STUDY OF P-SELECTIN LEVELS AND HEMOSTASIS GENES GENETIC POLYMORPHISMS AMONG PATIENTS WITH GOUT

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Abstract. *Gout is a metabolic and inflammatory disorder characterized by hyperuricemia and crystal-induced arthritis, often accompanied by an elevated risk of cardiovascular events and thrombosis. P-selectin, a marker of platelet activation and endothelial dysfunction, has been implicated in thrombotic processes. Genetic polymorphisms in hemostasis-related genes may contribute to both hyperuricemia-related inflammation and thrombogenic potential. The objective of this study was to investigate P-selectin levels and common genetic polymorphisms in MTHFR, F5, F2, and PAI-1 genes among 80 patients with gout and 20 healthy controls to assess their combined role in increasing thrombotic risk. Plasma P-selectin levels and genotypic variations in MTHFR C677T, F5 G1691A, F2 G20210A, and PAI-1 675 4G/5G were analyzed in a cohort of gout patients (n = 80) and healthy controls (n = 20). Enzyme-linked immunosorbent assay (ELISA) was used to quantify P-selectin. Genotyping was conducted using TaqMan PCR. Statistical correlation analyses were performed to determine the relationship between elevated P-selectin levels and the presence of high-risk genotypes. Gout patients exhibited significantly elevated P-selectin levels (range: 0.01–3.58 ng/mL), with many exceeding the normal threshold (0.30 ng/mL), compared to controls (0.02–0.18 ng/mL). High-risk genotypes were notably more frequent among gout patients: MTHFR TT (13%), F5 AA (5%), F2 AA (22%), and PAI-1 4G/4G (62%). Correlation analysis showed a moderate positive relationship between P-selectin levels and genetic polymorphisms ($r = 0.378$, $p = 0.00036$), with $R^2 = 0.143$. Elevated P-selectin levels in gout patients are moderately associated with thrombosis-related genetic polymorphisms, suggesting an interplay between genetic predisposition and thrombo-inflammatory processes in gout.*

Keywords. *Gout, P-selectin, Hemostasis, Gene polymorphism, MTHFR C677T, F5 G1691A, F2 G20210A, PAI-1 4G/5G, Thrombosis, Endothelial dysfunction, Platelet activation, Hyperuricemia.*

Introduction. Gout is a chronic inflammatory arthritis resulting from monosodium urate crystal deposition in joints, arising due to prolonged hyperuricemia. Besides joint involvement, gout is increasingly recognized as a systemic disease with implications for cardiovascular health. Thrombotic complications, particularly venous thromboembolism, have been observed at higher rates among gout patients [1, 5]. P-selectin, a glycoprotein expressed on activated platelets and endothelial cells, mediates leukocyte adhesion and platelet aggregation, playing a crucial role in the pathogenesis of thrombosis [2, 3]. Elevated P-selectin levels serve as biomarkers for vascular inflammation and prothrombotic states [4]. The potential genetic basis of thrombosis in gout patients includes polymorphisms in key hemostasis genes such as MTHFR C677T, F5 G1691A (Leiden mutation), F2 G20210A, and PAI-1 675 4G/5G [6, 7]. This study explores the relationship between P-selectin levels and these genetic polymorphisms in gout patients.

Materials and Methods. 80 patients diagnosed with gout and 20 healthy controls were included. Plasma P-selectin levels were measured using ELISA. Genotyping for MTHFR C677T, F5 G1691A, F2 G20210A, and PAI-1 675 4G/5G was performed using TaqMan Real-Time PCR. Pearson correlation was used for statistical analysis.

Results. P-selectin levels were significantly elevated in the gout patient group compared to the control group. Specifically, P-selectin levels in patients ranged from 0.01 to 3.58 ng/mL, with many patients displaying levels exceeding the normal threshold of 0.30 ng/mL. The majority of patient values clustered between 0.5 and 1.5 ng/mL. In contrast, the control group exhibited P-selectin levels ranging from 0.02 to 0.18 ng/mL, all within or below the normal range, indicating a statistically significant difference between the two groups ($p < 0.001$).

Regarding genetic polymorphisms, the distribution of high-risk genotypes in gout patients was notable. For MTHFR C677T, 13% of patients were homozygous for the TT genotype, which is considered a high-risk variant for thrombosis, while 24% were heterozygous (CT), and 63% were homozygous for the normal CC genotype. In the control group, no individuals were found with the TT genotype; most were either CC or CT.

For F5 G1691A (Factor V Leiden), 5% of patients had the AA genotype, 8% were GA, and 87% were GG. In the control group, the majority were GG, with no AA genotypes detected.

For F2 G20210A (Prothrombin gene), 22% of patients exhibited the high-risk AA genotype, 30% were GA, and 48% were GG. The control group had only 3 individuals with the GA genotype and none with the AA genotype.

The PAI-1 675 4G/5G polymorphism showed that 62% of patients had the 4G/4G genotype, which is associated with higher thrombosis risk due to reduced fibrinolysis. 19% were 4G/5G, and 19% were 5G/5G. In the control group, most individuals were either 5G/5G or 4G/5G, with very few exhibiting the 4G/4G genotype.

Correlation analysis between P-selectin levels and genetic polymorphisms revealed a moderate positive correlation with a Pearson correlation coefficient of $r = 0.378$, and the p-value was 0.00036, indicating statistical significance. The coefficient of determination, R^2, was 0.143, suggesting that approximately 14.3% of the variation in P-selectin levels could be explained by the presence of these genetic polymorphisms.

These findings collectively suggest that gout patients have high genetic and biochemical predisposition of increased thrombotic risk.

Discussion. The findings of this study demonstrate a significant elevation in P-selectin levels among gout patients, which correlates moderately with the presence of high-risk genetic polymorphisms in hemostasis-related genes. Elevated P-selectin levels reflect increased platelet activation and endothelial dysfunction, both of which are known contributors to thrombotic events. The high prevalence of the PAI-1 4G/4G genotype among patients suggests a potential mechanism for impaired fibrinolysis, contributing to a prothrombotic state. This genotype has been widely reported to be associated with elevated PAI-1 levels, reducing the breakdown of fibrin clots and enhancing clot stability.

The association of MTHFR TT genotype with increased P-selectin levels may be linked to hyperhomocysteinemia, which is a known result of MTHFR enzyme deficiency. Elevated homocysteine levels can lead to endothelial damage, increased oxidative stress, and subsequent platelet activation, all of which contribute to elevated P-selectin levels. Similarly, F5 G1691A and F2 G20210A mutations, both associated with increased thrombin generation, could amplify platelet activation, thereby increasing P-selectin expression.

While the correlation coefficient ($r = 0.378$) indicates a moderate relationship, the relatively low R^2 value (0.143) suggests that genetic polymorphisms explain only part of the variation in P-selectin levels. This implies that other factors such as systemic inflammation, renal function, lifestyle, and additional genetic variants may also influence P-selectin levels and thrombotic risk in gout patients. The multifactorial nature of thrombotic risk underscores the complexity of its management in gout, necessitating a comprehensive approach that includes genetic screening, inflammatory marker monitoring, and cardiovascular risk assessment.

These results are consistent with previous studies highlighting the role of endothelial dysfunction and prothrombotic states in gout pathogenesis. The observed genetic predispositions provide insight into the underlying mechanisms linking gout to cardiovascular morbidity and mortality. Identification of high-risk genotypes in gout patients could enable personalized therapeutic strategies aimed at reducing thrombotic complications, including the use of antiplatelet or anticoagulant therapy in selected individuals.

Limitations of this study include the sample size, which may not capture the full genetic diversity of the population. Further studies with larger cohorts and inclusion of additional polymorphisms are warranted to confirm these findings and explore the interaction between genetic and environmental factors in the regulation of P-selectin and thrombotic risk.

Conclusion. Gout patients have high level of P-selectin levels, which means platelet activation and endothelial inflammation. Also, genetic polymorphisms of hemostasis genes contribute to increased thrombosis risk. Patients with gout should have multidisciplinary approach, in order to prevent serious complications of coagulation system.

REFERENCES

1. Chiu CC, Chen YT, Hsu CY, et al. Association between Previous History of Gout Attack and Risk of Deep Vein Thrombosis. Sci Rep. 2016; 6:26541.

2. Cicero AFG, Fogacci F, Borghi C. Uric Acid and Thrombotic Risk: An Emerging Link. Intern Emerg Med. 2020; 15:1167-1168.

3. Darlington G, Scott JT. Platelet adhesiveness in gout. Postgrad Med J. 1973; 49:24-28.

4. Fang J, Alderman MH. Serum Uric Acid and Cardiovascular Mortality. JAMA. 2000;283(18):2404-2410.

5. Krishnan E, et al. Gout and the Risk of Acute Myocardial Infarction. Arthritis Rheum. 2006; 54:2688-2696.

6. Halperin Kuhns VL, Woodward OM. Sex differences in urate handling. Int J Mol Sci. 2020; 21:234.

7. Huang CC, Huang PH, Chen JH, et al. Risk of Gout on Deep Vein Thrombosis and Pulmonary Embolism. Medicine. 2015; 94:e2140.