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Original Article

Correlation Study of *Cotinine* and *Monocyte Chemoattractant Protein-1* (MCP-1) with Carotid Intima-Media Thickness (cIMT) in Male Active Tobacco Smoke

Sawitri Satwikajati[1*], Novi Kurnianingsih[2], Cholid Tri Tjahjono[2], Titin Andri Wihastuti[3], Djanggan Sargowo[2], Ardian Rizal[2]

[1]Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
[2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
[3]Department of Basic Nursing Science, Faculty of Health Sciences, Universitas Brawijaya, Malang, Indonesia

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ABSTRACT

Background: Tobacco smoke exposure induces intima-media thickness by reducing nitric oxide and increasing adhesive molecule activity, with circulating cotinine serving as a marker; we hypothesize a correlation between monocyte chemoattractant protein-1 (MCP-1) and carotid intima-media thickness (cIMT) in active male smokers.
Material and Methods: We conducted an observational cross-sectional analytic study involving 125 male participants, with 62 being active tobacco smokers and 63 non-smokers. Data were presented as mean ± SD, and the correlation between variables was analyzed using Pearson correlation.
Result: Cotinine and MCP-1 levels were significantly higher in the smoker population (p 0.000) compared to non-smokers. The incidence of positive cIMT findings was higher in the smoker group (5%) than in the non-smoker group (2%). In the active smoker population, cotinine (r 0.21; p 0.11) showed a positive but non-significant correlation with positive cIMT findings, while MCP-1 showed a negative correlation (r -0.19, p 0.14) with positive cIMT findings. Smoking duration (r 0.162; p 0.223) and the amount of tobacco smoke (r 0.003; p 0.982) demonstrated a positive correlation with cotinine. MCP-1 exhibited a non-significant positive correlation with smoking duration (r 0.122; p 0.345) and a non-significant negative correlation with the amount of tobacco smoke (r -0.002; p 0.989).
Conclusion: Among active tobacco smokers, cotinine showed a positive but non-significant correlation with positive cIMT findings, while MCP-1 exhibited a non-significant negative correlation with positive cIMT findings.

1. Introduction

The prevalence of active smokers in Indonesia was relatively high, at about 23.25% of the population.[1] The highest prevalence age group among active smokers was approximately 25-44 years old.[2,3] The hazardous substances in tobacco smoke, such as hydrocarbons, nicotine, aldehydes, and carbon monoxide, have a negative effect on vascular integrity. They promote oxidative stress, reducing the bioavailability of nitric oxide and initiating the inflammatory process. Circulating monocytes interact with the endothelium through adhesive molecules like monocyte chemoattractant protein-1 (MCP-1),[1] contributing to the progression of endothelial dysfunction. Monocyte will differentiated into macrophage. Macrophages ingest LDL and transform into foam cells. The apoptosis of foam cells leads to the accumulation of a lipid core. The release of inflammatory mediators induces the proliferation of smooth muscle cells, which develop into a fibrous cap, contributing to the progression of atherosclerosis disease.[4] Nicotine contained in tobacco smoke can be detected with cotinine, an active metabolite of nicotine.[2] Therefore, in this investigation, we aimed to identify any relationship between cotinine and MCP-1 with Carotid intima-media thickness (cIMT) among male individuals who are actively smoking.

2. Material and Methods

We conducted a cross-sectional observational analytic study involving 125 consecutive males aged 25-45 years who provided informed consent. Of the participants, 49.6% were active tobacco smokers, and 50.4% were neither smoking nor using electronic cigarettes. All participants were screened using a structured questionnaire to ensure no history of typical chest pain or coronary artery disease.

* Corresponding author at: Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
E-mail address: satwikajatis@gmail.com (S. Satwikajati).

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Data were collected in September 2021 through self-reporting, blood sampling, and carotid duplex ultrasound. The data collection took place at the Cardiovascular Department of RSUD Dr. Saiful Anwar and the Medical Faculty, Universitas Brawijaya, Malang.

Carotid duplex ultrasounds were collected by two cardiovascular residents, confirmed by a cardiologist vascular consultant. Patients were positioned supine, and we examined the right and left common carotid artery (CCA) and internal carotid artery (ICA) using Phillips Epic 7 5.0-7.5 MHz. Positive cIMT was defined as > 1.5 mm. All collected data underwent normality testing using Kolmogorov-Smirnov, and the Kappa examination was performed. Cotinine and MCP-1 were collected from blood samples and analyzed with Elisa at the Medical Faculty, Universitas Brawijaya. Baseline characteristic data were presented with mean ± SD and compared with independent T-test analysis. The correlation between variables was analyzed with Pearson correlation. Chi-square analysis was conducted to find the association of smoking with a positive finding of thickening of cIMT. Multivariate variables were analyzed with linear regression. This study had been approved by the ethical committee of RSUD Dr. Saiful Anwar No 400/097/K.3/302/2021 on May 27, 2021. Data analysis was performed using SPSS with a significant value of $p < 0.05$ and a 95% confidence interval.

3. Result

Data were collected from 125 participants, with 49.6% being active tobacco smokers and 50.4% non-tobacco smokers. All collected data were found to be normally distributed. The Kappa value was 0.14.

Among the active tobacco smoke study population, we found that 5% of them had a positive cIMT finding, while in the control study population, we only found 2% of participants with a positive cIMT finding. In the general study population, cotinine and MCP-1 levels were significantly higher in smokers than in non-smokers (p 0.000) (Table 1 and Figure 1). However, in the smoker study population, the levels of cotinine and MCP-1 were higher in the negative cIMT group than in the positive cIMT group (Figure 2), while in the non-smoker study population, the levels of cotinine and MCP-1 were higher in the positive cIMT group than in the negative cIMT group. In the positive cIMT study population, the mean duration of smoking was around 9.4 years, and the amount of tobacco smoke was 8.8, while in the negative cIMT study population, there was a longer duration of smoking (9.8 years) and a higher amount of cigarettes (11.8).

There was no significant difference in age between the smoker and non-smoker study populations. In the smoker study population, the mean duration of smoking was 10.4 years, and the daily amount of smoke was 12.1. Cotinine levels, MCP-1, IL-6, and IMT ICA D were significantly different in smokers compared with the non-smoker study population. The smoker study population had significantly higher cotinine, MCP-1, IL-6 (p 0.000), and IMT ICA D (p 0.004) than non-smokers. After conducting a correlational study, we found that cotinine showed a positive correlation in both smoker (r 0.21 p 0.11) and non-smoker study populations (r 0.01 p 0.92), while MCP-1 showed a negative correlation with cIMT among the smoker study population (r -0.19 p 0.14) and a positive correlation with cIMT among the non-smoker study population (r 0.15 p 0.25) (Table 2).

Table 1. Baseline Characteristic Data Among Study Population

	Smoker (n 62) (mean±SD) CI 95%	Non-Smoker (n 63) (mean±SD) CI 95%	*p*
Age	31.7±8.1	33.8±8.0	0.74
Duration of smoking (year)	10.4±6.7	0±0	-
Amount of Daily Smoking	12.1±5.4	0±0	-
Cotinine (ng/ml)	34.3±25.1	9.1±3.4	0.000
MCP-1	89.2±53.0	18.5±20.8	0.000
FBG (mg/dL)	93.5±11.5	93.9±12.1	0.313
IL-6 (ng/L)	69.3±24.7	41.9±6.9	0.000
IMT CCA D (mm)	0.7±0.9	0.6±0.8	0.57
IMT ICA D (mm)	0.7±1.0	0.4±0.5	0.004
IMT CCA S (mm)	0.5±0.3	0.4±0.4	0.93
IMT ICA S (mm)	0.5±0.4	0.4±0.4	0.97
Average IMT (mm)	0.6±0.5	0.5±0.5	0.24

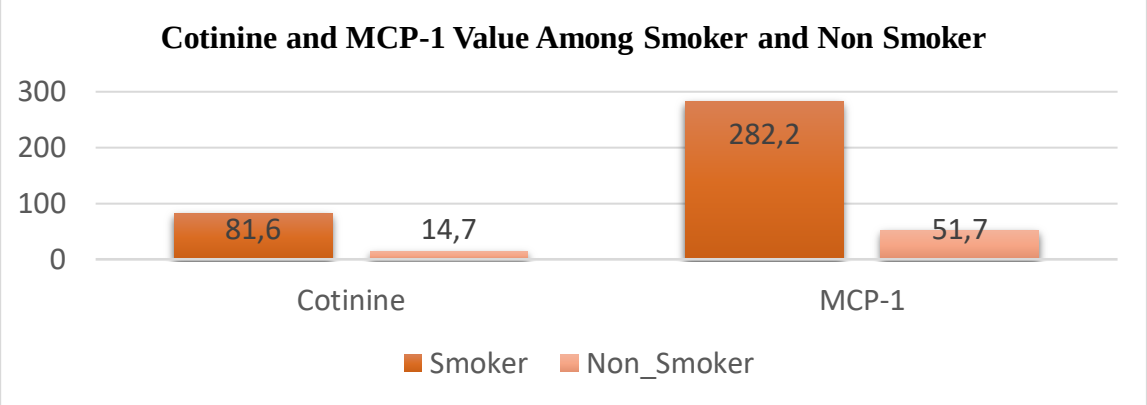

Figure 1. Cotinine and MCP-1 Value Among Smoker and Non-Smoker

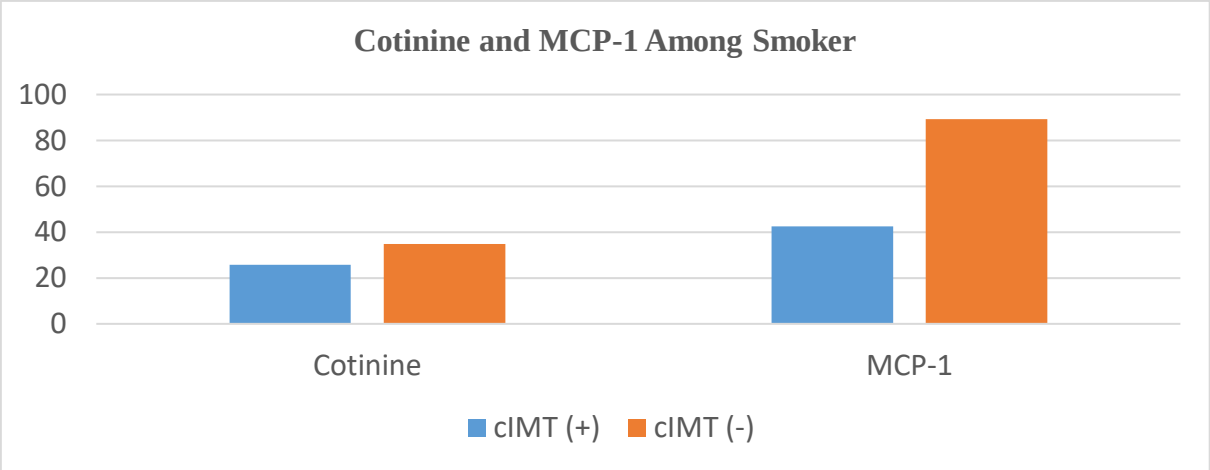

Figure 2. Cotinine and MCP-1 Value Among Smoker

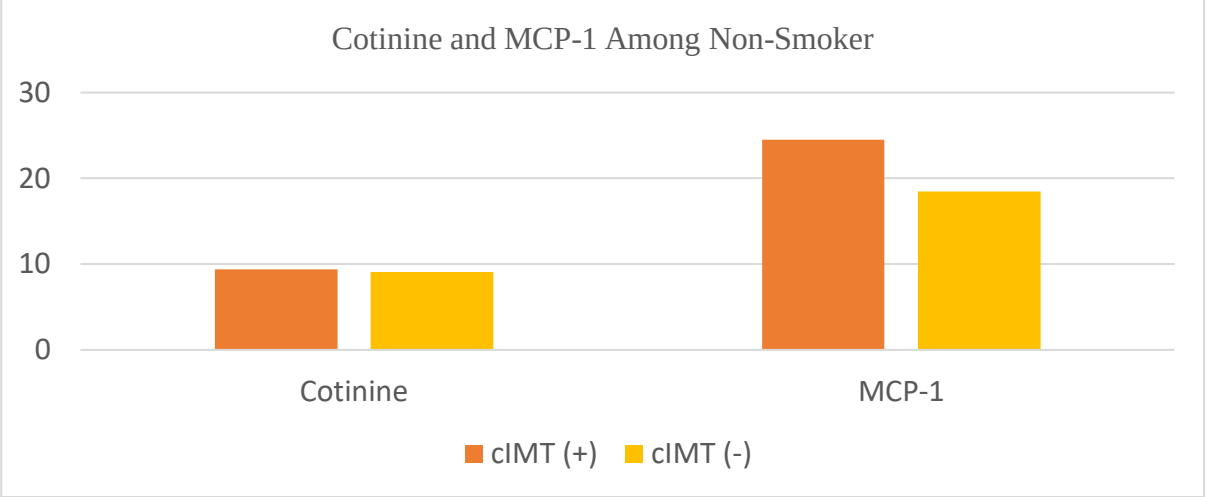

Figure 3. Cotinine and MCP-1 Value Among Non-Smoker

Table 2. Correlation Study of Cotinine and MCP-1 with cIMT Among Smoker and Non-Smoker

	r	*p*
All Study Population		
• Cotinine	0.72	0.32
• MCP-1	0.02	0.76
• IL-6	-0.09	0.46
• FBG	-0.18	0.15
Smoker Study Population		
• Cotinine	0.21	0.11
• MCP-1	-0.19	0.14
• IL-6	-0.47	0.71
• FBG	0.131	0.31
Non-Smoker Study Population		
• Cotinine	0.01	0.92
• MCP-1	0.15	0.25
• IL-6	-0.19	0.15
• FBG	-0.18	0.15

4. Discussion

Cigarette smoke contains hazardous substances such as nicotine, polycyclic aromatic hydrocarbons (PAH), aldehyde, nitrogen, metals, hydrocarbons, and free radicals. [6] Nicotine promotes oxidative stress, reducing the bioavailability of nitric oxide [7]. The reduction in nitric oxide bioavailability induces the release of inflammatory mediators and increases adhesive molecules such as MCP-1, leading to endothelial dysfunction. The interaction between circulating monocytes and MCP-1 facilitates the insertion of monocytes into the intima. Additionally, circulating LDL passes through the endothelium into the intima. Monocytes differentiate into macrophages, and the macrophages ingest oxidized LDL, forming foam cells. This process promotes a complex pathological inflammation process, inducing the proliferation of smooth muscle cells and apoptosis of the foam cells, ultimately leading to the formation of a lipid core and fibrous cap[8]. This pathological process induces impairment of the intima-media thickness. cIMT progression has recently been firmly established as a surrogate for cardiovascular disease (CVD) risk in large-scale meta-analysis [9].

The prevalence of positive cIMT was higher in the smoker population (5%) than in the non-smoker population (2%). Cotinine and MCP-1, which play pivotal roles in subclinical atherosclerosis, were investigated. The levels of cotinine and MCP-1 were higher in the smoker population than in the non-smoker population (p 0.000). These results are consistent with the findings of a recent study on the mechanism of subclinical atherosclerosis. In general, we found a positive correlation between cotinine (r 0.72; p 0.32) and MCP-1 (r 0.02; p 0.76) with a positive finding of cIMT.

Cotinine had a positive correlation with cIMT in both smoker and non-smoker populations. The correlation was stronger in the smoker population (r 0.21) than in the non-smoker population (r 0.01), although they were not significant (p 0.11; p 0.92).

In the smoking population, the duration of smoking (r 0.162, p 0.223) and the amount of tobacco smoke (r 0.003, p 0.982) showed a positive correlation with cotinine. MCP-1 had a positive correlation with smoking duration (r 0.122, p 0.345), but not with the amount of tobacco smoke (r -0.002, p 0.989).

Among the smoker study population, MCP-1 had a negative correlation (r -0.19) with cIMT. We suggest that longer smoke exposure will increase MCP-1 until a certain point, and it will decrease despite the progression of atherosclerosis plaque (chronic inflammation). This is supported by data on IL-6, supposed to be a marker of acute inflammation, which decreases when it shifts to chronic inflammatory processes. The study resulted in a negative correlation in both smoker and non-smoker populations, with a higher pathogenic role of IL-6 in smokers (r -0.47) than in non-smokers (r -0.19). The median duration of smoking was 10.4 ± 6.7 years. We suggest that the peak acute inflammatory process occurred before.

In this study, it is demonstrated that hyperglycemia can induce epigenetic changes in the vascular endothelium that are relevant for atherosclerosis development. Hyperglycemia played a role in atherosclerosis in this study. In the smoker study population, fasting blood glucose had a stronger correlation with cIMT (r 0.131, p 0.150) than in the non-smoker study population (r -0.18, p 0.15), and positive cIMT findings were observed in 7% of the hyperglycemic population (p 0.000).

5. Conclusion

Among active tobacco smokers, cotinine showed a positive but non-significant correlation with a positive cIMT finding, while MCP-1 showed a non-significant negative correlation with a positive cIMT finding.

6. Declaration

6.1 Ethics Approval and Consent to participate

The subjects in this study are humans, so ethical rules must be followed. This research has passed the ethical due diligence, approved based on the Certificate of Ethical Eligibility No. 400/097/K.3/302/2021 issued by the Health Research Ethics Committee at Dr. Saiful Anwar Malang.

6.2. Consent for publication

Not applicable.

6.3 Availibility of data and materials

Data used in our study were presented in the main text.

6.4 Competing interests

Not applicable.

6.5 Funding Source

Not applicable.

6.6 Authors contributions

Idea/concept: SS. Design: SS, NK. Control/supervision: NK, CTT, TAW, DS, AR. Data collection/processing: SS, NK. Analysis/interpretation: NK. Literature review: SS, NK. Writing the article: SS. Critical review: NK, CTT, TAW, DS, AR. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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