Zeitschrift für
Rheumatologie

Originalien

Z Rheumatol 2020 · 79:312–318
https://doi.org/10.1007/s00393-019-00689-y
Published online: 19 August 2019

S.-C. Bae[1] · **Y. H. Lee**[2,3]

[1] Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea (Republic of)

[2] Department of Rheumatology, Korea University College of Medicine, Seoul, Korea (Republic of)

[3] Division of Rheumatology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea (Republic of)

Association between plasminogen activator inhibitor-1 (*PAI-1*) *4G/5G* polymorphism and circulating PAI-1 level in systemic lupus erythematosus and rheumatoid arthritis

A meta-analysis

Introduction

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized with B cell hyperactivity, high level autoantibody production, immune-complex deposition, and multiple organ damage [26]. Renal involvement is observed in up to 60% of patients with SLE, and lupus nephritis (LN) is a predominant cause of morbidity and mortality in SLE. Rheumatoid arthritis (RA), a chronic autoimmune inflammatory disease, predominantly affects the synovial joints and causes hyperplasia of synovial cells and formation of new blood vessels; it is also associated with bone erosion and joint deformity [20]. Although the exact causes are not completely understood, genetic and environmental factors are thought to contribute to the pathogenesis of SLE and RA [15].

Plasminogen activator inhibitor-1 (PAI-1), a member of the serine protease inhibitor family, is involved in blood coagulation and serves as an inhibitor of the endogenous fibrinolytic system [28]. Plasminogen activators catalyze the conversion of plasminogen to plasmin, which degrades the extracellular matrix components through the activation of matrix metalloproteinases (MMPs). MMPs are recognized as important mediators of cartilage and bone destruction in RA [19]. The *PAI-1* gene is located on chromosome 7q22, and the polymorphism 4G/5G at −675 site in the promotor region of *PAI-1* (rs1799889) is associated with increased plasma PAI-1 levels [7]. The levels of PAI-1 in individuals with the *PAI-1 4G/4G* genotype are approximately 25% higher than in those with the *5G/5G* genotype [29].

Studies on circulating PAI-1 levels in patients with SLE/LN and RA and corresponding control subjects have reported heterogeneous results, and *PAI-1* polymorphisms have been known to be associated with the susceptibility to SLE and RA in some but not all studies [1, 2, 9, 22–24, 27, 30, 31]. To overcome the limitations of individual studies and resolve inconsistencies, we performed this meta-analysis [14, 16, 17]. The aim of this meta-analysis was to systematically review the evidence on the association between the *PAI-1 4G/5G* polymorphism and susceptibility to SLE/LN and RA as well as the relationship between circulating PAI-1 levels and these diseases.

Materials and Methods

Identification of eligible studies and data extraction

We performed a literature search for studies that examined the association between the *PAI-1* polymorphism and SLE/LN or RA, and circulating (serum or plasma) PAI-1 levels in patients with SLE/LN or RA and control subjects. We searched PubMed and EMBASE databases to identify all available articles (up to April 2019). The following keywords and subject terms were used: "plasminogen activator inhibitor-1", "serum or plasma", "polymorphism", "systemic lupus erythematosus", and "rheumatoid arthritis." In addition, the references cited were reviewed to identify additional studies excluded from the above-mentioned electronic databases. Eligible studies included (1) case–control

Table 1 Characteristics of individual studies included in the meta-analysis: PAI-1 polymorphism

Author	Country	Ethnicity	Disease	Number		4G allele (%)		Association			
				Case	Control	Case	Control	OR	95% CI		*p* value
Munoz, 2014 [23]	Argentina	Caucasian	SLE	179	223	40.2	46.0	0.791	0.597	1.048	0.103
Reshetniak, 2013 [24]	Russia	Caucasian	SLE	62	30	54.0	60.0	0.784	0.419	1.465	0.445
Bicakcigil, 2011 [2]	Turkey	Caucasian	SLE	93	84	47.3	46.4	1.036	0.682	1.574	0.868
Gong, 2007 [9]	China	Asian	SLE	101	128	57.9	57.0	1.037	0.714	1.506	0.848
Wang, 2001 [31]	China	Asian	SLE	118	103	59.3	59.2	1.004	0.686	1.469	0.983
Tassies, 2000 [30]	Spain	Caucasian	SLE	104	100	49.5	47.0	1.106	0.750	1.631	0.611
Munoz-1, 2014 [23]	Argentina	Caucasian	LN	86	223	37.2	46.0	0.697	0.486	0.999	0.050
Gong-1, 2007 [9]	China	Asian	LN	101	128	57.9	57.0	1.037	0.714	1.506	0.848
Wang-1, 2001 [31]	China	Asian	LN	93	103	59.1	59.2	0.997	0.666	1.492	0.987
Munoz, 2012 [22]	Mexico	LA	RA	100	100	33.0	35.0	0.915	0.605	1.384	0.673
Arlestig, 2007 [1]	Sweden	Caucasian	RA	467	672	54.3	57.8	0.866	0.732	1.025	0.095

Ref References, *SLE* Systemic lupus erythematosus, *LN* Lupus nephritis, *RA* Rheumatoid arthritis, *OR* Odds ratio, *CI* Confidence interval, *LA* Latin American, *PAI-1* plasminogen activator inhibitor 1

Table 2 Characteristics of individual studies included in the meta-analysis: PAI-1 level

Author	Country	Ethnicity	Disease	Sample size (number)		PAI-1 level (mean, ng/mL)		Statistical findings		
				Case	Controls	SLE	Controls	SMD[a]	Magnitude[a]	*p* value
Singh, 2013 [27]	Indian	Asian	SLE	10	10	19.23	15.00	0.712	Medium	0.123
Bicakcigil, 2011 [2]	Turkey	Caucasian	SLE	93	84	15.70	12.10	0.296	Small	0.050
Singh-1, 2013 [27]	Indian	Asian	RA	10	10	20.53	15.00	0.949	Large	0.044
Munoz, 2012 [22]	Mexico	Latin American	RA	113	28	19.60	21.10	–0.116	NA	0.582

PAI-1 Plasminogen activator inhibitor 1, *SMD* Standard mean difference, *SLE* Systemic lupus erythematosus, *RA* Rheumatoid arthritis, *NA* Not available
[a]Magnitude of Cohen's d effect size (SMD): 0.2–0.5, small effect: 0.5–0.8, medium effect: ≥ 0.8, large effect

studies, (2) studies evaluating the *PAI-1 4G/5G* polymorphism in case and control groups, and (3) studies providing data on PAI-1 levels in case and control groups. Language was restricted to English. Studies (1) containing overlapping or insufficient data or (2) reviews or case reports were excluded. Data on methods and results were extracted from original studies by two independent reviewers and discrepancies between the reviewers were resolved by consensus. The meta-analysis was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [21]. The following information was extracted from each study: primary author, year of publication, country, ethnicity, number of participants, mean and standard deviation (SD) of PAI-1 levels, and genotype and allele frequencies of the *PAI-1 4G/5G* polymorphism. Data presented as medians, interquartile ranges, or ranges were subjected to mean and SD computation using previously described formulae [13, 25].

Evaluation of statistical association

We performed meta-analyses using (1) allelic contrast, (2) recessive models, (3) dominant models, and (4) homozygote contrast of the PAI-1 polymorphism. In addition, we evaluated the relationship between the PAI-1 level in patients with SLE/LN or RA in this meta-analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for dichotomous data. For continuity of data, results were presented as standardized mean differences (SMDs) and 95% CI. SMDs were calculated by dividing the mean difference between two groups according to the pooled SD, and used when different scales were integrated to measure the same concept. This measure compares case and control arms in terms of standardized scores. The magnitude of SMD was considered as follows: 0.2–0.5, small effect; 0.5–0.8, medium effect; ≥0.8, large effect [3]. We assessed within-study and between-study variations and heterogeneities using Cochran's Q-statistics [6]. The heterogeneity test was used to evaluate the null hypothesis that all included studies that had evaluated the same effect. The random effect model was used in cases wherein a significant Q-statistic ($p < 0.10$) indicated heterogeneity [4]. In other cases, the fixed effect model was applied that assumed all studies estimated the same underlying effect and considered only the within-study variation [6]. We quantified the effect of heterogeneity using $I^2 = 100\% \times (Q\text{-}df)/Q$ [10], where I^2 is the measure of the degree of inconsistency between studies and investigates whether the percentage total variation across studies is attributable to heterogeneity rather than chance. I^2 values ranged between 0 and 100% and the values of 25%, 50%, and 75% were referred to as low, moderate,

Z Rheumatol 2020 · 79:312–318 https://doi.org/10.1007/s00393-019-00689-y

S.-C. Bae · Y. H. Lee

Association between plasminogen activator inhibitor-1 (*PAI-1*) *4G/5G* polymorphism and circulating PAI-1 level in systemic lupus erythematosus and rheumatoid arthritis. A meta-analysis

Abstract

Objective. This study systemically reviewed the evidence regarding the association between plasminogen activator inhibitor-1 (*PAI-1*) *4G/5G* polymorphism and susceptibility to systemic lupus erythematous (SLE)/lupus nephritis (LN) and rheumatoid arthritis (RA) and the relationship between circulating PAI-1 levels and SLE/LN and RA.

Methods. We conducted a meta-analysis on the association between the *PAI-1 4G/5G* polymorphism and SLE/LN or RA risk and serum/plasma PAI-1 levels in patients with SLE/LN and RA and healthy controls.

Results. Nine articles including 657 patients with SLE and 668 controls and 567 patients with RA and 772 controls were included. No association was revealed between SLE and *PAI-1 4G* allele in all study subjects (odds ratio [OR] = 0.944, 95% confidence interval [CI] = 0.808–1.102, $p = 0.463$). Ethnicity-based stratification showed no association between the *PAI-1 4G* allele and SLE among Europeans and Asians. No association was detected between LN and RA and the *PAI-1 4G* allele (OR = 0.886, 95% CI = 0.713–1.102, $p = 0.278$; OR = 0.8736, 95% CI = 0.747–1.020, $p = 0.088$, respectively) or between SLE/LN and RA and the *PAI-1 4G/5G* polymorphism using the recessive and dominant models and homozygote contrast. The circulating PAI-1 level was significantly higher in the SLE group than in the control group (standardized mean difference [SMD] = 0.337, 95% CI = 0.057–0.619, $p = 0.019$). However, serum/plasma PAI-1 level showed no significant difference between RA and control group (SMD = 0.333, 95% CI = –0.6989–1.35, $p = 0.527$).

Conclusions. There was no association between the *PAI-1 4G/5G* polymorphism and SLE/LN and RA development and significantly higher levels of circulating PAI-1 were observed in patients with SLE but not in those with RA.

Keywords

Matrix metalloproteinases · Serine proteinase inhibitors · Polymorphism, genetic · Autoimmune diseases · Case-control studies

Zusammenhang zwischen *PAI-1*(Plasminogenaktivator-Inhibitor)-*4G/5G*-Polymorphismus und zirkulierendem PAI-1 bei systemischem Lupus erythematosus und rheumatoider Arthritis. Eine Metaanalyse

Zusammenfassung

Zielsetzung. In der Studie wurde systematisch die Evidenz für einen Zusammenhang zwischen dem *PAI-1*(Plasminogenaktivator-Inhibitor)-*4G/5G*-Polymorphismus und der Suszeptibilität für systemischen Lupus erythematous (SLE)/Lupusnephritis (LN) bzw. rheumatoide Arthritis (RA) und für eine Beziehung zwischen der Höhe an zirkulierendem PAI-1 und SLE/LN bzw. RA untersucht.

Methoden. Wir führten eine Metaanalyse durch zum Zusammenhang zwischen *PAI-1-4G/5G*-Polymorphismus und SLE/LN- bzw. RA-Risiko sowie zwischen Serum/Plasma-PAI-1-Level bei Patienten mit SLE/LN und RA sowie gesunden Kontrollen.

Ergebnisse. Neun Publikationen (657 SLE-Patienten, 668 Kontrollen; 567 RA-Patienten, 772 Kontrollen) wurden in die Metaanalyse aufgenommen. Es zeigte sich kein Zusammenhang zwischen SLE und *PAI-1-4G*-Allel bei allen Teilnehmenden (Odds Ratio [OR] 0,944, 95 %-Konfidenzintervall [KI] 0,808–1,102; $p = 0,463$). Eine Stratifizierung nach Ethnizität zeigte keinen Zusammenhang zwischen dem *PAI-1-4G*-Allel und SLE bei Europäern und Asiaten, ebenso bestand keiner zwischen LN bzw. RA und dem *PAI-1-4G*-Allel (OR 0,886, 95 %–KI 0,713-1,102, $p = 0,278$; OR 0,8736, 95 %-KI 0,747-1,020, $p = 0,088$) bzw. zwischen SLE/LN bzw. RA und dem *PAI-1-4G/5G*-Polymorphismus unter Verwendung der rezessiven und dominanten Modelle und des „homozygote contrast". Der zirkulierende PAI-1-Wert war in der SLE-Gruppe signifikant höher als in der Kontrollgruppe (standardisierte mittlere Differenz [SMD] 0,337, 95 %-KI 0,057–0,619, $p = 0,019$), doch der PAI-1-Spiegel im Serum/Plasma wies keinen signifikanten Unterschied auf zwischen RA- und Kontrollgruppe (SMD 0,333, 95 %-KI -0,6989–1,35, $p = 0,527$).

Schlussfolgerungen. Es gab keinen Zusammenhang zwischen dem *PAI-1-4G/5G*-Polymorphismus und SLE/LN- bzw. RA-Entwicklung. Signifikant erhöhte Level an zirkulierendem PAI-1 wurden bei SLE-, nicht aber bei RA-Patienten beobachtet.

Schlüsselwörter

Matrixmetalloproteinasen · Serinproteinase-inhibitoren · Genetischer Polymorphismus · Autoimmunerkrankungen · Fall-Kontroll-Studien

and high estimate, respectively [10]. Statistical manipulation was performed with the Comprehensive Meta-Analysis computer program (Biostat, Englewood, NJ, USA).

Evaluation of heterogeneity and publication bias

To examine the potential sources of heterogeneity observed in the meta-analysis, we performed a subgroup analysis based on ethnicity. Sensitivity test was used to assess the influence of each individual study on the pooled OR after the omission of individual studies. The funnel plots often used to detect publication bias require diverse study types with varying sample sizes. Furthermore, their interpretations involve subjective judgment. Therefore, we assessed publication bias using Egger's linear regression test [5], which measures funnel plot asymmetry using a natural logarithmic scale of the ORs.

Table 3 Meta-analysis of the association between the *PAI-1 4G/5G* polymorphism and SLE, LN, and RA

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	*p* value	Model	*p* value	I^2
PAI-1 4G vs. *5G*	SLE	6	0.944	0.808–1.102	0.463	F	0.696	0
	European	4	0.906	0.749–1.097	0.312	F	0.474	0
	Asian	2	1.021	0.782–1.332	0.880	F	0.905	0
	LN	3	0.886	0.713–1.102	0.278	F	0.257	26.3
	RA	2	0.873	0.747–1.020	0.088	F	0.812	0
4G4G vs. *4G5G* + *5G5G* (recessive)	SLE	6	0.978	0.763–1.254	0.860	F	0.563	0
	European	4	0.877	0.637–1.209	0.423	F	0.537	0
	Asian	2	1.152	0.777–1.708	0.481	F	0.428	0
	LN	3	0.971	0.685–1.376	0.868	F	0.130	50.9
	RA	2	0.854	0.668–1.092	0.208	F	0.298	7.70
4G4G + *4G5G* vs. *5G5G* (dominant)	SLE	6	0.876	0680–1.129	0.307	F	0.848	0
	European	4	0.883	0.658–1.185	0.408	F	0.701	0
	Asian	2	0.857	0.522–1.409	0.544	F	0.4448	0
	LN	3	0.748	0.520–1.074	0.116	F	0.766	0
	RA	2	0.814	0.625–1.060	0.126	F	0.240	23.1
4G4G vs. *5G5G*	SLE	6	0.878	0.643–1.200	0.414	F	0.767	0
	European	4	0.838	0.575–1.222	0.359	F	0.505	0
	Asian	2	0.971	0.558–1.692	0.918	F	0.855	0
	LN	3	0.738	0.469–1.161	0.188	F	0.361	1.79
	RA	2	0.713	0.516–0.984	0.040	F	0.707	0

PAI-1 Plasminogen activator inhibitor 1, *OR* Odds ratio, *CI* Confidence interval, *R* Random effect model, *F* Fixed effect model, *SLE* Systemic lupus erythematosus, *LN* Lupus nephritis, *RA* Rheumatoid arthritis

Results

Studies included in the meta-analysis

We identified 209 studies from electronic and manual search methods. Eighteen of these were selected for full-text review based on the title and abstract. Of these 18 studies, nine were excluded owing to duplicate data, data on other polymorphisms, or no data on controls. Thus, nine articles satisfied the inclusion criteria [1, 2, 9, 22–24, 27, 30, 31]. These articles comprised 657 patients with SLE and 668 controls and 567 patients with RA and 772 controls (**Tables 1 and 2**). Six studies examined *PAI-1* polymorphisms in SLE and control groups, and two studies provided PAI-1 levels in SLE and control groups (**Tables 1 and 2**). Furthermore, two studies examined *PAI-1* polymorphisms in RA and control groups, while two studies indicated PAI-1 levels in RA and control groups. The characteristic features of the studies included in the meta-analysis are summarized in **Tables 1 and 2**.

Meta-analysis of the *PAI-1* polymorphism and susceptibility to SLE/LN or RA

The meta-analysis of all study subjects revealed the absence of any association between SLE and *PAI-1 4G* allele (OR = 0.944, 95% CI = 0.808–1.102, $p = 0.463$) (**Table 3**; **Fig. 1**). In addition, ethnicity-based stratification indicated no association between *PAI-1 4G* allele and SLE among European and Asian populations (**Table 3**). No association was noted between LN and RA and *PAI-1 4G* allele (OR = 0.886, 95% CI = 0.713–1.102, $p = 0.278$; OR = 0.8736, 95% CI = 0.747–1.020, $p = 0.088$, respectively) (**Table 3**; **Fig. 1**) as well as between SLE/LN and RA and the *PAI-1 4G/5G* polymorphism using the recessive and dominant models and homozygote contrast (**Table 3**).

Meta-analysis of circulating PAI-1 level in patients with SLE or RA and controls

The meta-analysis result revealed the significantly higher levels of circulating PAI-1 in SLE group than in control group (SMD = 0.337, 95% CI = 0.057–0.619, $p = 0.019$) (**Table 4**; **Fig. 2**). However, the serum/plasma PAI-1 level was not significantly different between RA and control group (SMD = 0.333, 95% CI = –0.6989–1.35, $p = 0.527$) (**Table 3**; **Fig. 2**).

Heterogeneity, sensitivity test, and publication bias

No between-study heterogeneity was detected during the meta-analysis of the *PAI-1* polymorphism in patients with SLE (**Table 3**). However, between-study heterogeneity was observed during the meta-analyses of PAI-1 levels in RA but not in SLE (**Table 4**). Sensitivity analysis results showed that no individual study had a significant effect

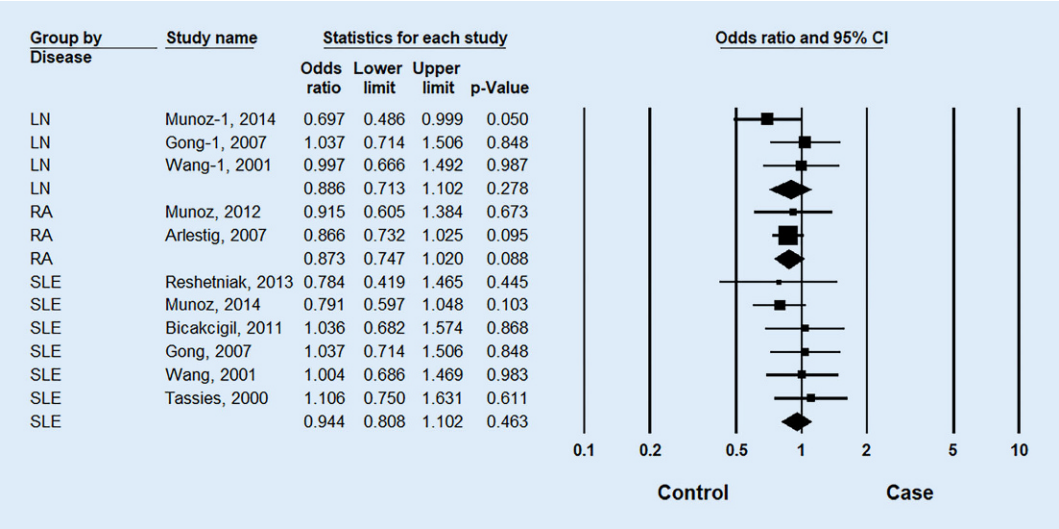

Fig. 1 ◀ Odds ratios (ORs) and 95% confidence intervals (*CIs*) of individual studies and pooled data for allelic association between the plasminogen activator inhibitor 1 (*PAI-1*) *4G/5G* polymorphism and systemic lupus erythematosus (*SLE*), lupus nephritis (*LN*), and rheumatoid arthritis (*RA*)

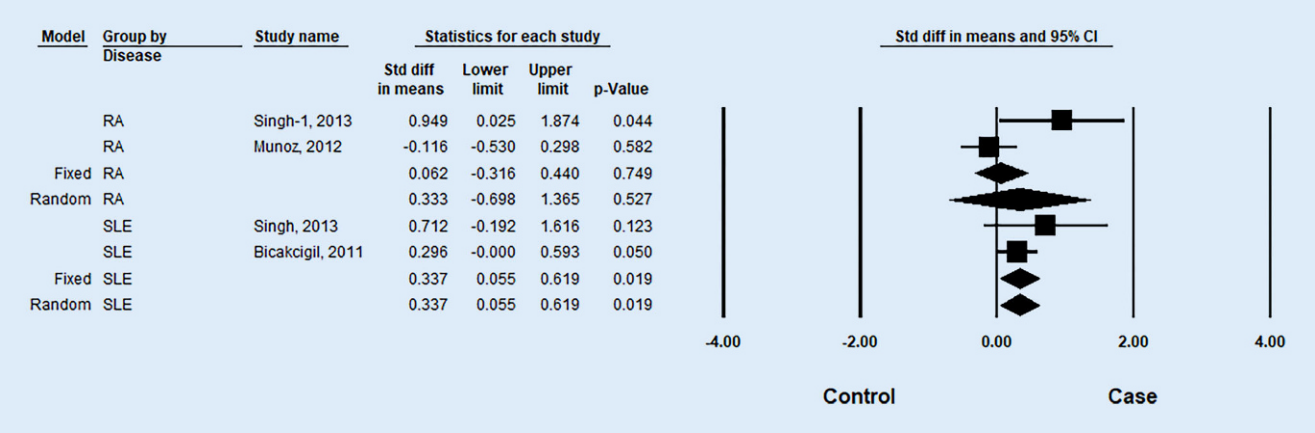

Fig. 2 ▲ Meta-analysis of the relationship between plasminogen activator inhibitor 1 (PAI-1) levels and systemic lupus erythematosus (*SLE*) and rheumatoid arthritis (*RA*). *Std diff* standard difference

on the pooled OR, indicative of the robustness of the results of this meta-analysis. Publication bias causes a disproportionate number of positive studies and poses a problem for meta-analyses. It was difficult to interpret the funnel plot used to detect publication bias because the number of studies included in the analysis was relatively small. However, we found no evidence of publication bias for all study subjects (Egger's regression test $p > 0.1$).

Discussion

In this meta-analysis, we combined the evidence of the association between the *PAI-1 4G/5G* polymorphism and susceptibility to SLE/LN and RA as well as the relationship between circulating PAI-1 levels and these diseases. We found no association between the *PAI-1 4G/5G* polymorphism and SLE/LN and RA, and the levels of circulating PAI-1 were significantly higher in the SLE group than in the control group. However, the PAI-1 level was not significantly different between the RA and control groups. These data indicate that the *PAI-1 4G/5G* polymorphism is not associated with SLE/LN and RA risk and that an increase in PAI-1 level is associated with SLE. Different components of the hemostatic system such as thrombin, fibrinogen, coagulation factor XIII and factors of the fibrinolytic system are mediators of inflammatory processes [11]. And fibrinogen and factor XIII A-subunit genotypes interactively influence C-reactive protein levels during inflammation, suggesting these haemostatic gene variants modulate inflammation by influencing fibrin crosslinking [12].

We found no association between SLE/LN as well as RA and *PAI-1* polymorphism. Our meta-analysis results for the *PAI-1 4G/5G* polymorphism are contradictory to the results of functional studies indicating the *PAI-1 4G/5G* polymorphism to be a major determinant of plasma PAI-1 levels. The *4G/4G* genotype has been associated with higher PAI-1 level as compared with *5G/5G* genotype [8]. Thus, the *PAI-1 4G/5G* polymorphism may affect PAI-1 level. Epidemiologic results occasionally do not coincide with the results of functional studies because SLE and RA are complex diseases, and multiple genes, different genetic backgrounds, and en-

Table 4 Meta-analysis of the association between circulating PAI-1 level and SLE and RA

Population	No. of studies	Test of association			Test of heterogeneity		
		SMD[a]	95% CI	*p* value	Model	*p* value	I^2
SLE	2	0.337	0.055–0.619	0.019	F	0.392	0
RA	2	0.333	–0.698–1.365	0.527	R	0.032	76.4

PAI-1 Plasminogen activator inhibitor-1, *SMD* Standard mean difference, *SLE* Systemic lupus erythematosus, *RA* Rheumatoid arthritis, *F* Fixed effect model, *R* Random effect model
[a]Magnitude of Cohen's d effect size (SMD): 0.2–0.5, small effect: 0.5–0.8, medium effect: ≥0.8, large effect

vironmental factors contribute to their development. Moreover, our meta-analysis results for *PAI-1* polymorphisms may be affected by a type II error (false-negative). We found that high PAI-1 level correlated with SLE, but no relationship was detected between PAI-1 level and RA. We cannot rule out the possibility that circulating PAI-1 level is increased in RA, as our study evaluating PAI-1 level in RA had a low statistical power. This is because only two studies with few subjects had sufficient relevant data, and our meta-analysis results for RA were not robust.

This meta-analysis differs from a previous meta-analysis conducted on the relationship between the *PAI-1 4G/5G* polymorphism and SLE risk by Li et al. [18] We performed this meta-analysis on the *PAI-1 4G/5G* polymorphism in LN and control subjects along with additional meta-analyses on the *PAI-1 4G/5G* polymorphism and RA and the relationship between circulating PAI-1 levels and SLE and RA. The result obtained in this study, that there is no association between the *PAI-1 4G/5G* polymorphism and SLE/LN, is in agreement with that of a previous study.

This meta-analysis has some limitations. First, most included studies had small sample sizes. Thus, the meta-analysis may be underpowered. Second, the studies included in the meta-analysis were heterogeneous in terms of demographic characteristics and clinical features. The heterogeneity, confounding factors, and limited clinical information provided by the study populations may affect the results. Third, publication bias could have adversely affected the analysis because studies that produced negative results may be unpublished or have been missed. Although Egger's regression test was used, the possibility of bias cannot be eliminated. Fourth, the *PAI-1 4G/5G* polymorphism may be associated with clinical manifestations, such as atherosclerosis and thrombosis aside from disease susceptibility because PAI-1 is a major regulator of the fibrinolytic system [28]. However, the limited amount of available data on the association between the *PAI-1 4G/5G* polymorphism and clinical features prevented an in-depth meta-analysis. Fourth, only one factor has been assessed, while SLE is a polygenic disease and the coagulation as well as fibrinolytic systems are multifactorial. Nevertheless, this meta-analysis also has its strengths. To the best of our knowledge, this meta-analysis is the first study that provides combined evidence for PAI-1 levels and polymorphisms in patients with SLE or RA. Individual studies included a population size ranging from 62 to 179 in SLE and 100 to 467 in RA alone, but our pooled analysis had 657 patients with SLE and 567 patients with RA. In comparison with individual reports, our study provides data that are more accurate by increasing the statistical power and resolution following pooling of the results of independent analyses.

In conclusion, our meta-analysis demonstrate that the *PAI-1 4G/5G* polymorphism shows no association with susceptibility to SLE/LN and RA and that the circulating PAI-1 level is significantly higher in patients with SLE but not in those with RA. This meta-analysis suggests that PAI-1 likely plays a role in the pathogenesis of SLE. Further studies are warranted to elucidate the direct contribution of PAI-1 to the pathogenesis of SLE.

Corresponding address

Y. H. Lee, MD, PhD
Division of Rheumatology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine
73, Inchon-ro, Seongbuk-gu, 02841 Seoul, Korea (Republic of)
lyhcgh@korea.ac.kr

Acknowledgements. This study was supported in part by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Ministry of Science & ICT (NRF-2017M3A9B4050335), Republic of Korea.

Compliance with ethical guidelines

Conflict of interest S.-C. Bae and Y. H. Lee declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

References

1. Arlestig L, Wallberg Jonsson S, Stegmayr B et al (2007) Polymorphism of genes related to cardiovascular disease in patients with rheumatoid arthritis. Clin Exp Rheumatol 25(6):866–871
2. Bicakcigil M, Tasan D, Tasdelen N et al (2011) Role of fibrinolytic parameters and plasminogen activator inhibitor 1 (PAI-1) promoter polymorphism on premature atherosclerosis in SLE patients. Lupus 20(10):1063–1071
3. Cohen J (1988) Statistical power analysis for the behavioral sciences, 2nd edn. Erlbaum, Hillsdale, New Jersey
4. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188
5. Egger M, Davey Smith G, Schneider M et al (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634
6. Egger M, Smith GD, Phillips AN (1997) Meta-analysis: principles and procedures. BMJ 315(7121):1533–1537
7. Eriksson P, Kallin B, van 't Hooft FM et al (1995) Allele-specific increase in basal transcription of the plasminogen-activator inhibitor 1 gene is associated with myocardial infarction. Proc Natl Acad Sci U S A 92(6):1851–1855
8. Festa A, D'Agostino R Jr, Rich SS et al (2003) Promoter (4G/5G) plasminogen activator inhibitor-1 genotype and plasminogen activator inhibitor-1 levels in blacks, Hispanics, and non-Hispanic whites: the Insulin Resistance Atherosclerosis Study. Circulation 107(19):2422–2427
9. Gong R, Liu Z, Li L (2007) Epistatic effect of plasminogen activator inhibitor 1 and beta-fibrinogen genes on risk of glomerular microthrombosis in lupus nephritis: interaction with environmental/clinical factors. Arthritis Rheum 56(5):1608–1617
10. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21(11):1539–1558

11. Hoppe B, Dörner TJNRR (2012) Coagulation and the fibrin network in rheumatic disease: a role beyond haemostasis. Nat Rev Rheumatol 8(12):738–746
12. Hoppe B, Häupl T, Skapenko A et al (2012) Fibrinogen and factor XIII A-subunit genotypes interactively influence C-reactive protein levels during inflammation. Ann Rheum Dis 71(7):1163–1169
13. Hozo SP, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5:13
14. Lee YH, Bae S-C, Choi SJ et al (2012) Associations between TNFAIP3 gene polymorphisms and rheumatoid arthritis: a meta-analysis. Inflamm Res 61(6):635–641
15. Lee YH, Bae S-C, Choi SJ et al (2012) Genome-wide pathway analysis of genome-wide association studies on systemic lupus erythematosus and rheumatoid arthritis. Mol Biol Rep 39(12):10627–10635
16. Lee YH, Bae SC, Song GG (2013) Hepatitis B virus reactivation in HB s A g-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARD s. Int J Rheum Dis 16(5):527–531
17. Lee YH, Song GG (2017) Comparative efficacy and safety of secukinumab and adalimumab in patients with active ankylosing spondylitis: A Bayesian network meta-analysis of randomized controlled trials. J Rheum Dis 24(4):211–219
18. Li W, Mao S, Wu L et al (2019) Association between the PAI-1 4G/5G gene polymorphism and the risk of systemic lupus Erythematosus/lupus nephritis. Crit Rev Eukaryot Gene Expr 29(1):85–94
19. Ma Z, Paek D, Oh C (2009) Plasminogen activator inhibitor-1 and asthma: role in the pathogenesis and molecular regulation. Clin Exp Allergy 39(8):1136–1144
20. Mellado M, Martínez-Muñoz L, Cascio G et al (2015) T cell migration in rheumatoid arthritis. Front Immunol 6:1–12
21. Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 6(7):e1000097
22. Munoz-Valle JF, Ruiz-Quezada SL, Oregon-Romero E et al (2012) PAI-1 mRNA expression and plasma level in rheumatoid arthritis: relationship with 4G/5G PAI-1 polymorphism. Rheumatol Int 32(12):3951–3956
23. Munoz SA, Aranda F, Allievi A et al (2014) 4G/5G plasminogen activator inhibitor-1 and -308 A/G tumor necrosis factor-alpha promoter gene polymorphisms in Argentinean lupus patients: focus on lupus nephritis. Clin Exp Med 14(1):83–89
24. Reshetniak TM, Ostriakova EV, Patrusheva NL et al (2013) Plasminogen activator inhibitor type 1 gene polymorphism and thromboses in patients with antiphospholipid syndrome. Ter Arkh 85(1):76–84
25. Ridout KK, Ridout SJ, Price LH et al (2016) Depression and telomere length: a meta-analysis. J Affect Disord 191:237–247
26. Ruiz-Irastorza G, Khamashta MA, Castellino G et al (2001) Systemic lupus erythematosus. Lancet 357(9261):1027–1032
27. Singh NK, Gupta A, Behera DR et al (2013) Elevated plasminogen activator inhibitor type-1 (PAI-1) as contributing factor in pathogenesis of hypercoagulable state in antiphospholipid syndrome. Rheumatol Int 33(9):2331–2336
28. Sprengers ED, Kluft C (1987) Plasminogen activator inhibitors. Blood 69(2):381–387
29. Stegnar M, Uhrin P, Peternel P et al (1998) The 4G/5G sequence polymorphism in the promoter of plasminogen activator inhibitor-1 (PAI-1) gene: relationship to plasma PAI-1 level in venous thromboembolism. Thromb Haemost 79(5):975–979
30. Tassies D, Espinosa G, Munoz-Rodriguez FJ et al (2000) The 4G/5G polymorphism of the type 1 plasminogen activator inhibitor gene and thrombosis in patients with antiphospholipid syndrome. Arthritis Rheum 43(10):2349–2358
31. Wang AY, Poon P, Lai FM et al (2001) Plasminogen activator inhibitor-1 gene polymorphism 4G/4G genotype and lupus nephritis in Chinese patients. Kidney Int 59(4):1520–1528

Bestmögliche Versorgung von Rheumapatienten mit COVID-19

EULAR schaltet Forschungs-Datenbank live

Die Europäische Liga gegen Rheuma (EULAR) hat soeben eine europäische Forschungs-Datenbank eingerichtet. Ziel ist die Überwachung und Meldung von COVID-19-Fällen bei Kindern- und Erwachsenen mit rheumatischen und muskuloskelettalen Erkrankungen.

EULAR ermutigt Rheumatologen aus ganz Europa, alle ihnen bekannten Fälle von COVID-19 bei Patienten mit rheumatischen Erkrankungen, unabhängig vom Schweregrad (einschließlich asymptomatischer Patienten, die durch Vorsorgeuntersuchungen im öffentlichen Gesundheitswesen entdeckt wurden), auf der Plattform zu melden.
Das Verstehen weniger schwerer oder sogar leichter Fälle wird dazu beitragen können, das Verständnis für diejenigen, die die schwerste Form der Erkrankung entwickeln, zu verbessern.

Es handelt sich um ein europäisches Projekt, das eng mit der Globalen Allianz für Rheumatologie COVID-19 zusammenarbeitet.

Die Datenbank kann über die Webseite aufgerufen werden:
https://www.eular.org

Besuchen Sie die Datenbank der Globalen Rheumatologie-Allianz hier:
https://rheum-covid.org

EULAR hat zudem ein Statement veröffentlicht:
https://www.eular.org/policy_statement_on_covid_19.cfm
Darin fordern Experten eine besondere Anleitung und Unterstützung von Patienten mit einer rheumatologischen Erkrankung während der laufenden COVID-19-Pandemie ein.

Quelle: EULAR