Yustinus Gugus Wahyu Endardiyanto

Pengaruh Ketergantungan Nikotin Terhadap Kadar Trigliserida Pada Perokok yang Terdiagnosis Hipertensi

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The Impact of Nicotine Dependence on Triglyceride Levels in Hypertensive Smokers

Erica Kusuma Rahayu Sudarsono[1] and Christine Patramurti[1]

[1] *Sanata Dharma University, Jl Affandi, Mrican, Yogyakarta, 55281*

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Abstract— Cardiovascular disease was one of the leading causes of world death. Cardiovascular disease accounts for 35% of total deaths in Indonesia. People who smoke tend to have a cardiovascular disease because smoking lead to an increase of lipolysis and triglyceride levels. The triglycerides levels are an early marker of increasing remnant cholesterol that caused cardiovascular disease. This research is an analytic observational study using cross-sectional approach which was focus on 31 hypertensive male smokers. This study aims to determine the effect of nicotine dependence on triglyceride levels as an early marker of increased cardiovascular risk. Nicotine dependency was analyzed using Fagerstorm Test for Nicotine Dependence (FTND). The effect of the nicotine dependence on triglyceride levels was analyzed using Fisher's test so that the odds ratio and p-value were obtained. The results showed that respondents with high nicotine dependence seems to had a higher risk of increasing triglyceride levels above the normal limit 0.333 times (OR 0.333; 95% CI 0.051-2.177) greater than low nicotine dependence although not statistically significant (p-value 0.370).

Keywords—cardiovascular disease, FTND, nicotine dependence, triglyceride level

Abstrak— Penyakit kardiovaskuler merupakan salah satu penyakit penyebab kematian terbesar di dunia dan menyumbang 35% kematian di Indonesia. Orang yang merokok lebih berisiko untuk mengalami kejadian penyakit kardiovaskuler, yang disebabkan karena adanya peningkatan lipolisis dan peningkatan trigliserida. Trigliserida merupakan penanda awal terjadinya peningkatan *remnant cholesterol* yang memicu penyakit kardiovaskuler. Penelitian ini merupakan penelitian observasional analitik dengan pendekatan *cross-sectional* yang dilakukan pada 31 orang laki-laki perokok yang terdiagnosis hipertensi. Tujuan dari penelitian ini adalah untuk mengetahui pengaruh ketergantungan nikotin terhadap kadar trigliserida sebagai penanda awal peningkatan risiko kardiovaskuler. Ketergantungan nikotin diukur dengan menggunakan kuesioner *Fagerstorm Test for Nicotine Dependence* (FTND). Pengaruh ketergantungan nikotin terhadap kadar trigliserida dianalisis dengan menggunakan uji fisher sehingga didapatkan nilai *odds ratio* dan *p-value*. Hasil penelitian menunjukkan responden dengan ketergantungan nikotin tinggi memiliki kemungkinan nilai trigliserida 150 mg/dL 0,333 kali (OR 0,333; 95% CI 0,051-2,177) lebih besar dibandingkan dengan responden dengan ketergantungan nikotin rendah meski tidak bermakna secara statistik (p-value 0,370).

Kata Kunci—FTND, kadar trigliserida, ketergantungan nikotin, penyakit kardiovaskuler

1. INTRODUCTION

Cardiovascular disease is one of the leading causes of death worldwide (Bentzon et al., 2014; Rigotti Clair, 2013) and accounts for 35% of total deaths in Indonesia (World Health Organization, 2018). The risk of developing cardiovascular disease is higher in individuals who smoke (Lee et al., 2017; Price et al., 2020). Smoking prevalence among individuals aged >15 years in Indonesia is 32.8%, and 62.9% male consume inhaled and chewed tobacco (Arjoso, 2020).

A person is diagnosed to have hypertension when experiencing an increase in blood pressure above 140/90 mmHg (Dipiro et al., 2011; James et al., 2014). The prevalence of hypertension in Indonesia is 8.36% (Badan Penelitian dan Pengembangan Kesehatan, 2019). The risk of cardiovascular disease can increase due to hypertension. Deaths caused by coronary heart disease and stroke will increase with every 20 mmHg increase in systolic or 10 mmHg increase in diastolic (James et al., 2014).

Several studies in Indonesia have shown that smokers have a greater risk of experiencing cardiovascular diseases (AR Indrawan, 2014; Pracilia et al., 2019). Research indicates that smoking can trigger central obesity, which can lead to cardiovascular diseases (Liu et al., 2012). Furthermore, a study by Koda et al (2016) demonstrated that current smokers with a visceral fat area (VFA) >100cm2 had a higher proportion of triglyceride levels ≥150 mg/dL (47.3%) compared to those who quit smoking (36.4%) and non-smokers (18.8%) (Koda et al., 2016).

Nicotine is one of the substances in cigarettes that can increase the risk of cardiovascular disease through the activa-

Penulis koresponden: Sudarsono, irinerica@gmail.com

tion of the sympathetic nerves and an increase in lipolysis (Alves-Bezerra Cohen, 2018; Bajaj, 2012; Benowitz Burbank, 2016). The increase in lipolysis results in an increase in free fatty acids in systemic circulation and triggers an increase in triglyceride synthesis by the liver (Alves-Bezerra Cohen, 2018; Andersson Arner, 2001). The increase in triglyceride levels is an early indicator of increased remnant cholesterol, which triggers the formation of atherosclerosis (Nordestgaard Varbo, 2014).

Nicotine can enhance dopaminergic activity, resulting in dependence and withdrawal syndrome. In addition, nicotine also stimulates other parts of the brain, including cholinergic, GABAergic, serotonergic, and noradrenergic systems, which produce sensations of satisfaction and pleasure (Tiwari et al., 2020). Dependence on nicotine can cause an individual to struggle with discontinuing nicotine use despite being aware of its harmful effects, due to changes in the brain such as increased focus, appetite, and mood resulting from the stimulation of nicotinic acetylcholine receptors (nAChR) (Picciotto Kenny, 2021).

This study focuses to analyze the effect of nicotine dependence on triglyceride levels. Nicotine dependence can be assessed using the Fagerstrom Test for Nicotine Dependence (FTND), which includes considering the time of first cigarette use after waking and the number of cigarettes consumed in a day (CPD).

2.Materials And Methods

1. Tools and Materials

Blood samples in tubes containing EDTA, FTND questionnaire, and LipidProTM.

2. Method

2.1 Data Collection

Data collection was conducted at the Kalasan Community Health Center in August-September 2022, following ethical approval from the Ethics Committees of Medical Research Duta Wacana University. The study involved 31 males with the inclusion criteria of being smokers diagnosed with hypertension at the Kalasan Community Health Center, aged between 30-65 years, consuming clove or filtered cigarettes, and willing to provide informed consent. The exclusion criteria for this study are patients who have been on regular medication to quit smoking in the past month, patients with conditions requiring total bed rest for ≥ 10 days in the past month, patients taking antiplatelet and/or anticoagulant, and patients diagnosed with cardiovascular diseases.

2.2 Data Collection and Analysis

Blood collection was performed by the laboratory staff at the Kalasan Community Health Center. The blood was placed in a K2 vacuumtainer tube containing EDTA (1.8 mg/mL of blood) and stored at a temperature of ± 4°C before the triglyceride levels were analyzed. Triglyceride analysis was conducted at the biochemistry laboratory of the Faculty of Pharmacy, Sanata Dharma University. Triglyceride levels were analyzed using the LipidProTM. Triglyceride levels were converted into categorical data with a cutoff of <150 mg/dL, indicating normal triglyceride levels. Interviews were conducted with patients to analyze nicotine dependence by adapting the Fagerstrom Test for Nicotine Dependence (FTND) instrument, which aims to measure nicotine dependence on a scale of 0-10. A higher FTND score indicates an increased dependence on nicotine. In this study, nicotine dependence is considered high when the score is ≥5. Factors in the study that may influence triglyceride levels, such as age, CPD, and type of cigarette, were analyzed using the Chi-Square or Fisher's test. The effect of nicotine dependence on triglyceride levels was analyzed using the Fisher's test. The analysis was conducted with a 95% confidence level ($p < 0.05$). The influence of nicotine dependence on triglyceride levels can be observed from the Odds Ratio (OR) and p-values.

Table 1: Characteristics of Respondents

Characteristics	Total	Percentage
Age		
Mean ± SD (years)	57.58 ± 6.93	
<45 years	1	3.23
≥45 years	30	96.77
Age of Hypertension		
Mean ± SD (years)	51.29 ± 10.34	
<45 years	6	19.35
45 years	25	80.65
Age of Smoking		
Mean ± SD (years)	20.13 ± 6.88	
15 years	6	19.35
>15 years	25	80.65
Number of Cigarettes per Day (CPD)		
10	16	51.61
11-20	11	35.48
21-30	4	12.91
Type of cigarette		
Clove cigarette	23	74.19
White cigarette	8	25.81
FTND Score		
Mean ± SD	3.16 ± 1.88	
5	25	80.65
>5	6	19.35
Triglyceride levels		
Mean ± SD (mg/dL)	160.16 ± 96.28	
<150 mg/dL	14	45.16
150 mg/dL	17	54.84

3.Result

The study was conducted on 31 male hypertensive respondents who were smokers within the age range of 30-65 years, and the characteristics of the respondents are described in Table 1. The analysis was conducted to examine the influence of other factors that may affect triglyceride levels, as presented in Table 2. Statistical analysis was conducted to examine the effect of nicotine dependence on triglyceride levels, as shown in Table 3.

4. Discussion

Characteristics of Respondents

The study was conducted on 31 hypertensive male patients who smoked within the age range of 30-65 years. The study found that the average age of respondents was 57.58 ± 6.93

TABLE 2: FACTORS AFFECTING TRIGLYCERIDE LEVELS

Factor	Triglyceride levels. ≥150 mg/dL	<150 mg/dL	p-value
Age			
45 years	17	13	0.452
<45 years	0	1	
Number of cigarettes per day (CPD)			
>10	9	6	0.576
10	8	8	
Type of cigarette			
Clove cigarette	14	8	0.097
White cigarette	2	6	

TABLE 3: THE EFFECT OF NICOTINE DEPENDENCE ON TRIGLYCERIDE LEVELS

Allel	Triglyceride Levels ≥150 mg/dL	<150 mg/dL	OR	p-value
High Dependency	2	4	0.333 (0.051-2.177)	0.370
Low Dependency	15	10		

years, and 96.77 % of respondents were aged 45 years. The age of ≥45 years is considered a higher risk for cardiovascular disease (Centers for Disease Control and Prevention, n.d.). This study also revealed that the proportion of respondents who were diagnosed with hypertension for the first time was greater in the age group of ≥45 years, at 80.65 %. These findings are consistent with the 2018 Riskesdas study, which found an increase in the prevalence of medically diagnosed hypertension by 6.89 % among individuals aged 45-54 years compared to the age range of 35-44 years. (Badan Penelitian dan Pengembangan Kesehatan, 2019).

This study also found that the average age at which respondents started smoking was 20.13 ± 6.88 years, and 19.35 % of respondents started smoking at the age of 15 years. These findings are consistent with the information stated in the Tobacco Atlas of Indonesia (2020), which reports that 23.1 % of the population in Indonesia aged 10-14 years are smokers (Arjoso, 2020).

More than half (51.61 %) of the respondents who participated in this study smoke 10 cigarettes per day, with an average FTND score of 3.16 ± 1.88 and a percentage of FTND scores 5 of 80.65 %. These results indicate a positive correlation between CPD and the FTND score, indicating respondents' dependence on nicotine.

Similar findings were also found in this study regarding the type of cigarettes consumed. Riskesdas (2018) indicates that 67.8 % of smokers in Indonesia consume clove cigarettes, followed by white cigarettes and hand-rolled cigarettes (Badan Penelitian dan Pengembangan Kesehatan, 2019).

Factors Influencing Triglyceride Levels

In Table 2, it was found that age and CPD did not have an association on triglyceride levels. These findings are consistent with other studies that found no association between age and triglyceride levels (Daud et al., 2018). However, there are other studies that indicate an increased risk of having triglyceride levels ≥150 mg/dL with advancing age (Cohen et al., 2010).

This study demonstrates no association between CPD and triglyceride levels. Similar findings were found in a study by Rashan et al. (2016), which reported no difference in triglyceride levels among respondents with different smoking intensities (Rashan et al., 2016) However, the findings obtained in this study differ from several previous studies that have shown that smoking intensity can affect triglyceride levels (Gossett et al., 2009; Moradinazar et al., 2020; Nath et al., 2022). Increasing smoking intensity has been found to have a positive correlation with elevated triglyceride levels (Nath et al., 2022).

The type of cigarette also does not have a significant influence on triglyceride levels, although clove cigarettes tend to have a higher proportion of experiencing an increase in triglyceride levels above the normal limit. This is because clove cigarettes contain nearly 5 times more nicotine compared to white cigarettes (Soetiarto, 1995). The Influence of Nicotine Dependence on Triglycerides.

The statistical test results indicate that respondents with high nicotine dependence have a 0.333 times (OR 0.333; 95 % CI 0.051-2.177) greater risk of having triglyceride values 150 mg/dL compared to respondents with low nicotine dependence. In other words, patients with low nicotine dependence are at a higher risk of experiencing an increase in triglyceride levels above the normal limit. However, these results are not statistically significant (p-value 0.370). These findings align with previous studies that showed no significant relationship between nicotine dependence and triglyceride levels (Gossett et al., 2009).

This research found a tendency of increased triglyceride levels above the normal limit in respondents with low nicotine dependence, although it was not statistically significant. The insignificance of nicotine dependence on triglyceride levels can occur because nicotine dependence does not directly reflect the nicotine levels in the blood. The nicotine levels in the blood are influenced by nicotine metabolic rate. The nicotine metabolic rate can be measured using a biomarker called nicotine metabolic ratio (NMR), which represents the ratio between two nicotine metabolites, 3-hydroxycotinine and cotinine (Schnoll et al., 2014; Siegel et al., 2020). Theoreti-

cally, individuals with normal metabolism tend to consume more nicotine compared to individuals with low metabolism (Benowitz et al., 2003; Fix et al., 2017). Several studies have reported a lack of correlation between NMR and nicotine dependence measured by FTND (Fix et al., 2017; Schnoll et al., 2014), However, NMR is known to have a correlation with CPD (Fix et al., 2017; Siegel et al., 2020). As explained earlier, the nicotine levels can be influenced by nicotine metabolic rate. Nicotine metabolism depends on the activity of CYP2A6 enzyme (Ho et al., 2009; NCBI, n.d.; Schnoll et al., 2014). The CYP2A6 gene possesses various forms of polymorphism and can influence the activity of the CYP2A6 enzyme (Hukkanen et al., 2005; NCBI, n.d.). Previous research has shown a high frequency of the CYP2A6 *4 allele in Indonesia, particularly among the Javanese ethnic group (Patramurti et al., 2015; Patramurti Fenti, 2017). The presence of the inactive allele form (CYP2A6*4) results in a decrease in nicotine metabolic rate, which means there is a higher risk of increased nicotine levels in the blood. The CYP2A6*4 gene is a deleted gene, leading to a reduction in enzyme activity and an increase in nicotine levels in the blood (Ito et al., 2015; Johani et al., 2020). The nicotine level in the blood can influence the triglyceride level because nicotine triggers an increase in lipolysis due to the activation of adrenoreceptors and an increase in catecholamine hormones, thereby increasing free fatty acids (Alves-Bezerra Cohen, 2018; Andersson Arner, 2001) and stimulating the synthesis of triglycerides by the liver (Cnop et al., 2003; Matsuzawa et al., 1995). The lack of significance in the p-value in this study may also be attributed to uncontrolled confounding variables such as BMI and dietary and physical activity patterns. BMI can influence the triglyceride levels (Cohen et al., 2010; Miller et al., 2011). Overweight and obese respondents tend to experience an increase in triglyceride levels compared to respondents with a normal BMI (<25 kg/m2) (Cohen et al., 2010). The study by Miller et al. (2011) also showed that respondents with a BMI <25 kg/m2 tend to have triglyceride levels <150 mg/dL and <200 mg/dL with proportions of 43 % and 39 %, respectively (Miller et al., 2011). Other studies have shown that the accumulation of adipose tissue in the subcutaneous abdomen and visceral regions, particularly visceral fat in both men and women, can influence triglyceride levels (Fox et al., 2007).

In addition to BMI, lifestyle factors such as dietary patterns and physical activity are correlated with changes in triglyceride levels. Triglyceride levels can be reduced by consuming low-fat and low-glycemic index foods (Patel et al., 2021). Furthermore, consumption of foods containing monounsaturated fat has been proven to lower triglyceride levels (p-value 0.017) (Daud et al., 2018). Physical activity also influences triglyceride levels. Individuals who engage in prolonged sedentary behavior have a higher risk of increased triglyceride levels (Daud et al., 2018). This is supported by research indicating that engaging in physical activity between periods of sitting can lower glycemic index and triglyceride levels (Loh et al., 2020).

5. Conclusion

Respondents with high nicotine dependence have a 0.333 times (OR 0.333; 95 % CI 0.051-2.177) greater risk of having triglyceride values 150 mg/dL compared to respondents with low nicotine dependence (p-value 0.370). It would be better to conduct a study with a larger sample size and to control/measure other variables such as BMI, dietary patterns, and physical activity that can affect triglyceride values.

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