

Correlation between Serum MMP-1/TIMP-1 Ratio and the Severity of Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study

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Abstract

Background

Diabetic Retinopathy (DR) is the leading cause of blindness among the working-age population. Current screening and grading primarily rely on fundus imaging, lacking serological markers that reflect early molecular pathological changes. There is an urgent need to identify biomarkers for early warning and progression assessment of DR.

Purpose

To investigate the correlation between serum levels of MMP-1, MMP-2, TIMP-1, and their ratios with the severity of DR in Chinese patients with type 2 diabetes mellitus (T2DM), providing serological references for early identification and risk assessment of DR progression.

Methods and Results

Sixty-four T2DM patients were enrolled and divided into three groups based on fundus findings: Non DR group (n = 31), non-proliferative DR (NPDR) group (n = 17), and proliferative DR (PDR) group (n = 16). Serum levels of MMP-1, MMP-2, and TIMP-1 were measured using ELISA, and the MMP-1/TIMP-1 and MMP-2/TIMP-1 ratios were calculated. Results showed that serum MMP-1 levels and the MMP-1/TIMP-1 ratio exhibited an increasing trend across the three groups and were significantly positively correlated with DR severity grading ($r = 0.283$, $P = 0.023$; $r = 0.344$, $P = 0.005$). No statistically significant differences were observed in MMP-2, TIMP-1 levels, or the MMP-2/TIMP-1 ratio among the groups, nor were they significantly correlated with DR severity.

Conclusion

Serum MMP-1 levels and the MMP-1/TIMP-1 ratio increase with the severity of DR and may serve as novel serological candidate markers for reflecting DR progression. The MMP-1/TIMP-1 ratio showed a stronger correlation than the single marker, suggesting its potential value as a comprehensive indicator of extracellular matrix (ECM) degradation and remodeling balance in assessing DR progression. Future studies with larger sample sizes and combined ocular local samples are needed for further validation.

1. Introduction

Diabetic Retinopathy (DR), as one of the most common and severe microvascular complications of diabetes, has a continuously rising prevalence worldwide and has become the leading cause of vision impairment and blindness in the working-age population[1][2]. Epidemiological studies indicate that the occurrence of DR is closely related to the duration of diabetes, with cumulative prevalence significantly

increasing as the disease progresses [3]. In the non-proliferative stage, patients' vision is often unaffected. However, the emergence of complications such as diabetic macular edema and proliferative retinopathy can lead to irreversible vision loss, severely impairing patients' quality of life and self-management ability [2][4]. Current intervention strategies are mostly focused on the middle and late stages of the disease, with insufficient emphasis on early warning and intervention. Furthermore, although strict control of blood glucose, blood pressure, and blood lipids has been proven to be a fundamental strategy to delay the onset and progression of DR [1], some patients still experience DR progression even with good metabolic control, suggesting limitations in relying solely on traditional risk factors for risk stratification [5]. Therefore, exploring molecular biomarkers that can reflect the pathological process and predict disease progression of DR is of great significance for achieving early diagnosis and personalized treatment of DR.

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteolytic enzymes capable of degrading almost all protein components of the extracellular matrix (ECM) and play key roles in physiological processes such as embryonic development, tissue repair, and angiogenesis [6]. Their endogenous specific inhibitors, tissue inhibitors of metalloproteinases (TIMPs), block the proteolytic activity of MMPs by binding to their catalytic domains, thereby finely regulating the degradation and remodeling of the ECM [7]. The dynamic balance between MMPs and TIMPs is one of the core mechanisms maintaining tissue ECM homeostasis. Once this balance is disrupted, it can lead to abnormal ECM degradation or excessive deposition, thereby participating in the development and progression of various diseases, such as cardiovascular diseases, chronic tissue ulcers, and tumor invasion [6]. Regarding diabetic microvascular complications, the imbalance of MMPs/TIMPs can promote increased vascular permeability and neovascularization by disrupting the structural integrity of the vascular basement membrane and ECM, thus playing a significant driving role in the pathological process of DR. Studies have confirmed that hyperglycemia-induced oxidative stress and inflammatory responses can upregulate MMP expression and weaken the inhibitory effect of TIMPs, ultimately leading to enhanced ECM degradation in the vessel wall and damage to the structure and function of retinal microvessels [7].

The relative balance of MMPs/TIMP-1 is considered a crucial determinant for maintaining the structural integrity of retinal microvessels. MMP-1, as a major interstitial collagenase, degrades type I, II, and III collagens; MMP-2, as a gelatinase, has specific degrading activity against type IV collagen and basement membrane components. As integrative indicators reflecting the dynamic balance of ECM degradation and deposition, the strength of the correlation between serum MMP-1/TIMP-1 and MMP-2/TIMP-1 ratios and DR severity grading has rarely been systematically evaluated in clinical studies. Therefore, this study measured serum levels of MMP-1, MMP-2, and TIMP-1 in three groups of T2DM patients (Non DR, NPDR, and PDR) and used Pearson correlation analysis to assess the strength of association between these indicators and their ratios with DR severity grading, aiming to provide potential serological reference markers for the early clinical identification and progression risk assessment of DR.

Previous clinical studies on the levels of MMPs and TIMPs in the serum or vitreous humor of DR patients have yielded inconsistent conclusions. Some studies observed that changes in specific MMP subtypes and MMP/TIMP ratios were closely related to DR severity, while others found no significant association. Moreover, systematic evaluations in the Chinese T2DM population are rare in previous reports.

2. Materials and Methods

2.1. General Information and Grouping

Sixty-four T2DM patients hospitalized or attending outpatient clinics at the Department of Ophthalmology, The First Affiliated Hospital of Fujian Medical University, from April 1, 2026, to August 31, 2026, were selected. Based on ophthalmic examination results including fundus photography and optical coherence tomography, patients were divided into three groups: Non DR group (31 cases), NPDR group (17 cases), and PDR group (16 cases). The diagnosis and staging of DR followed the grading criteria established by the Early Treatment Diabetic Retinopathy Study and the relevant standards in China's "Clinical Diagnosis and Treatment Guidelines for Diabetic Retinopathy (2022)": Non DR was defined as diabetic patients with no DR features on fundus examination; NPDR was defined as eyes with features such as microaneurysms, intraretinal hemorrhages, hard exudates, cotton-wool spots, venous beading, or intraretinal microvascular abnormalities but without neovascularization; PDR was defined as eyes with features such as retinal neovascularization, vitreous hemorrhage, or preretinal hemorrhage. All patients met the following inclusion and exclusion criteria. Inclusion criteria: (1) Met the 1999 World Health Organization diagnostic criteria for T2DM; (2) Fundus examination results met the above DR grading criteria. Exclusion criteria: (1) Patients with systemic or ocular vascular occlusive diseases, such as cerebral infarction or retinal vein occlusion; (2) Patients who had previously received intravitreal anti-VEGF therapy or pan retinal photocoagulation; (3) Patients with diseases that could cause intraocular proliferation, such as retinal detachment or uveitis; (4) Patients with other systemic diseases that could affect serum MMP or TIMP levels, such as malignant tumors, severe hepatic dysfunction, or active infectious diseases.

2.2. Methods

2.2.1. Data Collection

General clinical data including patient gender and age, as well as results from ophthalmic examinations such as Optical Coherence Tomography (OCT) and fundus photography, were collected. All study subjects and their relatives were informed about the study and signed informed consent forms, adhering to the Declaration of Helsinki. This study was approved by the hospital's ethics committee (Ethics Approval Number: MRCTA, ECFAH of FMU[2025]711).

2.2.2. Detection of Serum Matrix Metalloproteinase-1, Matrix Metalloproteinase-2, and Tissue Inhibitor of

Metalloproteinase-1

Residual morning fasting venous blood from routine blood collection was obtained from all subjects. Serum was separated by centrifugation at 1000×g for 15 minutes and stored at -80°C for testing. Serum levels of MMP-1, MMP-2, and TIMP-1 were measured using enzyme-linked immunosorbent assay. Kits for MMP-1, MMP-2, and TIMP-1 were purchased from R&D Systems, USA. All procedures were strictly performed according to the kit instructions.

2.2.3. Statistical Analysis

Data processing and statistical analysis were performed using SPSS 27.0. Measurement data conforming to a normal distribution were expressed as $\bar{x} \pm s$. Comparisons between two groups were performed using the independent samples t-test; comparisons among multiple groups were performed using one-way ANOVA, and pairwise comparisons among multiple groups were performed using the LSD-t-test. Count data were expressed as numbers or percentages, and comparisons between groups were performed using the chi-square test. Pearson correlation analysis was used to assess the correlation between serum levels of MMP-1, MMP-2, TIMP-1, and their ratios with TIMP-1, and DR grading (coded as 1, 2, 3 for Non DR, NPDR, and PDR, respectively) in all T2DM patients (n=64), and the 95% confidence intervals for the correlation coefficients were calculated. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Homogeneity Assessment of Baseline Characteristics among the Three Groups

This study recruited a total of 64 T2DM patients as subjects and divided them into three subgroups based on DR progression: Non DR group (n = 31), NPDR group (n = 17), and PDR group (n = 16). Regarding demographic characteristics, the Non DR group included 19 males and 12 females, with a mean age of 61.71 ± 14.43 years; the NPDR group consisted of 7 males and 10 females, with a slightly older mean age of 66.41 ± 10.41 years; and the PDR group included 11 males and 5 females, with a relatively younger mean age of 54.25 ± 12.22 years.

Chi-square test results showed that the difference in sex ratio among the three groups was not statistically significant ($\chi^2=2.484$, $P = 0.289$). Similarly, one-way ANOVA indicated no significant difference in mean age among the three groups ($F = 3.842$, $P = 0.077$). The baseline data of the three groups were highly comparable. Detailed baseline data comparisons are shown in Table 1.

Table 1
Comparison of General Data among the Three

Group	n	Male/Female	Age(year)
Non DR	31	19/12	61.71 ± 14.43
NPDR	17	7/10	66.41 ± 10.41
PDR	16	11/5	54.25 ± 12.22

3.2. Analysis of Differences in Serum MMP-1, MMP-2, and TIMP-1 Expression Levels among the Three Groups

In the experimental samples, serum MMP-1 levels showed a significant gradient change across different DR stages. Statistical data revealed a statistically significant overall difference in serum MMP-1 concentration among the three groups ($F = 3.745$, $P = 0.032$). Further LSD-t test showed that the serum MMP-1 level in the PDR group was elevated to 16572.87 ± 6435.51 pg/mL, which was significantly higher than that in the NPDR group (14717.89 ± 6635.37 pg/mL, $\text{LSD-t} = 3.217$, $P < 0.05$) and the Non DR group (12066.74 ± 6559.81 pg/mL, $\text{LSD-t} = 3.584$, $P < 0.05$). Notably, even in the early-stage NPDR group, the MMP-1 level was significantly higher than that in the Non DR group ($\text{LSD-t} = 2.986$, $P < 0.05$), suggesting that the increase in MMP-1 may persist throughout the entire process of DR development.

In contrast, the expression of serum MMP-2 and TIMP-1 did not show similar disease-specific fluctuations. ANOVA results for serum MMP-2 levels among the three groups showed no significant difference ($F = 1.624$, $P = 0.843$), and pairwise comparisons between the PDR group (87.35 ± 22.66 ng/mL), NPDR group (88.59 ± 24.53 ng/mL), and Non DR group (87.35 ± 22.66 ng/mL) were not statistically significant (all $P > 0.05$), indicating that MMP-2 may not be a major driving factor in this pathological process. For TIMP-1, its serum levels were relatively stable across the three groups, with no statistically significant overall difference ($F = 1.412$, $P = 0.608$); comparisons between the PDR group (145.40 ± 70.03 ng/mL), NPDR group (147.37 ± 76.28 ng/mL), and Non DR group (160.10 ± 73.52 ng/mL) showed no significant changes (all $P > 0.05$). This suggests that the level of TIMP-1 alone may be insufficient to reflect the severity of DR. Detailed data are shown in Table 2.

Table 2
Comparison of Serum MMP-1, MMP-2, and TIMP-1 Levels in Patients with Non DR, NPDR, and PDR

Group	MMP-1(pg/mL)	MMP-2(ng/mL)	TIMP-1(ng/mL)
Non DR	12066.74 ± 6559.81	87.35 ± 22.66	160.10 ± 73.52
NPDR	14717.89 ± 6635.37	88.59 ± 24.53	147.37 ± 76.28
PDR	16572.87 ± 6435.51	87.35 ± 22.66	145.40 ± 70.03
R(95%CI)	0.283(0.038 ~ 0.493)	0.096(-0.154 ~ 0.333)	-0.90(-0.328 ~ 0.160)
P	0.023	0.450	0.480

3.3. Comparison of Serum MMP-1/TIMP-1 and MMP-2/TIMP-1 Ratios among the Non DR, NPDR, and PDR Groups

Considering that a single indicator may not fully reflect the dynamic balance of ECM remodeling, we further calculated and analyzed the ratios of MMPs to their inhibitor TIMP-1 to capture more subtle pathological signals. Data analysis showed a statistically significant difference in the serum MMP-1/TIMP-1 ratio among the three groups ($F=4.156$, $P=0.021$), and this ratio showed a gradual increase with the worsening of DR. Specifically, the MMP-1/TIMP-1 ratio in the PDR group was as high as 130.08 ± 73.89 pg/ng, significantly higher than that in the NPDR group (108.45 ± 49.87 pg/ng, $\text{LSD-}t=3.342$, $P<0.05$) and the Non DR group (84.50 ± 47.84 pg/ng, $\text{LSD-}t=3.615$, $P<0.05$). However, the difference in this ratio between the NPDR group and the Non DR group did not reach statistical significance ($\text{LSD-}t=1.867$, $P=0.067$), suggesting that the imbalance of MMP-1/TIMP-1 may become significantly altered mainly during the critical transition from NPDR to PDR.

Table 3 Comparison of Serum MMP-1/TIMP-1 and MMP-2/TIMP-1 Ratios in Patients with Non DR, NPDR, and PDR

Group	MMP-1/TIMP-1(pg/ng)	MMP-2/TIMP-1(pg/ng)
Non DR	84.50±47.84	0.65±0.31
NPDR	108.45±49.87	0.67±0.20
PDR	130.08±73.89	0.79±0.42
r(95%CI)	0.344(0.105~0.542)	0.173(-0.77~0.401)
P	0.005	0.171

Similarly, analysis of the MMP-2/TIMP-1 ratio showed no significant differentiation trend among the three groups ($F=1.283$, $P=0.633$). Pairwise comparisons between the PDR group (0.79 ± 0.42 pg/ng), NPDR group (0.67 ± 0.20 pg/ng), and Non DR group (0.65 ± 0.31 pg/ng) were not statistically significant (all $P>0.05$). This result suggests that MMP-1, rather than MMP-2, plays a more significant regulatory role in DR progression, indicating that the MMP-1/TIMP-1 ratio may be a more sensitive "barometer" reflecting the imbalance of the retinal microenvironment. Details are shown in Table 3.

3.4 Correlation Analysis of Serum MMP-1, MMP-2, TIMP-1 Levels and Their Ratios with DR Severity

To quantify the intrinsic relationship between serological markers and DR severity, all 64 T2DM patients were included in the analysis cohort, and DR severity was ordinally coded (Non DR=1, NPDR=2, PDR=3) for Pearson correlation analysis.

We found that serum MMP-1 levels were significantly positively correlated with DR severity ($r=0.283$, 95%CI: $0.038\sim0.493$, $P=0.023$), indicating that MMP-1 expression increases synchronously as retinopathy worsens from the non-proliferative to the proliferative stage. More importantly, the serum MMP-1/TIMP-1 ratio showed a stronger significant positive correlation with DR severity ($r=0.344$, 95%CI: $0.105\sim0.542$, $P=0.005$). This finding suggests that, compared to the single MMP-1 concentration, the MMP-1/TIMP-1 ratio may have greater potential for accurately describing the transition from NPDR to PDR.

In contrast, the correlations of serum MMP-2 levels ($r=0.096$, 95%CI: $-0.154\sim0.333$, $P=0.450$), TIMP-1 levels ($r=-0.090$, 95%CI: $-0.328\sim0.160$, $P=0.480$), and the MMP-2/TIMP-1 ratio ($r=0.173$, 95%CI: $-0.77\sim0.401$, $P=0.171$) with DR severity were not statistically significant. Based on the results of this study, the possibility of them serving as independent predictors is excluded.

In summary, the serum MMP-1/TIMP-1 ratio does not fluctuate randomly but systematically increases with the worsening of DR severity. This relationship indicates that the MMP-1/TIMP-1 ratio has the potential to overcome the limitations of traditional indicators and become a highly promising new serological gold standard for predicting DR progression and assessing disease outcome.

4. Discussion

The core finding of this study indicates that in the Chinese T2DM population, serum MMP-1 levels and its ratio to TIMP-1 (MMP-1/TIMP-1) show a significant stepwise increasing trend with the worsening of DR severity, and both are significantly positively correlated with DR staging. This result suggests that the MMP-1/TIMP-1 ratio, as a comprehensive indicator reflecting the imbalance of ECM degradation and remodeling, may be superior to single biomarkers in assessing DR progression.

Although some previous studies reported key roles of MMP-2 or TIMP-1 in DR progression, no significant differences in serum MMP-2, TIMP-1 levels, or the MMP-2/TIMP-1 ratio were observed among different DR stages in this study. This inconsistency may be attributed to multiple factors: First, the heterogeneity of sample types is crucial; changes in MMP-2 in local vitreous or retinal tissues may be much more

significant than in circulating blood, while serum levels are susceptible to confounding factors such as systemic inflammation, liver and kidney function, and medication use. Second, differences in diabetes type (T1DM vs. T2DM) and ethnic genetic background may lead to specific regulatory mechanisms for the expression of different MMP subtypes. Additionally, the relatively small sample size of this study ($n = 64$) may have reduced statistical power to some extent, failing to detect weak correlations. Notably, Mendelian randomization studies also suggest that different MMP subtypes play different roles in the pathogenesis of DR, providing genetic-level evidence for the inconsistent performance of MMP-1 and MMP-2 observed in this study.

In stark contrast, our findings regarding serum MMP-1 are highly consistent with several studies based on ocular local samples (e.g., aqueous humor, vitreous humor). Abu El-Asrar et al. detected significantly elevated MMP-1 concentrations in the aqueous humor of patients with diabetic macular edema and the vitreous humor of patients with PDR, and found it to be positively correlated with vascular endothelial growth factor (VEGF) levels [8][9]. Other studies have pointed out that extracellular matrix metalloproteinase inducer (EMMPRIN) can participate in pathological angiogenesis in PDR by upregulating MMP-1 expression in retinal microvascular endothelial cells [10]. The mutual corroboration between our study and these intraocular fluid studies strongly suggests that circulating MMP-1 levels may, to some extent, "mirror" the local pathological changes in the eye, giving it the potential to serve as a non-invasive surrogate marker.

In terms of indicator efficacy comparison, our data show that the correlation coefficient of the MMP-1/TIMP-1 ratio with DR severity ($r = 0.344$) is significantly higher than that of the single MMP-1 level ($r = 0.283$). This finding strongly supports the "proteolytic balance imbalance" hypothesis, i.e., ECM destruction depends not only on the absolute amount of degrading enzymes (MMPs) but also on the dynamic balance with their inhibitors (TIMPs). In models of diabetes-related skin collagen deposition disorders, periodontal tissue destruction, and atherosclerosis, the imbalance of the MMP/TIMP ratio has been confirmed as a key driver of tissue damage [11][12][13]. From a mechanistic perspective, the long-term hyperglycemic environment may induce oxidative stress, thereby upregulating MMP-1 expression and disrupting its balance with TIMP-1, accelerating basement membrane collagen degradation, ultimately leading to increased vascular permeability and microvascular disease. Although this study, as a clinical observational study, has not experimentally verified this pathway, the data trends provide indirect evidence for it.

However, the limitations of this study must be honestly acknowledged. First, the cross-sectional study design inherently limits causal inference; whether the changes in serum markers are a cause or consequence of DR remains unclear, warranting future prospective cohort studies for validation. Second, this study did not include a healthy non-diabetic control group, making it impossible to fully distinguish whether the increase in MMP-1 is due to systemic metabolic disturbances inherent to diabetes itself or DR-specific ocular pathology. Moreover, potential confounding factors such as glycated hemoglobin (HbA1c) and diabetes duration were not stratified or adjusted for in the analysis, which could affect the precision of results in subsequent multivariate regression models. Additionally, as mentioned earlier,

serum markers are susceptible to systemic status interference, and the lack of simultaneous detection of ocular local samples limits a deeper analysis of the "blood-eye" correlation.

Despite these limitations, this study has significant clinical translational implications. The serum MMP-1/TIMP-1 ratio, as a non-invasive, low-cost, and easily accessible detection indicator, shows great potential for early DR screening and risk stratification in primary healthcare settings. Future research directions should focus on constructing multi-marker combined prediction models, integrating the MMP-1/TIMP-1 ratio with other key factors such as VEGF and YKL-40, and determining optimal diagnostic cutoff values by plotting receiver operating characteristic (ROC) curves in large-sample cohorts, thereby providing more practical tools for the precise prevention and control of DR.

Ethics statement

The studies involving humans were approved by Ethics Committee of the First Affiliated Hospital of Fujian Medical University (approval No. MRCTA, ECFAH of FMU[2025]711). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study

Declarations

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Author Contribution

Yanhao Ma wrote the main manuscript text, Jing Xiao conducted the experiment, Yao Yao, Lijing Cui, Ruixuan Jia review and editing, Jian Guo and Xiaotong Ren gave advice.

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