



# Platelet Membrane Selectin as a Risk Factor in the Development of Diabetic Retinopathy – A Pilot Study

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## Abstract

**Introduction** In the pilot study our aim was to observe the role of platelet membrane selectin (P-sel) and soluble platelet selectin (sP-sel) as risk factors for diabetic retinopathy. Our study is based on observations that have not previously been reported by other authors.

**Subjects and methods** The pilot study enrolled 49 patients with type 2 diabetes with and without retinopathy who attended regular ophthalmological screening due to their diabetes mellitus at the outpatient care facility of the Department of Ophthalmology, University of Debrecen. Analysis of P-sel by flow cytometry was performed, and the plasma levels of sP-sel were determined.

**Results** The mean fluorescence intensity of P-sel was significantly higher in the non-proliferative retinopathy group, compared to the control group ( $p=0.037$ ) and the no-retinopathy group ( $p=0.039$ ), and was found to be lower in the proliferative retinopathy group, compared to the non-proliferative group. Soluble P-sel significantly increased in patients with diabetic retinopathy ( $p=0.044$ ).

**Discussion** P-sel can lead to impairment in blood circulation on both the arterial and venous side, which contributes to the development of non-proliferative diabetic retinopathy. Upon the appearance of proliferation, it may lose its pathogenetic role. Soluble P-selectin can play a role in the development of any diabetic retinopathy, which is likely to occur through arteriosclerosis-induced hypoxia.

**Keywords** Diabetes mellitus · Diabetic retinopathy · Platelet membrane P-selectin · Soluble P-selectin

## 1 Introduction

Diabetes Mellitus (DM) has two forms: Type 1 (T1DM) and Type 2 (T2DM). Type 1 diabetes is an autoimmune  $\beta$ -cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood. Type 2 diabetes is a non-autoimmune progressive loss of adequate

$\beta$ -cell insulin secretion frequently on the background of insulin resistance and metabolic syndrome.

The diagnosis of T2DM is established when any one of the following criteria is met: fasting plasma glucose  $\geq 126$  mg/dL (7,0 mmol/L), 2 h plasma glucose  $\geq 200$  mg/dL (11,1 mmol/L) during an oral glucose tolerance test, HbA1c  $\geq 6,5\%$ , or random plasma glucose  $\geq 200$  mg/dL (11,1 mmol/L) with classic symptoms of hyperglycaemia [1].

Diabetic retinopathy is associated with microvascular damage and capillary occlusion, which lead to microangiopathy [2]. Platelets play an important role in this vascular occlusive process in patients with diabetic capillary occlusion and hypercoagulability [3].

P-selectin is localized in the  $\alpha$ -granules of unstimulated platelets and in the Weibel-Palade bodies of endothelial cells. There are two forms of P-selectin. One is bound in the membrane (P-sel), while the other becomes soluble by a shedding mechanism and circulates in the plasma (sP-sel).

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Under the effect of trigger mechanisms (e.g. thrombin and histamine), proteins are expressed on the surface of platelets [4]. A massive expression of P-selectin may lead to a firm leukocyte adhesion to the capillary endothelium, which may cause capillary obstruction and retinal ischemia. Endothelial dysfunction is a well-known feature of diabetes.

Several studies have reported the role of elevated plasma sP-sel levels in the pathogenesis of systemic diseases [5–7] such as hypertension (HT) [8], atherosclerosis [9], ischemic heart disease (IHD) [10, 11], ischemic stroke [7], peripheral vascular disease [12] and hypercholesterolemia [13]. Since elevated sP-sel can lead to endothelial damage, arteriosclerosis, capillary narrowing, and hypoxia, it may also play a role in the development of diabetic retinopathy.

The aim of the pilot study was to evaluate P-sel and sP-sel levels in the plasma of patients with diabetes mellitus to determine whether there was a correlation between their levels and the presence of retinopathy. We also investigated their association with the duration of DM and glycemic control (via glycated hemoglobin levels), as well as other general risk factors and co-morbidities, such as HT, IHD and hypercholesterolemia.

## 2 Subjects and methods

Our hypothesis-driven pilot study enrolled T2DM patients with and without retinopathy who attended regular ophthalmological screenings due to DM at the outpatient care facility of the Department of Ophthalmology, University of Debrecen in a 6-month period.

Our pilot study was designed by the following criteria: small sample size, age- and sex matched participants in Caucasian ethnicity with DM. Patients with a history of cardiovascular failure, stroke, severe nephropathy or anticoagulant therapy were excluded from the study. Any previous or existing ophthalmic pathology other than diabetic retinopathy was also an exclusion criterion. We enrolled a total of 75 patients with DM in our pilot study; we had to exclude 26 patients because they met one or more exclusion criteria.

The control group consisted of twenty-four patients with no clinical and/or anamnestic data relating to any previous vascular or ophthalmic inflammatory disease or tumors. Control patients being treated with antithrombotic or antiplatelet agents were also excluded.

Each patient's full medical history was taken, including type and duration of DM, any other diseases (IHD, HT or hypercholesterolemia) and current medication regimen. All patients underwent full ophthalmological examination: slit lamp evaluation and dilated fundus biomicroscopy by a masked examiner. The same examiner performed the examinations on all patients. Color fundus photography was

also performed. The diagnosis of non-proliferative diabetic retinopathy (NDPR) and proliferative diabetic retinopathy (PDR) were made in accordance with Early Treatment Diabetic Retinopathy Study (ETDRS) guidelines. NDPR fundus findings are microaneurysm, haemorrhages, cotton wool spots, exudates, macular oedema, vessel abnormality. PDR fundus findings are all abnormalities of NDPR with retinal or papillary neovascularisation and vitreous haemorrhages.

In each case, routine laboratory investigations and the glycated hemoglobin level (HbA1C) test were performed. Blood glucose, total cholesterol and triglyceride levels were measured on a Cobas 6000 Analyzer (Roche, Mannheim, Germany), and the HbA1C level was measured by high-performance liquid chromatography (HPLC) (BioRad, Hercules, CA, USA).

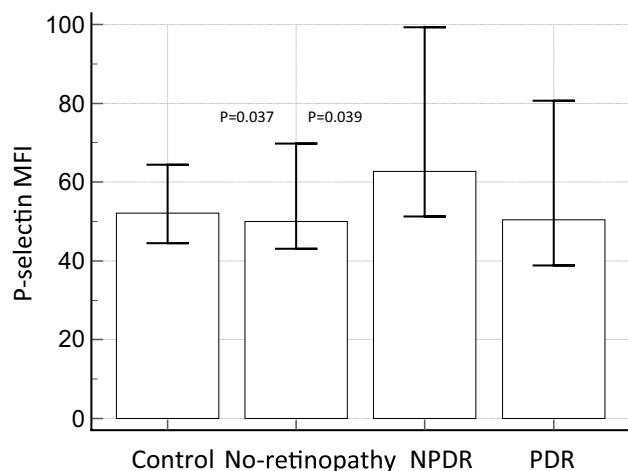
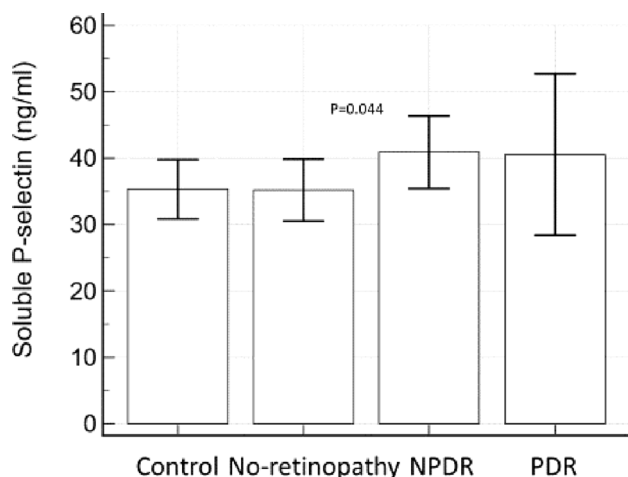
Analyses of P-sel by flow cytometry were performed as previously described [14]. Venous blood samples were collected from the antecubital vein, using syringe and 21-gauge needle, and anticoagulated with sodium citrate 0.105 M. Venous stasis and artificial activation of platelets during blood collection were avoided. Paraformaldehyde 1% was used for fixation each whole blood sample within 2 h. Platelet count was determined by Advia 120 Hematology System (Bayer Diagnostics, Tarrytown, NJ, USA). Platelets were obtained by centrifugation for 15 min at 1300xg twice, and the pellet was resuspended in phosphate-buffered saline in each case. Samples were incubated with FITC-conjugated monoclonal antibodies directed against GPIX receptor (CD42a). P-selectin expression was detected by PE-labeled anti-P-selectin antibodies (CD62, Becton Dickinson). Analyses of platelet activation were performed by a FACS Calibur flow cytometer (Becton Dickinson), and ten thousand events were collected for each sample. Results were expressed as MFI values of CD62-positive platelets. Plasma levels of sP-sel were determined by using a commercially available ELISA (R&D Systems, Minneapolis, MN, USA) kit, based on the manufacturer's instructions.

Informed consent was obtained from all patients, and the Institutional Review Board approved the study protocol in accordance with the Declaration of Helsinki (RKEB/IKEB 3763).

Statistical analysis was performed using MedCalc (Version 19.6.0) statistical software. The normality of data was tested with the Kolmogorov-Smirnov test. If normality was accepted, the independent t-test was used. If normality was rejected, the Mann-Whitney U test was performed. For continuous variables, data was expressed as a median, and a 95% confidence interval (95% CI) was taken for the median. We performed statistical tests for age and gender. We used the Shapiro-Wilk W test for age data, which followed a normal distribution. For gender data, which was not

**Table 1** Demographic features of the control group, no retinopathy group, NPDR and PDR group

|                                                       | Control group<br>(N=24)       | No retinopathy group<br>(N=17) | NPDR group<br>(N=20)          | PDR group (N=12)               |
|-------------------------------------------------------|-------------------------------|--------------------------------|-------------------------------|--------------------------------|
| Mean age at examination(95% confidence interval)      | 63.5 ±<br>9.54(57,69 - 68,21) | 63.8 ±<br>11.6(60,00 - 70,22)  | 63.5 ±<br>11.6(58,82 - 70,65) | 63.25 ±<br>10.7(47,78 - 64,65) |
| Duration of diabetes (years)(95% confidence interval) |                               | 9.4 ± 10.6(3,40 - 13,01)       | 14.3 ±<br>10.7(4,56 - 18,00)  | 22.75 ±<br>8.6(14,56 - 24,44)  |
| HbA1C%(95% confidence interval)                       | 5.8 ±<br>0.79(5,20 - 5,81)    | 6.52 ± 0.57(6,16 - 7,40)       | 7.5 ±<br>1.8(6,20 - 7,82)     | 8.1 ±<br>1.5(7,08 - 9,31)      |
| Hypertension(95% confidence interval)                 | 16(0,00 - 1,00)               | 15(1,00 - 1,00)                | 19(1,00 - 1,00)               | 12(1,00 - 1,00)                |
| Ischaemic heart disease(95% confidence interval)      | 3(0,00 - 0,00)                | 3(0,00 - 0,00)                 | 9(0,00 - 1,00)                | 3(0,00 - 1,00)                 |
| Hypercholesterolaemia(95% confidence interval)        | 9(0,00 - 1,00)                | 8(0,00 - 1,00)                 | 7(0,00 - 1,00)                | 4(0,00 - 1,00)                 |

**Fig. 1** We used Mann-Whitney U test to compare the p-selectin values among the control group, no retinopathy group, NPDR group and PDR group. The vertical axis shows the Mean fluorescence intensity (MFI) values for p-selectin, while the horizontal axis shows the control group ( $N=24$ ), no retinopathy group ( $N=17$ ), NPDR group ( $N=20$ ) and PDR group ( $N=12$ ), respectively. P-sel was significantly higher in the NPDR group, compared to the control group ( $p=0.037$ ) and the no retinopathy group ( $p=0.039$ )**Fig. 2** We analysed with Mann-Whitney U test the soluble P-selectin level in the control group ( $N=24$ ), NPDR group ( $N=20$ ) and PDR group ( $N=12$ ), respectively. sP-sel was significantly higher in patients with diabetic retinopathy ( $p=0.044$ )

normally distributed, we used the chi-square test. A p-value of  $<0.05$  was considered statistically significant.

### 3 Results

Forty-nine patients with T2DM (who met the conditions mentioned above) were enrolled in the pilot study, seventeen of whom had no retinopathy (five males and twelve females; mean age:  $62.27 \pm 11.06$ ), twenty had NPDR (nine males and eleven females; mean age:  $63.5 \pm 11.6$  years) and twelve patients had PDR (four males and eight females; mean age  $63.25 \pm 10.7$  years). Based on our statistical analysis, the study group and the control group were age- and sex-matched. Regarding age data in the control group, in relation to the no diabetic retinopathy group, the NPDR group and the PDR group, we obtained  $p_1=0.548$ ,  $p_2=0.948$ ,  $p_3=0.109$ . Regarding sex data in the control group, in relation to the no diabetic retinopathy group, the NPDR group and the PDR group, we obtained  $p_4=0.853$ ,  $p_5=0.853$ ,  $p_6=0.424$ . DM duration and occurrence of other co-morbidities can be seen in Table 1.

Mean fluorescence intensity (MFI) of P-sel showed different values in each group. The median MFI of P-sel in the no retinopathy group, NPDR group, PDR group and control group was 50.0 (37.6–83.4 95% CI), 62.7 (51.3–99.3 95% CI), 50.5 (38.83–80.7 95% CI) and 52.1 (44.48–64.42 95% CI), respectively. P-sel was significantly higher in the NPDR group, compared to the control group ( $p=0.037$ ) and the no retinopathy group ( $p=0.039$ ), and was found to be lower in the PDR group, compared to the NPDR group but in this case the difference was not significant (Fig. 1).

The mean sP-sel level in the no retinopathy group, NPDR group, PDR group and control group was 35.2 ng/ml (30.5–39.8 95% CI), 40.9 ng/ml (35.4–46.4 95% CI), 40.5 ng/ml (28.35–52.7 95% CI) and 35.3 ng/ml (30.9–39.7 95% CI), respectively. Soluble P-sel was found to be significantly higher in patients with NPDR and PDR ( $p=0.044$ , Fig. 2).

Correlation analyses were performed for groups with diabetic retinopathy. P-sel showed a significant negative

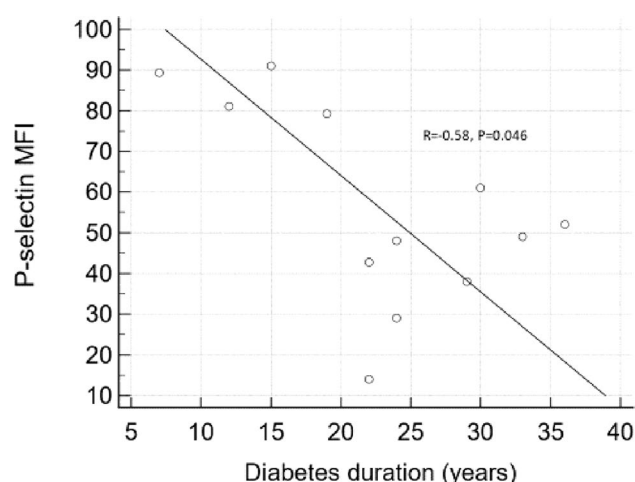


**Fig. 3** Using correlation analysis, we found a significant negative correlation between P-selectin levels and the duration of DM in the PDR group ( $r = -0.58$ ,  $p = 0.046$ )

correlation with diabetes duration in the PDR group ( $r = -0.58$ ,  $p = 0.046$ ; Fig. 3).

## 4 Discussion

Diabetic patients often suffer from co-morbidities such as hypertension, hypercholesterolemia and IHD [15–19], which has been verified in our pilot study; HbA1C levels are also elevated in diabetic patients [20], and this, too, was borne out by our results. The pathogenetic role of sP-sel has previously been described in the case of stroke, coronary disease and the development of atherosclerosis [6, 9–11].

It is well known that diabetic retinopathy is caused by capillary occlusions that result from microvascular thrombi formed by red blood cells, platelets and leukocytes. Platelets can play an important role in this vascular occlusive process [21, 22]. Activated platelets present P-selectin on their surface, which increases their capability for aggregation.

Several authors have published that accord with our results that the P-sel and the sP-sel level is higher in the plasma of diabetic patients, although most of these articles discuss the association between P-selectin and diabetes itself. Unlike our study, these authors did not examine the significance of the p-value in the individual diabetes groups [23–25].

Few studies can be found that consider whether sP-sel is also related to the development of diabetic retinopathy. Penman et al. studied sP-sel and its relationship with diabetic retinopathy and found that sP-sel is an independent risk factor for both non-proliferative and proliferative diabetic retinopathy [26].

According to our results, P-sel values were found to be higher in the NPDR group and lower in the PDR group. The

increase was significant in the NPDR group, compared to the control group and the no retinopathy group. On the other hand, a decrease in P-sel activity was observed in the PDR group, compared to the NPDR group. According to our data, sP-sel levels are lower in PDR, in contrast to the findings of other authors [23–26].

Capitao et al. found in their research, that it is possible that inflammatory mediators may contribute to the development of PDR, and their role may even exceed that of sP-sel [27].

Qiao-Yun Gong et al. published that inflammatory mediators were significantly elevated in vitreous humor from patients with PDR compared to those without PDR [28].

Takeru Yoshimura et al. examined the level of interleukin 6, 8 and monocyte chemoattractant protein-1 levels in PDR patients too, and they reported significantly higher levels of inflammatory mediators than control group [29].

Jung et al. researched that IL-6 trans-signalling functions as an independent promoter of vitreoretinal vascular disease, such as PDR [30].

The results of correlation analyses indicated a significant negative correlation in the PDR group between P-sel and diabetes duration, which confirms the process described by other authors, that in the proliferative phase of diabetic retinopathy, other factors override the initial effect of P-sel. Our results suggest that systemic disease severity could influence P-sel levels and other inflammatory mediator levels too.

A limitation of our study is the small sample size. We plan to continue our research in the future with a larger sample size. The relatively limited number of participants reflects the strict inclusion and exclusion criteria applied in order to minimize confounding factors affecting platelet activation and endothelial dysfunction. Patients with cardiovascular failure, stroke, severe nephropathy, anticoagulant therapy, and other ophthalmic pathologies were excluded. In addition, the pilot study involved technically demanding flow cytometric assessment of platelet membrane P-selectin expression together with soluble P-selectin measurements, which limited recruitment capacity.

Despite the modest sample size, statistically significant differences were identified between groups, suggesting that the observed associations may be biologically relevant. We believe that the combined evaluation of membrane-bound and soluble P-selectin provides novel preliminary data that may support future larger prospective studies.

Summary, our results, platelet membrane P-selectin may be a risk factor in the development of NPDR. In the case of increased P-selectin, it may be useful to consider the use of antiplatelet medication, but it may warrant further investigation rather than clinical recommendations.

**Author Contributions** A.V.: manuscript preparation, patient examination M.K.: patients examination, data collection D.L.N.: data collection, manuscript preparation E.S.: statistical analysis, figure preparation Sz.B.: data collection, statistical analysis, figure preparation Zs.F.: laboratory investigation (flow cytometry, ELISA) M.F.: patient examination, additional examination V.N.: study design, manuscript preparation and review.

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**Data Availability** No datasets were generated or analysed during the current study.

## Declarations

**Conflict of interest** The authors declare no competing interests.

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