ORIGINAL ARTICLE

CONTENTS

L-selectin as a systemic biomarker of retinal damage in type 2 diabetes

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ABSTRACT

Aim: To evaluate the clinical significance of serum L-selectin (sCD62L) levels as a biomarker of retinal damage in patients with type 2 diabetes mellitus (T2DM) by correlating its concentration with the stages of diabetic retinopathy (DR) and clinical and morphological parameters of the retinal state.

Materials and Methods: A total of 124 patients (124 eyes) were examined: 95 patients with T2DM (ranging from mild non-proliferative to proliferative DR) and 29 age- and sex-matched controls. Diagnostic techniques included BCVA assessment, SD-OCT (Topcon 3D OCT-1000), and serum ELISA for L-selectin determination.

Results: A significant 2.5-fold increase in serum L-selectin levels was identified in the T2DM cohort compared to controls ([mean ± standard error] 31.2 ± 8.6 ng/mL vs. 12.5 ± 3.5 ng/mL; $p < 0.001$). A progressive upward trend in marker concentration was observed relative to pathology severity: from (median [interquartile range]) 24.7 (20.4–29.0) ng/mL in mild non-proliferative DR ($p < 0.001$ vs. control group [12.5 (10.1–14.9)] ng/mL) to 39.5 (35.1–43.9) ng/mL in the proliferative stage ($p < 0.001$ vs. control group). Positive correlations were found between L-selectin levels and HbA1c ($rs = 0.816$, $p < 0.001$), as well as central retinal thickness ($rs = 0.467$, $p = 0.002$).

Conclusions: CD62L is a significant biomarker of systemic inflammation and vascular dysfunction in T2DM, reflecting the severity of diabetic retinopathy and the risk of blood-retinal barrier disruption.

KEY WORDS: ophthalmology, optometry, diabetic retinopathy, inflammatory biomarker

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INTRODUCTION

Diabetes mellitus (DM) has reached pandemic proportions, emerging as one of the most significant global health challenges of the 21st century. Current projections suggest that the number of individuals living with diabetes will increase to 700 million by 2045 [1]. Among its various microvascular complications, diabetic retinopathy (DR) remains a leading cause of preventable blindness in the working-age population, affecting approximately 22.27% of patients worldwide [1, 2]. Despite advances in laser therapy and anti-VEGF treatments, the social and economic burden of DR continues to grow, necessitating a deeper understanding of its early developmental stages [2].

The pathogenesis of DR is traditionally viewed through the lens of microvascular damage; however, contemporary research increasingly emphasizes the role of chronic low-grade systemic inflammation and neurodegeneration [2, 3]. Chronic hyperglycaemia triggers a cascade of metabolic disturbances, including oxidative stress and activation of the polyol pathway, which collectively stimulate the release of pro-inflammatory cytokines and adhesion molecules [4–6]. These biochemical shifts often manifest as subtle neuroretinal alterations even before the clinical appearance of microaneurysms or haemorrhages [2, 4]. Consequently, there is an urgent clinical demand for sensitive and specific systemic biomarkers capable of identifying patients at high risk of rapid disease progression before irreversible structural damage occurs [5, 6].

Leukostasis — the abnormal adherence of leukocytes to the retinal capillary endothelium — is a critical early event in the breakdown of the blood-retinal barrier (BRB) [4, 5]. This process is mediated by a specialized family of cell adhesion molecules known as selectins. Among them, L-selectin (CD62L), which is constitutively expressed on the surface of most circulating leukocytes, plays a pivotal role in the initial "rolling" phase of leukocyte recruitment [3, 4, 7]. Upon cellular activation, the extracellular domain of L-selectin is proteolytically cleaved from the cell surface in a process termed "shedding", leading to increased levels of its soluble form (sCD62L) in the systemic circulation [3, 7].

Despite its theoretical importance, the diagnostic and prognostic value of soluble L-selectin in type 2 diabetes mellitus (T2DM) remains a subject of ongoing debate. While some studies have suggested depletion of L-selectin due to chronic receptor exhaustion in advanced stages of metabolic disease, others, most notably Karadayi et al. [8], have reported a significant elevation of the marker correlating with the severity of retinal ischemia [8–10]. These discrepancies in the literature underscore the necessity for a systematic evaluation of sCD62L dynamics across the full clinical spectrum of DR — from mild non-proliferative changes to advanced proliferative disease [9, 10].

Furthermore, while the correlation between systemic inflammation and DR is well documented, few studies have integrated biochemical markers with precise structural parameters obtained via spectral-domain optical coherence tomography (SD-OCT) [10]. Establishing a clear link between sCD62L concentrations and clinico-morphological indicators, such as central retinal thickness, could provide a more comprehensive framework for personalized screening and risk stratification in patients with T2DM [7, 10].

AIM

To evaluate the clinical significance of L-selectin as a biomarker of retinal damage in patients with type 2 diabetes mellitus (T2DM) by comparing its levels across different stages of diabetic retinopathy (DR) and correlating them with clinical and morphological parameters.

MATERIALS AND METHODS

The research was designed and conducted as a prospective cohort study using a case-control framework. The study analysed clinical and laboratory data from a total of 124 eyes belonging to 124 subjects. The primary study cohort consisted of 95 patients with confirmed type 2 diabetes mellitus complicated by various stages of diabetic retinopathy (DR). For comparison, a control group was formed, consisting of 29 subjects with no history of carbohydrate metabolism disorders or systemic inflammatory diseases, matched to the main group by age and gender.

The demographic profile of the participants was recorded at the time of inclusion. The mean age in the main cohort (T2DM patients) was 66.8 ± 0.75 years, while the mean age in the control group was 64.2 ± 1.20 years. Within the main cohort, the gender distribution comprised 65 women (68.4%) and 30 men (31.6%). In the control group, there were 16 women (55.2%) and 13 men (44.8%).

The metabolic status of the participants was assessed using standard laboratory tests. In the main cohort, the mean fasting blood glucose level was 8.51 ± 0.82 mmol/L, and the mean glycated haemoglobin (HbA1c) level was 7.36 ± 0.15%.

According to the clinical severity of retinal pathology, patients with T2DM were stratified into three subgroups: Group 1 (n = 29) included patients with mild non-proliferative diabetic retinopathy (NPDR); Group 2 (n = 35) consisted of patients with moderate and severe NPDR; and Group 3 (n = 31) comprised patients with proliferative diabetic retinopathy (PDR).

Ophthalmological screening was performed in a specialised clinical setting and included a comprehensive range of standard and advanced techniques. Initial assessments included visometry (best-corrected visual acuity [BCVA]), autorefractometry, non-contact tonometry, and computerised static perimetry. Anterior segment biomicroscopy and gonioscopy were performed to exclude comorbidities. Detailed fundus ophthalmoscopy was conducted under pharmacological mydriasis (using 1% tropicamide) with a Volk SuperField aspheric lens (USA) and a Goldmann three-mirror contact lens. These examinations strictly followed the international Early Treatment Diabetic Retinopathy Study (ETDRS) protocol to ensure diagnostic consistency.

For the objective assessment of clinico-morphological retinal changes, spectral-domain optical coherence tomography (SD-OCT) was utilised. Scans were performed using a 3D OCT-1000 device (Topcon, Japan), with a focus on measuring central retinal thickness (CRT). All retinal complications and stages of diabetic retinopathy were classified in accordance with the International Clinical Diabetic Retinopathy Disease Severity Scale developed by the American Academy of Ophthalmology (AAO, 2002) [1].

The biochemical analysis involved measuring the concentration of soluble L-selectin (sCD62L) in blood serum. Samples were processed using an enzyme-linked immunosorbent assay (ELISA) with Human sL-selectin INSTANT kits (Invitrogen, USA), according to the manufacturer's instructions.

Statistical analysis was performed using IBM SPSS Statistics v. 27.0. The normality of continuous variable distributions was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean (M) ± standard error of the mean (SEM) for normally distributed data, and as median (Me) with interquartile range (Q1–Q3) for non-normally distributed variables; categorical variables are expressed as counts and percentages. Two-group comparisons were per-

Table 1. Clinical and laboratory parameters of the studied groups (M ± SEM)

Parameter	Control group (n=29)	Main group (n=95)	p
BCVA, decimal units	0.95±0.05	0.60±0.03	< 0.01
CRT (SD-OCT), μm	265±8.4	318±11.2	< 0.05
L-selectin, ng/mL	12.5±3.5	31.2±8.6	< 0.001

Source: compiled by the authors of this study

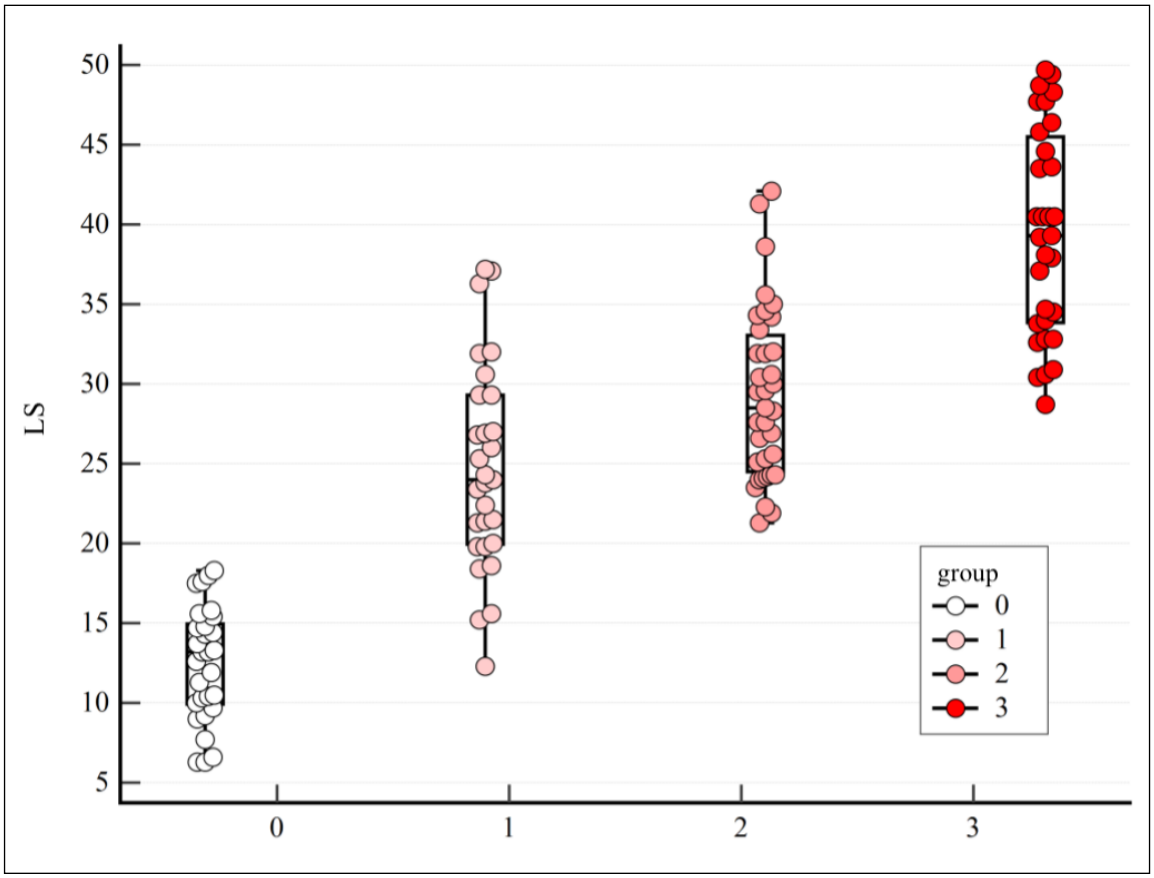

Fig. 1. The L-selectin levels (ng/ml) across the studied groups (box-and-whisker plot with dot plot). Group 0: controls; group 1: mild NPDR; group 2: moderate/severe NPDR; group 3: PDR. Pairwise comparisons: $p_{0-1} < 0.001$; $p_{0-2} < 0.001$; $p_{0-3} < 0.001$; $p_{1-2} = 0.006$; $p_{1-3} < 0.001$; $p_{2-3} = 0.004$
Picture taken by the authors

formed using Student's t-test or the Mann–Whitney U test, as appropriate. Comparisons among four groups were made using one-way ANOVA with Scheffé post hoc testing or the Kruskal–Wallis test with post hoc Mann–Whitney U tests for pairwise comparisons. Correlations were assessed using Spearman's coefficient (rs). A two-sided p-value < 0.05 was considered statistically significant (with Bonferroni correction applied).

ETHICS

The researchers followed all protocols and procedures required by the Biomedical Research Ethics Committee and conformed to the Ukrainian legislation on health care, the Declaration of Helsinki (2000), and European Society Directive 86/609 on human participation in biomedical research, ensuring adherence to all standards for the adequate protection and well-being of participants. Written informed consent was obtained from all participants (or their legal representatives) prior to inclusion in the study, following a full explanation of the study's nature, aims, and potential risks. The study protocol and the informed consent form were reviewed and officially approved by the local Ethics Committee.

FRAMEWORK

The work was carried out at the Department of Postgraduate Ophthalmology and Optometry of the Institute of Postgraduate Education of the Bogomolets

Table 2. The correlations of L-selectin level with certain clinical and clinico-morphological parameters (total cohort, n=124)

Parameters	Correlation coefficient (rs)	Significance (p)
HbA1c, %	0.816	< 0.001
Fasting glucose	0.526	< 0.001
CRT	0.467	0.002
BCVA	–0.412	0.004

Source: compiled by the authors of this study

National Medical University and is a fragment of the department-initiated research project «Theoretical and practical aspects of improving clinical and experimental methods of diagnosis, treatment and prevention of diseases and injuries of the organ of vision and their complications» (state registration number 0123U104207; term: 2023-2026).

RESULTS

Analysis of demographic indicators confirmed the comparability of the main and control groups. No statistically significant difference was found in mean age (66.8 ± 0.75 years vs. 64.2 ±1.20 years; p =0.089). Gender distribution was homogeneous: the study cohort included 65 women (68.4%) and 30 men (31.6%), while the control group included 16 women (55.2%) and 13 men (44.8%) (p = 0.265).

Significant functional and structural alterations were observed in the T2DM cohort compared to healthy controls (Table 1).

Serum concentrations of L-selectin exhibited a distinct, stepwise upward trend that directly correlated with the clinical severity of DR (Fig. 1).

Thus, in early manifestations (mild NPDR), serum L-selectin levels showed a 2.0-fold increase (Me = 24.7; Q1–Q3: 20.4–29.0 ng/mL) compared with the control group (Me = 12.5; Q1–Q3: 10.1–14.9 ng/mL; p < 0.001). As the pathology progressed to moderate and severe NPDR, the concentration increased 2.3-fold (Me = 28.5; Q1–Q3: 24.9–32.1 ng/mL; p < 0.001 vs. control group). The proliferative stage (PDR) was characterised by peak values — 3.2 times higher than in the control group (Me = 39.5; Q1–Q3: 35.1–43.9 ng/mL; p < 0.001 vs. control group).

The correlation analysis revealed a strong positive association between sCD62L and HbA1c levels (rs = 0.816, p < 0.001). Additionally, moderate positive correlations were found with fasting glucose (rs = 0.526, p < 0.001) and CRT (rs = 0.467, p = 0.002), while a moderate negative correlation was identified with BCVA (rs = –0.412, p = 0.004), indicating that higher biomarker levels are associated with functional visual decline (Table 2).

DISCUSSION

Our study identified a significant 2.5-fold increase in serum sCD62L levels in the total T2DM cohort (n = 95) compared with healthy controls, confirming the systemic nature of inflammatory responses in diabetic microangiopathy [1, 2]. These results demonstrate a strong correspondence with the foundational data of Karadayi et al. [8], supporting the universal nature of leukocyte activation mechanisms in retinal damage, regardless of regional characteristics of the clinical sample [8]. Such stability of the indicator underscores the role of L-selectin as a reliable marker of systemic inflammation in diabetes mellitus [1, 8].

The pathogenetic significance of elevated sCD62L is explained by the mechanism of intensive "shedding" — the proteolytic cleavage of the molecule from the surface of activated immune cells. According to studies by A. Ivetić (2018) [3], this process, mediated by metalloproteinases such as ADAM17, is a critical step in the initiation of leukocyte–endothelial interaction, particularly the "rolling" phase. High concentrations of the soluble form reflect hyperactivation of neutrophils and lymphocytes, facilitating their subsequent diapedesis through the blood-retinal barrier into retinal tissues [4, 5, 7].

The strong positive correlation established in this work between L-selectin levels and HbA1c identifies prolonged hyperglycaemia as a primary trigger for shedding of adhesion molecules [6, 7]. This inflammatory cascade disrupts the integrity of endothelial tight junctions, leading to plasma exudation and formation of macular oedema [5, 10]. The direct correlation with CRT according to SD-OCT data provides morphological evidence that sCD62L acts as a key mediator of structural macular changes during diabetes progression [10].

In contrast to earlier theories regarding potential receptor exhaustion, our results demonstrate a stepwise increase in sCD62L corresponding to the severity of DR, which aligns with contemporary data by Siddiqui et al. (2023) [7]. This confirms the marker's potential as a prognostic factor for the transition of the disease into advanced, vision-threatening stages [9, 10]. While the study design does not allow definitive establishment of causal links, the obtained data

open prospects for the development of targeted therapies aimed at inhibiting adhesion molecules to prevent irreversible complications of T2DM [5, 7].

LIMITATIONS OF THE STUDY

Despite the significant findings, several limitations should be acknowledged. First, the cross-sectional design of the study allows identification of associations but precludes definitive establishment of causal relationships between sCD62L levels and DR progression. Second, the sample size, while sufficient for statistical analysis, was limited to a single clinical centre; larger multicentre longitudinal studies are required to validate these biomarkers across diverse populations. Third, the current analysis focused on a single adhesion molecule; future research incorporating a broader panel of inflammatory and angiogenic markers could provide a more comprehensive understanding of molecular interactions in the diabetic retina. Finally, the study did not evaluate dynamic changes in L-selectin levels following therapeutic interventions, such as anti-VEGF therapy or laser photocoagulation, which remains a promising direction for further investigation.

CONCLUSIONS

1. Serum L-selectin levels increase stepwise with DR severity, reflecting intensified systemic leukocyte-endothelial activation.
2. Positive correlations with glycemic markers identify chronic hyperglycemia as a primary driver of systemic L-selectin shedding.
3. Elevated sCD62L levels correlate with increased CRT, supporting its role in blood-retinal barrier disruption.
4. Serum L-selectin serves as a potential supplementary biomarker for identifying patients at risk for advanced microvascular complications.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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