSG-14 (mg/L)	ALBP (ng/mL)	EGLN1 (ng/mL)
Mild group	124	21.68±3.28	19.82±3.78	210.27±23.29
Moderate group	108	32.65±4.65	31.27±4.89	319.65±26.98
Severe group	82	46.28±5.75	42.61±5.635	412.28±29.66
F		374.087	296.411	748.841
P		<0.001	<0.001	<0.001

Table IV Analysis of influencing factors of severe DME.

Factor	B	SE	Wald x^2	P	OR	95%CI
TSG-14	1.415	0.315	20.480	<0.001	4.108	2.220–7.569
ALBP	1.280	0.435	8.875	0.003	3.624	1.556–8.447
EGLN1	1.089	0.468	5.456	0.020	2.965	1.194–7.362

Table V Evaluation value of serum TSG-14, ALBP, EGLN1 in patients with severe DME.

Indicator	AUC	95%CI	Sensitivity (%)	Specificity (%)	truncation value
TSG-14	0.781	0.690–0.883	75.61	76.91	43.634 mg/L
ALBP	0.805	0.729–0.871	76.27	75.66	39.657 ng/mL
EGLN1	0.817	0.737–0.896	79.89	74.27	401.647 ng/mL
Joint detection	0.950	0.910–0.999	95.35	73.18	

The serum levels of TSG-14, ALBP, and EGLN1 in patients with diabetic macular oedema (DME) are closely correlated with disease severity. As DME severity increases, the expression levels of these three biomarkers show a significant upward trend. The serum biomarker levels in patients with mild DME are relatively low, while those in patients with moderate DME show a significant increase, and the levels in patients with severe DME reach the highest value. This trend indicates that TSG-14, ALBP, and EGLN1 may be involved in the pathophysiology of DME and can serve as important indicators for evaluating disease severity.

Analysis of the influencing factors of severe DME

The severity of DME (severe = 1, mild to moderate = 0) was used as the dependent variable, and the different indicators mentioned above (all input as original values) were included as independent variables in the logistic equation (stepwise forward method). The findings indicated that TSG-14, ALBP, and EGLN1 were risk factors influencing severe DME (all $P<0.05$), as shown in *Table IV*.

Evaluation of the serum TSG-14, ALBP, and EGLN1 levels in patients with severe DME

The severity of DME (severe = 1, mild to moderate = 0) served as the status variable, whereas TSG-14, ALBP, and EGLN1 levels served as test variables. ROC curves were constructed. The findings showed that the AUCs for serum TSG-14, ALBP, and EGLN1, both separately and in combination, were 0.781, 0.805, 0.817, and 0.950, respectively, for assessing patients with severe DME. The combined evaluation's AUC ($Z=2.699$, 2.714, 2.717; all $P<0.05$) was higher than in the individual evaluations, as shown in *Table V*.

Discussion

Diabetes is a disease characterized by high blood sugar, caused by insufficient insulin secretion. It can lead to a series of complications, such as cardiovascular and cerebrovascular diseases and kidney failure. The most common complication is DR, and DME is the main cause of vision impairment in DR patients. Its incidence is also increasing annually (13, 14). DME is a pathological change caused by increased vascular permeability in the macular area

due to high blood sugar and lipid metabolism disorders in the body. Most DR patients have no symptoms before developing macular oedema, and blindness may even occur as the disease progresses (15, 16). Currently, fundus fluorescein angiography is primarily used in clinical practice to diagnose DME. Still, some patients often have concurrent diseases, such as heart and kidney dysfunction, and cannot undergo examination (17). Therefore, in clinical practice, it is important to identify indicators of DME to evaluate the patient's condition and guide treatment.

TSG-14 is a member of the pentraxin protein family and an acute-phase protein. It is initially released by neutrophils and later released by vascular endothelial cells, macrophages, etc. It can participate in the body's immune-inflammatory response by recognizing pathogens and activating the complement pathway. Under normal circumstances, its content is relatively low. However, it rapidly increases in the lesion area under the stimulation of inflammatory responses and other stimuli, thereby aggravating inflammatory damage (18). NF-κB is the promoter of the transcription pathway of TSG-14. When the body mounts an inflammatory response, inflammatory factors activate the NF-κB pathway, thereby increasing TSG-14 expression (19, 20). Moreover, its level increased with the increasing severity of the disease. These findings indicate that this finding is related to the severity of the patient's condition. It is speculated that this may be because, when TSG-14 levels increase, it promotes increased blood sugar levels, inflammation, and insulin resistance, thereby affecting the progression of DME and aggravating the patient's condition.

ALBP, a molecule that can coordinate intracellular lipid responses, can regulate the immune and metabolic responses of the body. It can exert oxidative stress by inhibiting the PPARγ signalling pathway and can also activate signalling pathways, such as the NF-κB pathway, to promote inflammatory responses (21). Recent studies have shown that ALBP can participate in the DR process. It can exacerbate the inflammation of retinal pigment epithelial cells triggered by elevated glucose levels by activating NF-κB, and its expression can be suppressed by modulating PPARγ expression, thereby mitigating the oxidative stress caused by high glucose in the retina (22). ALBP is significantly elevated in the serum of patients with retinal vein occlusion and is associated with the severity of secondary macular oedema and patient prognosis. The results of this study revealed that the serum ALBP level was elevated in the DME group, suggesting that it may be related to the occurrence of DME. The level of ALBP increased with disease severity, suggesting that it is related to the severity of the patient's condition. A possible reason is that increased ALBP levels cause beta-cell dysfunction and promote insulin resistance. Elevated blood sugar disrupts tear film function and can also increase inflammation and oxidative stress by regulating related signalling pathways, damaging tear film tissue, reducing tear secretion, increasing the risk of DME, and aggravating the progression of the patient's condition (23).

EGLN1 is an intracellular oxygen sensor that can regulate HIF activity and stability. HIF-1α is hydroxylated by EGLN1 under normal oxygen conditions, leading to rapid degradation. In a hypoxic environment, EGLN1 activity is inhibited, and the reaction catalysing the hydroxylation of HIF-1α is hindered, leading to its accumulation in the cytoplasm. Then, it enters the nucleus and binds to HIF-1β, inducing the formation of new blood vessels (24). The serum EGLN1 level increased as the disease progressed, suggesting a relationship with the patient's condition. A possible reason is that when EGLN1 levels increase, the reaction catalysing HIF hydroxylation is hindered, and the accumulated HIF-1α induces the expression of the downstream gene VEGF, thereby contributing to the progression of DME and aggravating the patient's condition (25).

This study also showed that logistic regression identified TSG-14, ALBP, and EGLN1 as significant factors for severe DME. These findings indicate that these factors may all be related to severe DME. After the confounding factors were analysed using the stepwise forward method, no differences were observed, thereby eliminating their influence. The ROC curve showed that the integrated evaluation of serum TSG-14, ALBP, and EGLN1 in patients with severe DME had a superior AUC compared to individual assessments, suggesting that combined testing can improve diagnostic value for patients with severe DME.

Conclusion

The levels of TSG-14, ALBP, and EGLN1 in the serum of DME patients were significantly increased. These three signs are related to the severity of the condition. The combined detection approach has certain clinical utility for evaluating severe DME. There are several limitations to this study. The sample size was modest, and the study was single-centred. In the future, the sample size should be expanded, and multicentre studies should be conducted to further the mechanisms involved. Moreover, this study did not explore the interactions among TSG-14, ALBP, and EGLN1. Further verification will be conducted in the future.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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