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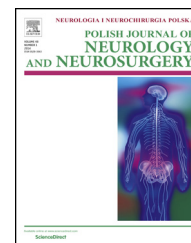
Original research article

sP- and sE-selectin in stroke patients with metabolic disorders

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ABSTRACT

Background: Activation of platelets and endothelial cells plays an important role in the pathogenesis of atherosclerosis and thrombotic disorders.

The aim of our study was to assess the relationship between the metabolic disorders and markers of platelet activity and vascular injury in patient with acute ischemic stroke.

Material and methods: The study group consisted of 84 patients with acute non-lacunar ischemic stroke divided into four subgroups with: (1) normolipidemia and normoglycemia, (2) normolipidemia and hyperglycemia, (3) hyperlipidemia and normoglycemia, (4) hyperlipidemia and hyperglycemia. 21 healthy subjects served as controls. We analyzed the concentration of adhesion molecules sP-selectin and sE-selectin in serum collected from all studied groups using ELISA method.

Results: We observed significantly higher sE- and sP-selectin concentration in patients with hyperglycemia and hyperlipidemia compared to both control subjects and patients with normolipidemia and normoglycemia. We did not observe additional effect of comorbid hyperlipidemia and hyperglycemia on studied markers. Soluble E- and P-selectin concentration correlated positively with LDL, TC and HbA_{1c} level in all stroke patients.

Conclusion: Soluble E- and P-selectin, blood markers of vascular injury and platelet activation, could be useful in the assessment of atherothrombotic properties of hyperglycemia and hyperlipidemia in stroke patients.

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1. Introduction

Ischemic stroke is thought to be the consequence of atherosclerosis, plaque inflammation and rupture, thrombosis and brain infarction. The key role in the pathogenesis of atherothrombosis play changes in the vascular endothelium and platelets activation [1].

E-selectin and P-selectin are glycoproteins belonging to the selectin family of adhesion molecules. They regulate adhesive

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interactions between certain blood cells and vascular endothelium and are believed to play an important role in atherogenesis and plaque inflammation [2]. P-selectin is a membrane molecule of the α-granules in platelets and of the endothelial Weibel-Palade bodies. E-selectin is expressed on activated vascular endothelium only. Soluble form of P- and E-selectin are released into the serum by a shedding mechanism and their rise are observed in plasma of patients with vascular diseases and reflect activation of endothelial cells and platelets as well [3]. The increased plasma concentration of soluble P-selectin reflects the release of these adhesion molecule from activated platelets or damaged endothelial cells whereas high soluble E-selectin reflects only vascular endothelium damage. Elevated concentration of sP-selectin can exert procoagulant activity [4] and it might play an important role in thrombotic disorders. Assessment of soluble P-selectin, originating from platelets and endothelial cells, may be a marker of increased membrane P-selectin expression connected with vascular dysfunction and platelet activation. This adhesion molecule may provide complete information on dynamic interactions between endothelial and circulating cells [5].

Hyperglycemia and dyslipidemia are significant and independent risk factors for the vascular diseases. They are the key factors in the platelet activation and development of atherosclerosis. Hyperglycemia plays an important role in the blood abnormalities leading to a prothrombotic state in diabetes mellitus (DM) patients [6,7]. The most important factors are increased coagulation, impaired fibrinolysis, endothelial dysfunction and platelet hyperreactivity [8,9]. Platelets from patients with DM have increased expression of adhesion molecules. It was showed that platelets from these patients have a greater expression of platelet activation markers (CD31, CD49b, CD62P and CD63) compared with the age-matched non-diabetic control group, and a significant positive correlation between HbA_{1c} concentration and both CD62P and CD63 expression have been observed [10]. Platelet dysfunction in diabetic patients is caused by several mechanisms, such as hyperglycemia, insulin deficiency and associated metabolic conditions like dyslipidemia [11]. Modification of lipoprotein in diabetic states, including peroxidation and glycation, may be one of the mechanisms responsible for diabetic complications [12,13]. Oxidation may increase atherogenicity of lipoproteins, whereas glycation may enhance the oxidative stress of the lipoproteins [14]. Low-density lipoproteins (LDLs) have been reported to activate platelets and increase platelets reactivity to platelet agonists [15]. Platelets activated by native and oxidized LDL (ox-LDL) release factors which increase the number of LDL receptors on macrophages and stimulate LDL accumulation in these cells [16]. Thus, ox-LDL may impair vascular functions, resulting in increased risk of occlusive thrombotic events [17].

These findings show that the interaction of hyperglycemia and dyslipidemia may increase the risk of vascular complications independently as well as synergistically.

The aim of this study was to access the influence of hyperlipidemia and hyperglycemia on soluble P- and E-selectin concentration in the blood of patients with acute ischemic stroke.

The study was approved by the Ethics Committee of Medical University of Lodz, Poland (No. RNN/465/11/KB).

2. Material and methods

The study group consisted of 84 patients admitted to the Department of Neurology and Stroke Medical University of Lodz, Poland with a diagnosis of acute ischemic stroke. The diagnosis was established by history, clinical examination, and cerebral CT or MRI scans. Patients with non-lacunar stroke and metabolic disorders like hyperlipidemia and hyperglycemia were included to the study. The diagnosis of diabetes mellitus in patients with hyperglycemia was established before the hospitalization and diabetic patients were included to the study if HbA_{1c} was higher than 7% in spite of hypoglycemic treatment (metformin, glimepiride, gliclazide, insulin therapy). The hyperlipidemia was recognized on the basis of low-density lipoproteins cholesterol (LDL-C) level ≥ 2.6 mmol/l (100 mg/dl).

The stroke patients were divided into four groups:

(1) 21 patients with normolipidemia and normoglycemia – NL/NG: LDL < 2.6 mmol/l (100 mg/dl) [18], mean 2.20 ± 0.32 mmol/l.; HbA_{1c} ≤ 7% [19], mean 5.7 ± 0.3%; 10 males, 11 females, mean age 75.76 ± 10.9 years;
(2) 21 patients with normolipidemia and hyperglycemia – NL/HG: LDL < 2.6 mmol/l (100 mg/dl), mean 2.33 ± 0.34 mmol/l; HbA_{1c} > 7%, mean 7.67 ± 0.82%; 12 males, 9 females, mean age 73.8 ± 12.6 years;
(3) 21 patients with hyperlipidemia and normoglycemia – HL/NG: LDL ≥ 2.6 mmol/l (100 mg/dl), mean 3.23 ± 1.28 mmol/l; HbA_{1c} ≤ 7%, mean 5.53 ± 0.33%; 9 males, 12 females, mean age 71.04 ± 13.05 years;
(4) 21 patients with hyperlipidemia and hyperglycemia – HL/HG: LDL ≥ 2.6 mmol/l (100 mg/dl), mean 3.26 ± 0.56 mmol/l; HbA_{1c} > 7%, mean 7.91 ± 1.16%; 13 males, 8 females, mean age 70.1 ± 10.76 years.

All studied stroke patients received 300 mg of ASA (acetylsalicylic acid) on the first day of hospitalization and they continued the treatment receiving 75 mg of ASA during the next days. The patients in control group received ASA 75 mg /day.

Control subjects consisted of patients hospitalized in the Department of Neurology and Stroke (n = 21; 10 males, 11 females, mean age 60.2 ± 14.6 years) with normolipidemia and normoglycemia without a history of cerebrovascular diseases.

The exclusion criteria involved a history of infection shortly before stroke, severe liver disease, renal failure, evidence of malignant, chronic inflammatory diseases and haemorrhagic diathesis. The risk factors for ischemic stroke (arterial hypertension, ischemic heart disease and body mass index) were similar in the study groups and the controls, and patients in all groups were receiving antihypertensive drugs, such as ACE inhibitors, calcium channel blockers, β-blocker).

The blood lipid profile and HbA_{1c} level in study groups are presented in Table 1. Complete blood cell count, HbA_{1c}, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C),

Table 1 – The blood lipid profile and HbA$_{1c}$ level (means ± SD) in study groups.

Parameters	NL/NG	NL/HG	HL/NG	HL/HG	CS
TC [mmol/l]	3.61 ± 0.58	3.77 ± 0.46	5.38 ± 0.74	5.86 ± 0.46	4.06 ± 0.5
LDL [mmol/l]	2.20 ± 0.35	2.33 ± 0.34	4.18 ± 1.01	4.28 ± 0.56	2.45 ± 0.13
HDL [mmol/l]	1.08 ± 0.33	1.07 ± 0.31	1.3 ± 0.29	1.14 ± 0.25	0.95 ± 0.17
TG [mmol/l]	1.39 ± 0.77	1.56 ± 0.7	1.81 ± 0.91	1.67 ± 0.61	1.31 ± 0.48
HbA$_{1c}$ [%]	5.71 ± 0.3	7.5 ± 0.9	5.54 ± 0.34	7.66 ± 1.3	5.22 ± 0.37

SD, standard deviation; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; HbA$_{1c}$, glycosylated hemoglobin A$_{1c}$.
NL/NG, normolipidemic/normoglycemic group; NL/HG, normolipidemic/hyperglycemic group; HL/NG, hyperlipidemic/normoglycemic group; HL/HG, hyperlipidemic/hyperglycemic group; CS, control subjects.
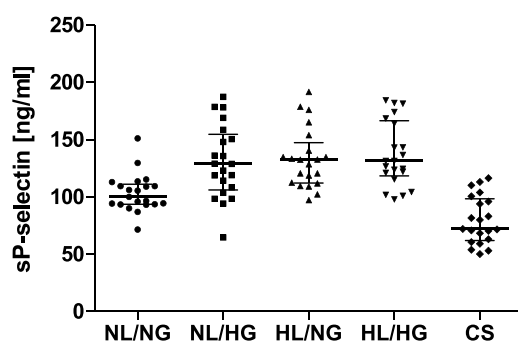
Fig. 1 – Soluble P-selectin concentration in study groups. NL/NG, normolipidemic/normoglycemic group; NL/HG, normolipidemic/hyperglycemic group; HL/NG, hyperlipidemic/normoglycemic group; HL/HG, hyperlipidemic/hyperglycemic group; CS, control subjects.
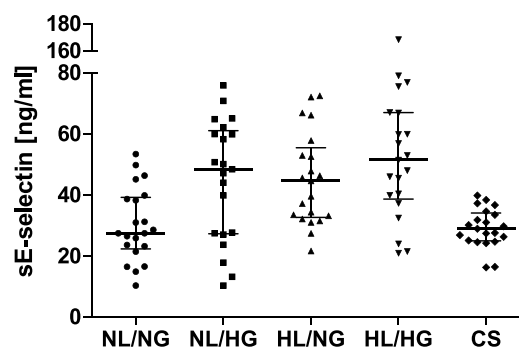
Fig. 2 – Soluble E-selectin concentration in study groups. NL/NG, normolipidemic/normoglycemic group; NL/HG, normolipidemic/hyperglycemic group; HL/NG, hyperlipidemic/normoglycemic group; HL/HG, hyperlipidemic/hyperglycemic group; CS, control subjects.

low-density lipoproteins cholesterol (LDL-C) levels were done in fasting state in all patients. Serum LDL-C levels were calculated with Friedewald's formula. Biochemical determinations were performed with the Olympus AU640 Analyzer (Olympus Optical Co., Ltd., Shizuoka, Japan). Plasma samples were taken within 7 days after onset of symptoms. After 10 min of centrifugation, the blood plasma obtained from EDTA-anticoagulated samples was stored at −80 °C until measurements. Blood concentration of sP-and sE-selectin were measured with commercially available ELISA kits (R&D Systems, Abingdon, UK). Measurement was performed according to the manufacturers' instructions.

3. Statistical methods

Since all study variable did not passed D'Agostino normality test differences between groups were analyzed with the Kruskal-Wallis test followed by post-hoc Duna test for multiple comparisons adjustment. A Spearman's correlation was run to assess the relationship between continuous variables. All of the statistical analyses were performed using Statistica for Windows ver. 8.0. The null hypothesis was rejected if $p < 0.05$.

Table 2 – Medians of soluble P- and E-selectin concentration in blood of the study patients and control subjects.

Study parameters	Median				
	CS	NL/NG	NL/HG	HL/NG	HL/HG
sP-selectin [ng/ml]	72.15	100.1	128.9[**,#]	132.7[**,##]	131.5[**,##]
sE-selectin [ng/ml]	28.95	27.42	48.38[*]	44.61[*,#]	51.44[**,##]

NL/NG, normolipidemic/normoglycemic group; NL/HG, normolipidemic/hyperglycemic group; HL/NG, hyperlipidemic/normoglycemic group; HL/HG, hyperlipidemic/hyperglycemic group; CS, control subjects.
[#] $p < 0.05$ vs NL/NG.
[*] $p < 0.05$ vs CS.
[##] $p < 0.01$ vs NL/NG.
[**] $p < 0.001$ vs CS.

4.   Results

The data of our research confirm the significant influence of metabolic disturbances on sP- and sE-selectin serum concentration level in stroke patients. We observed significantly higher sP-selectin concentration in patients with hyperglycemia and hyperlipidemia as compared to control subjects (NL/HG, HL/NG, HL/HG vs CS, $p < 0.001$) and group without comorbid hyperglycemia and hyperlidipemia (NL/HG vs NL/NG, $p < 0.05$; HL/NG, HL/HG vs NL/NG, $p < 0.01$ (Table 2 and Fig. 1).

Table 3 – The correlation between soluble P- and E-selectins concentration, lipid parameters and HbA$_{1c}$ in study patients.					
Parameters	TC	LDL	HDL	TG	HbA$_{1c}$
sP-selectin [ng/ml]	$p < 0.01$	$p < 0.01$	$p > 0.05$	$p > 0.05$	$p < 0.01$
	$R = 0.288$	$R = 0.404$	$R = -0.08$	$R = 0.097$	$R = 0.433$
sE-selectin [ng/ml]	$p < 0.01$	$p < 0.01$	$p > 0.05$	$p < 0.05$	$p < 0.01$
	$R = 0.312$	$R = 0.386$	$R = -0.127$	$R = 0.225$	$R = 0.370$

TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; HbA$_{1c}$, glycosylated hemoglobin A$_{1c}$.
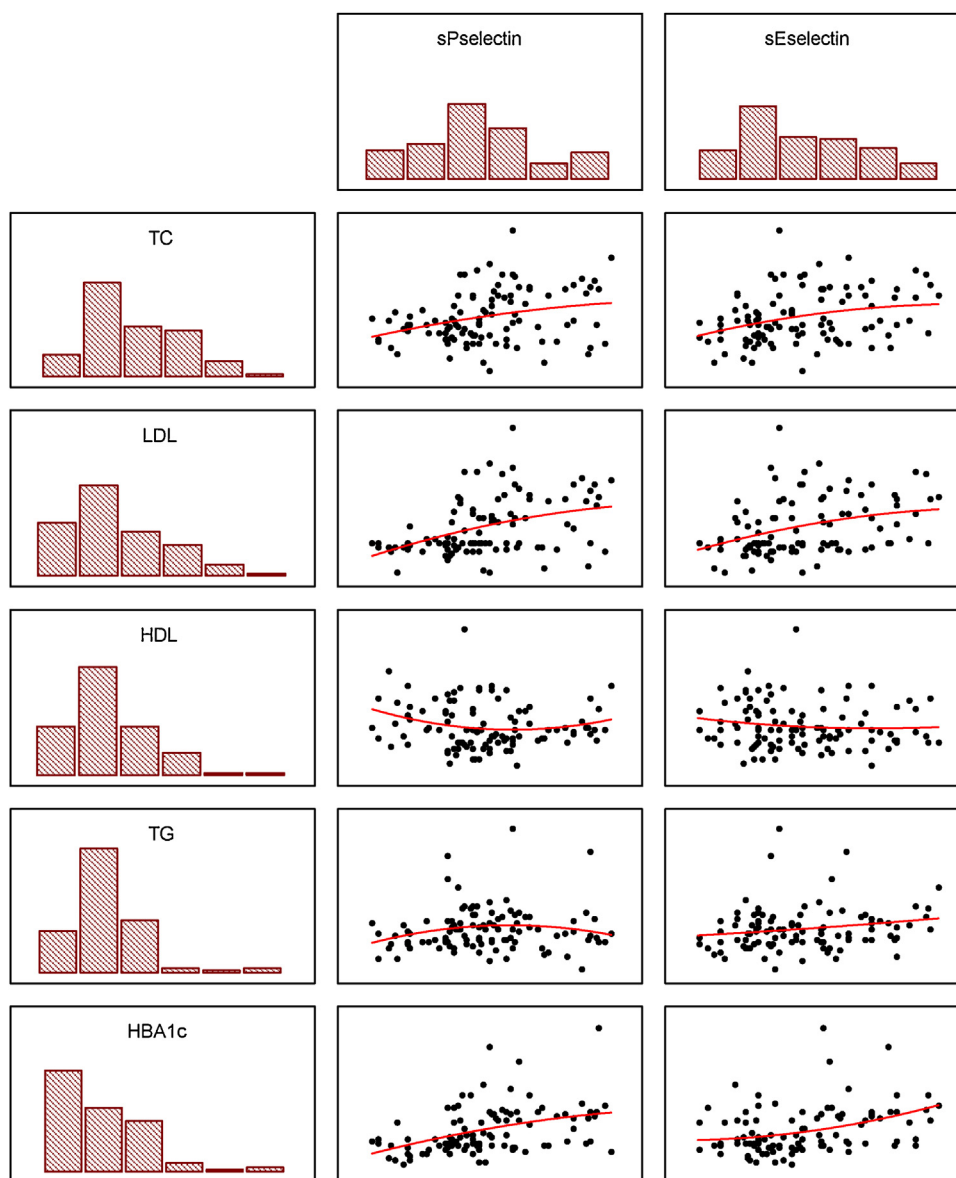

Fig. 3 – Correlation between soluble P- and E-selectin concentration and lipid parameters and HbA$_{1c}$ in study patients. TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; HbA$_{1c}$, glycosylated hemoglobin A$_{1c}$.

Similar observation concerns sE-selectin serum concentration. Higher serum concentration of sE-selectin was noticed in stroke patients with metabolic disorders compared to control subjects (NL/HG, HL/NG vs CS, $p < 0.05$; HL/HG vs CS, $p < 0.001$) and compared to stroke patient with normolipidemia and normoglycemia (HL/NG vs NL/NG, $p < 0.05$, HL/HG vs NL/NG, $p < 0.01$) (Table 2 and Fig. 2).

Positive correlations between serum concentration of sP- and sE-selectin and total cholesterol, LDL, HbA$_{1c}$, $p < 0.01$) (Table 3 and Fig. 3) were observed.

Against all expectations we did not observe significantly higher concentration of sP- and sE-selectin in group of patient with comorbid hyperlipidemia and hyperlipidemia compared to patients with hyperlipidemia or hyperglycemia.

5. Discussion

Hyperlipidemia and the hyperglycemia are considered as the major risk factors for the development of atherosclerosis and platelet activation.

The principal finding of our study is a significant correlation of hyperlipidemia and hyperglycemia with increased serum concentration of sP-selectin and sE-selectin in stroke patients. Our study also showed significant positive correlation between the increased LDL, total cholesterol, HbA$_{1c}$ level and the high concentration of soluble E-selectin and P-selectin. In spite of our expectations, we did not observe additional effect of comorbid hyperlipidemia and hyperglycemia on serum concentration of studied markers.

The pathophysiological significance of the increased P-selectin serum level in hypercholesterolemic or hyperglycemic patients still remains unclear. Making under consideration the origin of sP-selectin we cannot be sure if high sP-selectin level observed in our study is the result of platelet activation or endothelial cells injury. However, in our study soluble E-selectin as a marker of endothelial activation has also been found to be elevated in all stroke patients with dyslipidemia and hyperglycemia. It has been proposed that these soluble cell adhesion molecules may represent a marker of the endothelial atherosclerotic damage. These findings partly suggest endothelial origin of sP-selectin. Further, it is believed that metabolic disturbances like hyperlipidemia and hyperglycemia are the factors with strong atherogenic properties. The positive correlation between high lipid profile (LDL and total cholesterol), high HbA$_{1c}$ level and markers of endothelial damage: sE- and sP-selectin, confirm this observation. Similarly, Ferroni et al. [20] and Davi et al. [5] demonstrated the relationship between the increased LDL concentration and the plasma sP-selectin level. Elevated soluble P-selectin level in hyperlipidemic patients with type 2 diabetes, and association with increased oxidised LDL were also demonstrated by Nomura et al. [21]. In other study E-selectin as a marker of endothelial dysfunction have also been elevated in dyslipidemic patients [22]. Possible reasons for the increase in blood marker of endothelial dysfunction is activation of the symptomatic atherosclerotic plaque. Significant increase of vascular injury markers in stroke patients with metabolic disturbances confirm important influence of hyperlipidemia and hyperglycemia on atherosclerosis progression and ath-

erosclerotic plaque instability. However, the role of blood platelets in the development and proliferation of atherosclerotic lesions is also significant and largely results from their interactions with damaged endothelial cells [23].

Circulating atherogenic lipoproteins have been shown to activate circulating blood platelets, and thereby contribute to the pathogenesis and progression of atherothrombosis [24,25]. Furthermore, hyperglycemia plays an important role in platelet dysfunction, including altered adhesion and aggregation, even in the absence of vascular injury [11]. Thus, increased sP-selectin concentration observed in our study may reflects not only endothelial dysfunction but also platelets activation in stroke patients with metabolic disturbances. This observation is concordant with findings of the other studies that confirmed the influence of hyperlipidemia and high glucose concentration on platelet activity and enhanced expression of platelet P-selectin [26–28].

The results of our study also confirmed earlier reports of a significant increase of sP-selectin and sE-selectin concentrations in acute ischemic stroke [29–32]. We observed elevated blood markers of endothelial and platelet activation during the first 7 days after brain ischemia in all groups of stroke patients even without concomitant hyperlipidemia and hyperglycemia. The early increase of sP-selectin and sE-selectin may be a result of inflammation and activation of the atherosclerotic plaque, atherothrombosis after plaque eruption, and ischemic neuronal damage causing expression of factors that promote a further reactions that involve these markers [29]. Moreover, elevated concentration of sP-selectin can exert its own procoagulant activity [4] resulting from induction of tissue factor expression in circulating monocytes [33]. These findings suggest that an increase in plasma P-selectin concentration may induce a hypercoagulability state and this adhesive molecule may represent a risk factor itself [29]. It was also established that E-selectin plays an important role in the pathogenesis of tissue injury after cerebral ischemia and reperfusion [34]. These observations and our findings suggest that the increase of sP- and sE-selectin serum level in acute stroke patients may be not a consequence of atherosclerosis complication only in patients with comorbid hyperlipidemia and hyperglycemia but is also observed in stroke patients without metabolic disturbances and may be the results of tissue injury after brain ischemia. It suggests that E-selectin and P-selectin blockade may be clinically useful in stroke treatment.

However, the limitation of our study is the pretty large time from the stroke onset to the collection of blood samples. Some study suggested that lipid and lipoprotein levels of patients with TIA or stroke should be assessed within a maximum of 48 h after the acute event [35].

Summing up, results of our study point to the leading role of hyperglycemia and hyperlipidemia in enhanced concentration of soluble P-selectin and E-selectin, molecules reflecting vascular injury and platelet hyperreactivity. The increased concentration of these soluble adhesion molecules in atherosclerotic ischemic stroke is a consequence of hyperlipidemia and hyperglycemia influence on atherogenesis and platelet activation but on the other hand may also be secondary to acute ischemic events and may induce a hypercoagulability status representing a risk factor itself [29]. Measurements of

sP- and sE-selectin concentration might be useful as a predictive marker for the risk of cerebrovascular events caused by atherothrombotic complication.

Conflict of interest

None declared.

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