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Profiles of Plasminogen Activator Inhibitor-1 Levels in Healthcare Workers with Latent Tuberculosis and Non-Latent Tuberculosis Infections (Healthy Control)

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Abstract

BACKGROUND: *Mycobacterium tuberculosis* infection causes the release of pro-inflammatory cytokines affecting hemostasis. Although the plasminogen activator inhibitor-1 (PAI-1) has a vital role in the fibrinolysis system, little is known about its profile among people with latent tuberculosis (TB).

METHODS: This is a cross-sectional study that involves 80 healthcare workers. The study was conducted in two academic medical centers of Makassar city, Indonesia, from September to October 2021. PAI-1 levels were measured using the enzyme-linked immunosorbent assay technique. The statistical test results were significant if $p < 0.05$.

RESULTS: Although there was no statistically significant difference ($p > 0.05$) in PAI-1 levels, PAI-1 level among participants in the latent TB infection (LTBI) group was found to be lower (4.9 ng/mL) than in the healthy control group (6.0 ng/mL). In addition, participants in the LTBI group with a history of being infected (9.6 ng/mL) with the COVID-19 had higher PAI-1 levels than those who had never been infected (2.3 ng/mL), which is statistically significant ($p = 0.004$). Although there was no statistically significant difference ($p > 0.05$) in PAI-1 levels among participants in the healthy control group, those with a history of being infected (6.7 ng/mL) demonstrated higher PAI-1 levels than those who had never been infected (4.8 ng/mL).

CONCLUSIONS: PAI-1 levels were lower in LTBI participants, which potentially is due to more participants in the healthy control group having a history of COVID-19 infection.

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. Although *M. tuberculosis* itself has been known for hundreds of years and a number of eradication efforts have been carried out, this disease remains a major health problem around the world [1].

Globally, there were an estimated 10 million new cases of TB in 2017 [2]. Less than ten new cases occur per 100,000 population in developed countries, while in countries with a high burden of TB, including Indonesia, this figure reaches 150–500/100,000 population. In addition, Indonesia accounts for 8% of all TB cases worldwide. In 2017, there were 420,994 new cases of TB in Indonesia, with a prevalence of 759/100,000 population aged ≥15 years in 2013–2014 [3].

In most infected individuals, TB can be clinically or microbiologically latent for several years. This condition is known as latent TB infection (LTBI) [4]. However, in the event of a failure of the immune system, the bacteria multiply, causing a case of active TB [4]. LTBI itself is estimated to affect 1.7 million people worldwide [5]. A cross-sectional study by Hamidah *et al*. (2020) at two Indonesian hospitals on 128 healthcare workers found that the prevalence of LTBI was 61.7% (n = 79) [5].

M. tuberculosis infection causes the release of proinflammatory cytokines; interleukin IL-1, IL-6, and IL-8, as well as tumor necrosis factor, affecting hemostasis, namely, an increase in procoagulation activity, a decrease in anticoagulant factors, and suppression of the fibrinolytic system that causes hypercoagulable states [6]. These proinflammatory cytokines are an important stimulator of plasminogen activator inhibitor-1 (PAI-1) expression [7].

PAI-1 itself is an important regulator of inflammation and fibrinolysis. It acts as an inhibitor of plasminogen activation, tissue-type plasminogen

activator (t-PA), and urokinase-type plasminogen activator (u-PA), as well as regulate systemic fibrinolysis mechanisms [7]. Meanwhile, the increase in PAI-1 activity can be influenced by several factors including age, gender, and obesity [8].

Age has a close relationship with thrombosis, where there is a decrease in the fibrinolytic system which results in prothrombotic changes in the hemostatic mechanism [8]. Gleerup and Winther (1995) observed the effect of age on platelet function and fibrinolytic activity. The results of this study showed that in men aged 44–72 years (n = 12), there was a decrease in the fibrinolysis system characterized by a lengthening of the euglobulin clot lysis time and an increase in PAI-1 and t-PA, which were statistically significant ($p < 0.01$) [9]. This occurs due to the increased risk of metabolic conditions such as insulin resistance and atherothrombotic. Excess adipose tissue increases PAI-1 production since it is partially produced and released in adipose tissue. Eriksson *et al*. examined PAI-1 activity in adipose tissue in their study on obese and non-obese subjects and reported that PAI-1 secretion in adipose tissue increased in obese subjects [10]. In regard to gender, PAI-1 in women is associated with the roles of estrogen in nitric oxide synthesis, fibrinolytic balance, lipid metabolism, and extracellular matrix production [11].

This study was conducted during the COVID-19 pandemic, where many healthcare workers were infected with COVID-19. It is known that there is an association between elevated PAI-1 levels in patients with a history of COVID-19, where hypercoagulable states may occur. COVID-19 survivors are at risk for thrombosis. Activated endothelial cells express increased levels of PAI-1.

Although the PAI-1 has a vital role in the fibrinolysis system, little is known about its profile among people with latent TB. Due to the knowledge gap in the literature exists and the absence of similar studies carried out in Indonesia, hence, an understanding of its profile is deserved further investigation. Therefore, this study aimed to observe the profile of PAI-1 in LTBI.

Methods

Study design and setting

The present study is an observational study with a cross-sectional design. This study was conducted in Wahidin Sudirohusodo Hospital and the Center for Community Lung Health from September to October 2021. These two academic medical centers were part of the healthcare system of Makassar city, South Sulawesi province, Indonesia.

Participants

The research participants in this study were healthcare workers working at the academic medical centers at the time of research. The inclusion criteria of participants are as follows: (1) aged ≥18 years, (2) had been diagnosed with LTBI for the LTBI group and healthy for the control group, and (3) provided consent to participate in the study.

Data collection

Data regarding gender, age, and COVID-19 history were collected through a self-administered questionnaire. Body mass index (BMI) was calculated as each subject weight in kilograms divided by height in meters. Interferon-γ release assay (IGRA) was used to assess LTBI among participants. Furthermore, PAI-1 test was measured using the sandwich technique or enzyme linked immunosorbent assay using the Technoclone GmbH PAI-1 kit.

Ethical statement

This study obtained approval from the Commission for Biomedical Research on Human Participants, Faculty of Medicine, Universitas Hasanuddin (Reference Number: 644/UN4.6.4.5.31/PP36/2021). Participants' rights during and after the completion of this were considered. A written informed consent form was signed, and their responses were kept confidential.

Statistical analysis

Data analyses were conducted with IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA). Mean and standard deviation values were calculated for descriptive statistics measured as continuous variables, while frequencies were obtained for categorical variables. The Kolmogorov–Smirnov and the Mann–Whitney test were used to assess the normality of data. The statistical test results were significant if $p < 0.05$.

Results

Description of participant characteristics

A total of 80 participants were eligible and participated in this study. As displayed in Table 1, participants in the present study were predominantly female (57.5%). A high proportion of participants were aged ≤32 years old (85.0%) and not obese (62.5%). Of the 80 participants who tested for IGRA, 14 (17.5%) participants were positively diagnosed with LTBI.

Table 1: Distribution of Subject Characteristics (n = 80)

Characteristics	n (%)	Mean (SD)	Range
Gender			
Male	34 (42.5)		
Female	46 (57.5)		
Age		32.0 (6.2)	21–53
≤32 years old	68 (85.0)		
>32 years old	12 (15.0)		
Body mass index			
Not obese	50 (62.5)		
Obesity	30 (37.5)		
Interferon-γ gamma release assay			
Positive	14 (17.5)		
Negative	66 (82.5)		
COVID-19 history			
Yes	46 (57.5)		
No	34 (42.5)		

Furthermore, 46 (57.5%) participants reported having a history of COVID-19.

PAI-1 levels in latent TB and healthy control groups

As presented in Table 2, although there was no statistically significant difference ($p > 0.05$) in PAI-1 levels, PAI-1 level among participants in the LTBI group was found to be lower (4.9 ng/mL) than in the healthy control group (6.0 ng/mL).

Table 2: PAI-1 levels in latent TB infection and healthy controls

Group	n	Minimum	Maximum	Mean (SD)	p-value
Latent TB infection	14	1.3	14.6	4.9 (4.5)	0.540
Healthy controls	66	0.4	16.6	6.0 (4.9)	

PAI-1: Plasminogen activator inhibitor-1, TB: Tuberculosis

PAI-1 levels across groups based on participant characteristics

Table 3 displays the PAI-1 levels in latent TB and healthy control groups based on participant characteristics. There was no statistically significant difference in PAI-1 level based on each gender category ($p > 0.05$). However, the observed mean PAI-1 among male participants in the LTBI group was higher in the LTBI group (6.2 ng/mL) than in the healthy control (5.6 ng/mL). On the contrary, the mean PAI-1 level among female participants was lower in the LTBI group (4.6 ng/mL) than in the healthy control group (6.3 ng/mL).

Table 3: PAI-1 levels in latent TB infection and healthy controls by characteristics

Characteristics	Latent TB infection		Healthy controls		p-value
	n	Mean (SD)	n	Mean (SD)	
Gender					
Male	3	6.2 (7.3)	31	5.6 (4.8)	1.000
Female	11	4.6 (3.7)	35	6.3 (5.1)	0.445
Age					
≤32 years old	9	4.6 (4.7)	42	6.5 (5.3)	0.414
>32 years old	5	5.5 (4.5)	24	5.0 (4.1)	0.889
Body mass index					
Not obese	8	5.1 (5.3)	42	5.8 (5.2)	0.765
Obesity	6	4.7 (3.6)	24	6.2 (4.6)	0.527

PAI-1: Plasminogen activator inhibitor-1, TB: Tuberculosis.

Regarding age category, there was no statistically significant difference in PAI-1 level ($p > 0.05$). However, the average PAI-1 level among participants aged ≤32 years was found to be lower in the LTBI group (4.6 ng/mL) compared to the healthy control group (6.5 ng/mL). In contrast, the mean PAI-1 level was higher in the LTBI group (5.5 ng/mL) than in the healthy control group (5.0 ng/mL) among participants aged >32 years.

Similarly, there was no statistically significant difference in PAI-1 level based on each BMI category ($p > 0.05$). However, the average PAI-1 level among non-obese participants was lower in the LTBI group (5.1 ng/mL) than in the healthy control group (5.8 ng/mL). Furthermore, the mean PAI-1 level was higher in the LTBI group (4.7 ng/mL) than in the healthy control group (6.2 ng/mL) among obese participants.

PAI-1 levels in LTBI and healthy control groups with a history of COVID-19

As shown in Table 4, participants in the LTBI group with a history of being infected (9.6 ng/mL) with the COVID-19 had higher PAI-1 levels than those who have never been infected (2.3 ng/mL), which is statistically significant ($p = 0.004$). Although there was no statistically significant difference ($p > 0.05$) in PAI-1 levels among participants in the healthy control group, those with a history of being infected (6.7 ng/mL) demonstrated higher PAI-1 levels than those who had never been infected (4.8 ng/mL).

Table 4: PAI-1 levels in LTBI and healthy controls with risk factors COVID-19

Participants	COVID-19 history				p-value
	Yes		No		
	n	Mean (SD)	n	Mean (SD)	
Latent TB infection	5	9.6 (4.7)	9	2.3 (1.0)	0.004*
Healthy controls	41	6.7 (5.1)	25	4.8 (4.4)	0.100*

*$p < 0.05$. PAI-1: Plasminogen activator inhibitor-1, LTBI: Latent TB infection, TB: Tuberculosis.

Discussion

The present study aimed to observe the profile of PAI-1 in LTBI. This study showed that PAI-1 levels were lower in the LTBI group (4.92 ng/mL) than in the healthy control group (5.98 ng/mL); this condition exhibited no hypercoagulable states. A previous study conducted by Shitrit *et al.* (2005) analyzed hypercoagulable states in LTBI patients by measuring the levels of D-dimer in LTBI. Both PAI-1 and D-dimer are fibrinolytic agents. There was no increase in D-dimer levels of the observed LTBI patients in this study [12]. Meanwhile, Kager *et al.* studied that hypercoagulable states by examining the hemostatic profile in patients with active pulmonary TB and found a significant increase in PAI-1 levels compared to healthy controls [13].

In this study, higher PAI-1 levels were found in male LTBI subjects than healthy controls, but not statistically significant. ($p > 0.05$). In female subjects, PAI-1 levels were found to be lower in LTBI group than

in healthy control group, but not statistically significant ($p > 0.05$). Similarly, Nkansah *et al*. analyzed PAI-1 levels in type 2 diabetes mellitus (T2DM) patients and proved that there was no statistically significant relationship between men and women in both T2DM patients and healthy controls [14]. As stated previously, PAI-1 in women is associated with the roles of the estrogen in nitric oxide synthesis, fibrinolytic balance, lipid metabolism, and extracellular matrix production. Gebara *et al*. reported in their study that postmenopausal women who did not receive hormone replacement therapy had higher PAI-1 levels than those who received it [15].

With regard to subjects' age, this study found higher mean PAI-1 level in LTBI group than in healthy control group for the age category of >32 years, but not statistically significant. Kartini *et al*. (2016) revealed a relationship between PAI-1 levels and asthma control degree in connection with subjects' age. For subjects in the age category of <50 years with uncontrolled asthma, the mean serum PAI-1 level was found to be significantly higher. Whereas in subjects aged ≥50 years, PAI-1 levels were not significantly different between subjects with controlled and uncontrolled asthma, but the PAI-1 levels were also seen to increase [16]. Furthermore, the aging process is related to increased PAI-1 levels. Cesary *et al*. (2010) proved that PAI-1 levels were significantly elevated in a variety of clinical conditions typical of the aging process (e.g., obesity, insulin resistance, psychosocial stress, decreased immune response, increased inflammation, and vascular sclerosis/remodelling) [8].

The results of the present study indicated that in both obese and non-obese subjects, the mean PAI-1 level was lower in LTBI group than in healthy control group, but not statistically significant. In this regard, Somodi *et al*. reported a relation between obesity and PAI-1 levels, where PAI-1 level was significantly higher in obese subjects with T2DM ($p < 0.0001$) than healthy controls. Adipose has the ability to synthesize various cytokines called adipokines which have proinflammatory properties. PAI-1 is one of them. Excess adipose tissue increases PAI-1 production, leading to disruption of the fibronolytic system. Furthermore, obesity occurs at low levels of inflammation, where there is the release of pro-inflammatory cytokines, especially IL-6 and TNF- α, which induce PAI-1 expression [17].

This study was conducted during the COVID-19 pandemic, where many healthcare workers were infected with COVID-19. In the anamnesis obtained from the research subjects, there were 46 people who have been infected with this virus within a certain time (Table 6). It is known that there is an association between elevated PAI-1 levels in patients with a history of COVID-19, where hypercoagulable states may occur. COVID-19 survivors are at risk for thrombosis; one of the characteristics of COVID-19 infection is leukocyte sequestration, especially neutrophils, in the pulmonary microvasculature which contributes to alveolar injury and inflammation. The proinflammatory condition is triggered by the formation of Neutrophil Extracellular Traps which result in the production of proinflammatory cytokines. These cytokines trigger endothelial cell activation and promote the release of t-PA and PAI-1. Activated endothelial cells express increased levels of PAI-1, inhibit t-PA and u-PA, and trigger a shift in the hemostatic balance to a procoagulant state [18].

In this study, LTBI subjects within the infected with COVID-19 category had high PAI-1 levels compared to those who had never been infected, and this was statistically significant ($p < 0.05$). In the healthy control group, PAI-1 levels were higher in subjects within the infected with COVID-19 category than those who had never been infected, but not statistically significant ($p > 0.05$). Meijenfeldt *et al*. (2021) reported a hemostatic profile 4 months after COVID-19 infection where PAI-1 levels were found to increase and statistically significant compared to healthy controls ($p < 0.0001$). The pathogenesis of COVID-19 suggests the involvement of components of the fibrinolytic system in various pathways of the renin aldosterone angiotensin system. Plasmin and other proteases, namely, trypsin and TMPRSS2, act on the SARS-CoV-2 protein to bind to ACE-2 on the cell surface. By binding, the virus attacks the host cell, while ACE-2 cannot process the breakdown of ACE-2. Excess ACE-2 causes an increase in PAI-1 and a decrease in fibrinolysis, resulting in a hypercoagulable state. This condition also leads to lung injury and pulmonary edema with formation of hyaline membranes with fibrin in the alveoli, which is cleaved by plasmin with the formation of a D-dimer. Diffuse alveolar damage with alveolar Type II cell injury incites a decrease in surfactant, which produces the induction of the p53 pathway and an increase in PAI-1 [19].

The limitations of this study were the lack of samples of patients with LTBI, and other markers such as pro-inflammatory cytokines (IL-6, IL-8, and IL-12), hemostasis, and fibrinogen were not examined. In further studies, it is highly necessary to examine other inflammatory and hemostatic markers for a complete assessment of the hypercoagulable states in LTBI patients.

Conclusions

PAI-1 levels were lower in LTBI participants than in healthy control participants, which potentially is due to more participants in the healthy control group having a history of COVID-19 infection.

Credit Authorship Contribution Statement

Study conceptualization: SNT, NAT, SS. Methodology: SNT, SB, RM, FA. Data curation: SNT, AS. Investigation: SNT. Formal analysis: AS. Supervising: SNT, SS, SB. Writing-Original draft preparation: All authors. Writing-Review and Editing: All authors

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