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CORRELATION ANALYSIS OF SERUM TSG-14 AND CORS26 LEVELS WITH DIABETIC RETINOPATHY

KORELACIONA ANALIZA IZMEĐU NIVOA TSG-14 I CORS26 U SERUMU I DIJABETIČKE RETINOPATIJE

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Summary

Background: To investigate the relationship between serum Cartilage Oligomeric Matrix Protein Like 26 (CORS26), TNF-stimulated gene 14 (TSG-14), and diabetic retinopathy (DR).
Methods: 276 patients with type 2 diabetes mellitus (T2DM) who were admitted to our hospital between April 2023 and April 2025 participated in a single-centre cross-sectional analysis. These patients were divided into a DR group (156 patients) and a non-DR group (120 patients) based on the diagnostic findings. A nonproliferative DR (NPDR) group comprising 98 individuals and a proliferative DR (PDR) group comprising 58 patients were divided from the DR group. The associations between the markers of glycolipid metabolism, TSG-14 and CORS26, were examined using the Pearson correlation method. A logistic analysis was conducted to examine the variables influencing DR in individuals with type 2 diabetes. The diagnostic utility of serum TSG-14 and CORS26 for DR in T2DM patients was assessed using ROC curves.
Results: The overall information for the two patient groups was similar. While the level of HDL-C was lower than that of the non-DR group, the levels of serum TSG-14, CORS26, TC, TG, LDL-C, and HOMA-IR were higher in the DR group (all P<0.05). The PDR group's serum

Kratak sadržaj

Uvod: Cilj je bio da se ispita odnos između nivoa proteina sličnom oligomernom matriks proteinu hrskavice (Cartilage Oligomeric Matrix Protein Like 26 – CORS26), gena 14 stimulisanog TNF-om (TSG-14) u serumu i dijabetičke retinopatije (DR).
Metode: U jednocentričnu studiju preseka uključeno je 276 pacijenata sa dijabetes melitusom tipa 2 (T2DM), hospitalizovanih u periodu od aprila 2023. do aprila 2025. godine. Na osnovu dijagnostičkih nalaza, pacijenti su podeljeni u grupu sa DR (156 pacijenata) i grupu bez DR (120 pacijenata). U okviru DR grupe izdvojene su podgrupe: neproliferativna DR (NPDR, 98 ispitanika) i proliferativna DR (PDR, 58 pacijenata). Veza između parametara glikolipidnog metabolizma, TSG-14 i CORS26 je analizirana Pearsonovom metodom. Korišćena je logistička regresiona analiza za ispitivanje faktora koji utiču na pojavu DR kod osoba sa dijabetesom tipa 2. Dijagnostička vrednost serumskih TSG-14 i CORS26 za DR kod pacijenata sa T2DM je procenjena pomoću ROC krivih.
Rezultati: Opšti podaci za obe grupe pacijenata su bili slični. Nivo HDL-C bio je niži u DR grupi u poređenju sa grupom bez DR, dok su nivoi serumskih TSG-14, CORS26, ukupnog holesterola (TC), triglicerida (TG), LDL-C i HOMA-IR bili viši u DR grupi (sve P<0,05). Se-

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levels of TSG-14 and CORS26 were higher than those of the NPDR group (both P<0.05). Serum TSG-14 and CORS26 showed negative associations with HDL-C and positive associations with TC, TG, LDL-C, and HOMA-IR (all P<0.001). In patients with type 2 diabetes, logistic regression analysis revealed that the following risk factors were associated with DR: diabetes duration, TC, TG, LDL-C, HOMA-IR, TSG-14, and CORS26 (all P<0.05). Serum TSG-14 and CORS26 areas under the curve (AUCs) for diagnosing DR in patients with type 2 diabetes (T2DM) were 0.833, 0.832, and 0.918, respectively, as determined by ROC analysis. The AUC of the combined diagnosis was greater than that of TSG-14 or CORS26 alone (Z=2.811, 2.827; P=0.018, 0.015).

Conclusion: The levels of serum TSG-14 and CORS26 are closely related to the occurrence of DR in patients with T2DM. Combined detection has certain clinical value for diagnosing DR in patients with T2DM.

Keywords: TNF-stimulated gene 14 (TSG-14), cartilage oligomeric matrix protein like 26 (CORS26), type 2 diabetes, diabetic retinopathy

rumski nivoi TSG-14 i CORS26 bili su viši u PDR grupi u odnosu na NPDR grupu (oba P<0,05). TSG-14 i CORS26 u serumu su pokazali negativnu povezanost sa HDL-C i pozitivnu korelaciju sa TC, TG, LDL-C i HOMA-IR (sve P<0,001). Logistička regresiona analiza je pokazala da su sledeći faktori rizika povezani sa pojavom DR kod pacijenata sa dijabetesom tipa 2: trajanje dijabetesa, TC, TG, LDL-C, HOMA-IR, TSG-14 i CORS26 (sve P<0,05). Površine ispod ROC krive (AUC) za serumske TSG-14 i CORS26 u dijagnostici DR kod pacijenata sa T2DM iznosile su 0,833, 0,832 i 0,918. AUC kombinovane dijagnostike bio je veći nego za TSG-14 ili CORS26 pojedinačno (Z=2,811; 2,827; P=0,018; 0,015).

Zaključak: Nivoi TSG-14 i CORS26 u serumu su usko povezani sa pojavom dijabetičke retinopatije kod pacijenata sa dijabetesom tipa 2. Njihova kombinovana detekcija ima određenu kliničku vrednost u dijagnostici DR kod ovih pacijenata.

Ključne reči: gen 14 stimulisan TNF-om (TSG-14), protein sličan oligomernom matriks proteinu hrskavice 26 (CORS26), dijabetes tipa 2, dijabetička retinopatija

Introduction

Type 2 diabetes mellitus (T2DM), which accounts for more than 90% of all instances of diabetes, is typified by abnormal insulin secretion, problems with lipid and protein metabolism, and persistent hyperglycaemia. Its pathogenesis involves disorders of insulin production and insulin resistance, leading to an inability to control blood sugar levels. Pancreatic β-cell damage subsequently affects adiponectin and insulin production, including increased levels of proinflammatory factors, which are also major causes of T2DM (1). With economic development, the number of T2DM patients in China continues to increase. Microscopic and macroscopic vascular diseases, including encephalopathy and diabetic retinopathy (DR), which can affect a patient's cognitive function and vision, are common complications of T2DM (2). DR is a complication of T2DM and is usually caused by metabolic disorders, long-term hypoxia and ischemia of the retina, thickening of the basal membrane, and damage to vascular wall cells, resulting in capillary dilation and further damage to the retinal barrier, causing symptoms such as retinal haemorrhage, oedema, and decreased vision in patients. If not treated promptly, it can lead to massive retinal cell apoptosis, retinal fibrosis, and even permanent visual impairment (3, 4). Therefore, identifying markers of DR and intervening early can improve patients' quality of life. Leukocyte-derived chemotaxin 2 (TSG-14) is an immune chemotactic protein that regulates immune function and plays a role in cell differentiation, growth, and the development of various metabolic diseases. Abnormal expression of TSG-14 may lead to vascular endothelial cell dysfunction and promote or inhibit angiogenesis, thereby affecting the progression of DR (5–7).

The adipokine family includes complement C1q/tumour necrosis factor-related protein 5 (CORS26), which regulates the body's energy metabolism. It participates in inflammatory responses and is closely related to processes such as insulin resistance and glucose metabolism. It may be involved in the progression of diabetic retinopathy (DR) by activating oxidative stress-related signalling pathways, increasing oxidative stress-induced apoptosis and inflammatory responses (8–11).

There are currently limited studies on the connections between the prevalence of DR in T2DM patients and serum levels of TSG-14 or CORS26. This investigation aimed to determine the relationship between serum TSG-14 and CORS26 levels and the incidence of DR in T2DM patients.

Materials and Methods

General information

276 T2DM patients who were admitted to our hospital between April 2023 and April 2025 were included in a single-centre cross-sectional study. Sample size calculation: PASS 15 software (two-tailed test, setting $\alpha=0.05$, power = 80%, d=0.50) was used to calculate. Considering a 10% dropout rate, 276 patients were included. During hospitalization, fluorescein fundus angiography was performed on all patients (after routine disinfection of the elbow vein, 3–5 mL of fluorescein sodium was slowly infused intravenously, and changes in the eyes were observed within 10 seconds). A no-DR group (120 patients) and a DR group (156 patients) were created based on diagnostic and examination results.

Inclusion criteria: (1) met the criteria for T2DM; (2) were first diagnosed with T2DM; (3) provided complete clinical data; and (4) signed the informed consent form.

Exclusion criteria: (1) patients with T1DM; (2) patients with other types of DR; (3) patients with ocular diseases such as glaucoma or cataracts; (4) patients with immune dysfunction; (5) patients with mental abnormalities or communication disorders; (6) patients with functional disorders of important organs.

This study was approved by the ethics committee of our hospital (No. A0275).

Detection of serum TSG-14 and CORS26 levels

All research subjects had blood samples collected in 5 millilitres from veins after a 10-hour fast in the early morning. The collected blood samples were left to stand at room temperature for 30 minutes, then centrifuged at 3500 rpm for 15 minutes. The upper serum was carefully collected and aliquoted into sterile EP tubes, which were stored at -80 °C for future use. Serum levels of TSG-14 and CORS26 were measured using enzyme-linked immunosorbent assay (ELISA). The TSG-14 detection kit was purchased from the US company R&D (item number: DY4715), and the CORS26 detection kit was purchased from the US company Cusabio (item number: CSB-EL015868HU). The operation was carried out strictly in accordance with the instructions of the kits; standard curves and quality control samples were set up, and each sample was tested in two wells. The average value was taken as the final result. To ensure test results are reliable, all sample tests were performed using the same batch of kits. The intra-batch coefficient of variation was 8.2–11.5%, and the inter-batch coefficient of variation was 9.7–13.8%, both of which were less than 15%, indicating that the detection method in this experiment has good stability and repeatability.

Detection of glycolipid metabolism and related indicators of insulin resistance

Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were all detected using an automated biochemical analyser. The blood glucose meter was used to measure fasting plasma glucose (FPG); an automatic electrochemiluminescence analyser was used to detect fasting insulin (FINS); and the homeostatic model assessment of insulin resistance index (HOMA-IR) = FPG (mmol/L) × FINS (μU/mL)/22.5 was computed.

Statistical analysis

Software called SPSS 25.0 was used to process the data. Using the Shapiro-Wilk test, the measurement data were found to be normally distributed. An independent sample t-test was then used to compare them after they were expressed as $x \pm s$. The count data were assessed and presented as n (%) using the χ^2 test. The associations between TSG-14, CORS26, and glycolipid metabolism markers were assessed using Pearson's correlation, and the factors influencing DR in T2DM patients were assessed using logistic regression. The DeLong test was used to compare the area under the curve (AUC), and ROC curves were used to assess the diagnostic usefulness of serum TSG-14 and CORS26 for DR in T2DM patients.

Results

Comparison of clinical data between the DR group and the non-DR group

There was no statistically significant difference between the two groups' overall statistics (all P values > 0.05). In contrast to the non-DR group, the DR group had greater levels of TC, TG, LDL-C, and HOMA-IR and had experienced diabetes for a longer period of time. However, their HDL-C level was lower (all P<0.05). *Table I* shows that the other data did not differ significantly (all P>0.05).

Comparison of the serum TSG-14 and CORS26 levels between the DR group and the non-DR group

The serum TSG-14 and CORS26 levels in the DR group were greater than those in the non-DR group (both P<0.001), as shown in *Table II*.

As the severity of DR progresses, the levels of serum TSG-14 and CORS26 show a significant upward trend, suggesting that these two markers' levels may be related to the progression of DR. Correlation analysis indicates that TSG-14 and CORS26 are closely associated with lipid and glucose metabolism indicators. They are negatively correlated with high-density lipoprotein cholesterol, while positively correlated with total cholesterol, triglycerides, low-density lipoprotein cholesterol, and insulin resistance index.

Comparison of the serum TSG-14 and CORS26 levels between the PDR group and the NPDR group

The serum TSG-14 and CORS26 levels in the PDR group were greater than those in the NPDR group (both P<0.001), as shown in *Table III*.

Table I Comparison of clinical data between the DR group and the non-DR group.

Indicator		DR group (n=156)	No DR group (n=120)	t/X^2	P
Age ($\bar{x}\pm s$, years)		53.49±10.65	52.49±10.31	0.557	0.584
Gender (Cases,%)	Male	82 (52.6)	58 (48.3)	0.246	0.625
	Female	74 (47.4)	62 (51.7)		
BMI ($\bar{x}\pm s$, kg/m^2)		23.08±3.12	23.17±3.26	0.166	0.873
Smoking history (Cases, %)		44 (28.2)	28 (23.3)	0.410	0.511
Drinking history (Cases, %)		54 (34.6)	34 (28.3)	0.619	0.435
Hypertension (Cases, %)		56 (35.9)	36 (30.00)	0.534	0.469
Systolic blood pressure ($\bar{x}\pm s$, mmHg)		131.79±21.48	130.65±22.54	0.306	0.765
Diastolic blood pressure ($\bar{x}\pm s$, mmHg)		83.14±7.46	82.88±8.44	0.195	0.841
Course of diabetes ($\bar{x}\pm s$, a)		8.24±1.80	6.46±1.64	5.886	<0.001
TC ($\bar{x}\pm s$, mmol/L)		5.49±1.37	4.51±1.15	4.105	<0.001
TG ($\bar{x}\pm s$, mmol/L)		2.23±0.63	1.71±0.57	4.259	<0.001
HDL-C ($\bar{x}\pm s$, mmol/L)		1.13±0.35	1.32±0.31	4.866	<0.001
LDL-C ($\bar{x}\pm s$, mmol/L)		3.91±0.87	3.30±0.78	4.421	<0.001
AST ($\bar{x}\pm s$, U/L)		26.07±3.63	25.88±3.65	0.300	0.760
ALT ($\bar{x}\pm s$, /L)		27.95±4.29	27.72±4.26	0.171	0.852
FPG ($\bar{x}\pm s$, mmol/L)		8.44±2.07	8.10±1.91	0.697	0.482
HOMA-IR		3.88±1.26	3.30±1.02	2.389	0.011
Blood creatinine ($\bar{x}\pm s$, mmol/L)		81.61±6.37	81.41±6.45	0.186	0.858
Urea nitrogen ($\bar{x}\pm s$, mmol/L)		4.69±0.55	4.65±0.59	0.436	0.669

Table II Comparison of serum levels of TSG-14 and CORS26 between DR group and non-DR group ($\bar{x}\pm s$, ng/mL).

Group	n	TSG-14 (ng/mL)	CORS26 (ng/mL)
DR group	156	38.14±9.06	54.81±13.37
No DR group	120	24.49±6.78	33.64±9.27
T		9.793	10.555
P		<0.001	<0.001

As diabetic retinopathy progresses to the proliferative stage, the expression of TSG-14 and CORS26 shows a significant upward trend, suggesting that these two biomarkers may reflect the severity of retinopathy and its progression. Correlation analysis further confirmed that TSG-14 and CORS26 are closely associated with indicators of glycolipid metabolism disorder. Their elevated levels may be involved in the pathophysiological process of diabetic retinopathy, especially in the key stage when the disease progresses to the proliferative stage.

Correlations between serum TSG-14 and CORS26 and indicators of glycolipid metabolism

The Pearson correlation analysis revealed that serum TSG-14 and CORS26 levels were positively correlated with TC, TG, LDL-C, and HOMA-IR levels and negatively correlated with HDL-C levels (all P<0.001), as shown in *Table IV*.

The levels of serum TSG-14 and CORS26 were negatively correlated with high-density lipoprotein cholesterol (HDL-C) and positively correlated with total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and the insulin resistance index (HOMA-IR). All these correlations were statistically significant, indicating that TSG-14 and CORS26 may be involved in the pathological physiological process of abnormal glucose and lipid metabolism in patients with type 2 diabetes. As inflammatory factors, elevated levels of TSG-14 and CORS26 may mutually promote insulin resistance and lipid metabolism disorders, thereby jointly contributing to the occurrence and progression of diabetic retinopathy.

Analysis of factors influencing the occurrence of DR in T2DM patients

The occurrence of DR (yes = 1, no = 0) was used as the dependent variable, and the abovementioned different indicators (all inputs as original values) were used as independent variables. After multicollinearity was detected, the expansion factor for HDL-C was ≥10, and an interaction effect was observed, so it was excluded from subsequent analysis. The duration of diabetes, TC, TG, LDL-C, HOMA-IR, TSG-14, and CORS26 were risk factors for DR in T2DM patients, as determined by logistic regression (P<0.05; *Table V*).

Table III Comparison of serum levels of TSG-14 and CORS26 between PDR group and NPDR group ($\bar{x}\pm s$, ng/mL).

Group	n	TSG-14 (ng/mL)	CORS26 (ng/mL)
PDR group	58	49.01±10.57	72.68±16.02
NPDR group	98	31.65±8.16	44.30±11.74
T		8.199	8.941
P		<0.001	<0.001

Table IV Correlation analysis between serum TSG-14 and CORS26 and glucose and lipid metabolism indicators.

Indicator	TSG-14		CORS26	
	r	P	r	P
TC	0.505	<0.001	0.517	<0.001
TG	0.488	<0.001	0.496	<0.001
HDL-C	-0.491	<0.001	-0.515	<0.001
LDL-C	0.515	<0.001	0.510	<0.001
HOMA-IR	0.509	<0.001	0.516	<0.001

Table V Analysis of Factors Influencing DR in T2DM Patients.

Indicator	B	SE	Wald X^2	P	OR	95 %CI
Course of diabetes	0.766	0.323	5.680	0.010	2.148	1.149–4.019
TC	0.979	0.249	15.746	<0.001	2.657	1.632–4.291
TG	0.643	0.267	5.885	0.018	1.890	1.134–3.186
LDL-C	1.109	0.348	10.262	0.001	3.024	1.539–5.943
HOMA-IR	0.744	0.268	7.812	0.008	2.091	1.241–3.520
TSG-14	1.148	0.318	13.202	<0.001	3.145	1.698–5.829
CORS26	0.831	0.317	7.127	0.001	2.315	1.242–4.271

Table VI Diagnostic Value of Serum TSG-14 and CORS26 for DR in T2DM Patients.

Item	AUC	95% CI	Sensitivity (%)	Specificity (%)	Cut off value (ng/mL)	P
TSG-14	0.833	0.767–0.890	77.52	84.29	32.217	<0.001
CORS26	0.832	0.777–0.906	78.65	79.59	50.217	<0.001
Joint Detection	0.918	0.861–0.952	86.22	77.68	-	<0.001

The diagnostic value of serum TSG-14 and CORS26 for the occurrence of DR in T2DM patients

A ROC curve was created using TSG-14 and CORS26 levels as the test variables, with the DR group as the positive group and the group without DR as the negative group. According to the findings, the AUCs for serum TSG-14, CORS26, and their combination in identifying DR in T2DM patients were 0.833, 0.832, and 0.918, respectively. *Table VI* demonstrates that the combined diagnosis's AUC was greater than those of TSG-14 and CORS26 alone (Z=2.811 and 2.827, P=0.018 and 0.015).

Discussion

T2DM is a complex process that may be linked to genetics and fat. Weight loss, along with extreme thirst and hunger, is among the symptoms patients may display. A prolonged period of elevated blood sugar can cause several problems for the body, including DR and skin lesions (12, 13). DR is a microvascular complication of T2DM characterized by early vascular dysfunction and retinal neuronal disorders. It often progresses to the formation of new blood vessels, leading to vision impairment due to cumulative pathological changes in the retina caused by long-term hyperglycaemia in T2DM patients (14). The early symptoms of DR are not obvious and can be detected only through fundus screening. As the disease progresses, retinal detachment, vitreous haemorrhage, glaucoma, and even permanent vision damage may occur (15). Therefore, identifying markers that can efficiently assess DR in T2DM patients is particularly crucial in clinical practice.

TSG-14 is secreted mainly by liver cells. It can cause peripheral insulin resistance, disrupt insulin signalling, reduce insulin sensitivity, and lead to elevated blood sugar levels in patients (16). The serum TSG-14 level in patients with immune-related liver diseases is elevated. It is speculated that immune-related liver diseases are inflammatory injuries of the liver. TSG-14 exerts a regulatory effect on inflammation, leading to elevated expression (17). Patients with gestational diabetes have higher serum TSG-14 levels, which are strongly associated with insulin resistance. Finding evidence of its expression can be utilized to evaluate a patient's health and serve as a foundation for clinical diagnosis and care. The study's findings showed that patients with DR had higher serum TSG-14 levels, while those with PDR had even higher levels. A possible reason is that as its level increases, it regulates inflammatory signalling pathways and activates transcription of downstream inflammatory genes, thereby elevating systemic inflammation in DR patients and damaging retinal nerve cells (18). This may be because the bodies of DR patients have been in an inflammatory state for a long time. The inflammatory response not only aggravates insulin resistance, leading to abnormal lipid levels in patients, but also damages vascular endothelial cells, resulting in vascular lesions and worsening the patient's condition (19).

CORS26 is expressed in various tissues, with the highest expression in adipose tissue. It plays a regulatory role in inflammatory and metabolic-related functions. An increase in CORS26 expression can exacerbate the inflammatory response and disrupt glycolipid metabolism, leading to microvascular complications in patients with T2DM (20). CORS26 is also a regulatory factor that negatively affects glucose metabolism. It is expressed at relatively high levels in T2DM patients and affects their blood glucose metabolism, exacerbating their condition and triggering various complications. It also acts as a proinflammatory factor, promoting the secretion of various inflammatory mediators, leading to chronic retinal inflammation and damage to the retinal vascular endothelium, which can lead to DR (21). The serum CORS26 level is elevated in elderly T2DM patients and is associated with disorders of glycolipid metabolism. This may be because when its level increases, it can promote oxidative stress-related signalling pathways and increase oxidative stress-induced apoptosis and inflammatory responses, thereby promoting the progression of DR (22–24). The reason for this is that an increase in the CORS26 level leads to disorders of glycolipid metabolism, stimulating signalling pathways such as transforming growth factor, resulting in abnormal vascular endothelial function and increasing the risk of DR.

This study revealed that the AUC of combined TSG-14 and CORS26 detection for diagnosing DR in T2DM patients is 0.918, which is close to that reported in the above studies, indicating that the combined detection of these two factors has clinical value for diagnosing DR in T2DM patients. Multivariate regression analysis revealed that diabetes duration and TC, TG, LDL-C, HOMA-IR, TSG-14, and CORS26 levels are risk factors for DR in patients, indicating their association with DR. Therefore, in clinical practice, targeted preventive measures can be taken for patients with higher baseline levels of TSG-14 and CORS26 to reduce the risk of DR.

Conclusion

Serum TSG-14 and CORS26 levels are strongly correlated with the incidence of DR in T2DM patients. When diagnosing DR in T2DM patients, combined detection has some clinical use. With the advancement of high-throughput protein technologies, the new indicators identified in this study and the identification of new therapeutic targets have great potential.

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Conflict of interest statement

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

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