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Smoking as a risk factor for dyslipidemia: study among type 2 diabetes mellitus patients on private hospital in Yogyakarta

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ABSTRACT: Smoking behavior is known to be a significant factor that has adverse effects on people with type 2 diabetes (T2DM). Nicotine in cigarettes stimulate adrenoreceptors and promotes lipolysis, leading to the synthesis of free fatty acids, which in turn increase the susceptibility to dyslipidemia and the development of cardiovascular disorders. This study aimed to examine the relationship between smoking status and the occurrence of dyslipidemia in patients with T2DM in a private hospital in Yogyakarta. A total of 107 T2DM patients participated in this cross-sectional observational study. Through live interviews, we collected smoking status conducted using the Fagerström Test for Nicotine Dependence (FTND) questionnaire. The fasting blood samples taken from participants were used to analyze the lipid profiles, including triglycerides (TG), total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). The chi-square test revealed a significant association between smoking status and the risk of dyslipidemia among the participants, with $\chi^2(2) = 13.463$, $p = 0.001$. The findings suggest that smoking increases the risk of dyslipidemia among T2DM patients. These results highlight the importance of smoking cessation as a preventive measure to reduce metabolic complications in individuals with T2DM.

KEYWORDS: Dyslipidemia; lipid profile; smoking; type 2 diabetes mellitus.

INTRODUCTION

Diabetes is one of the major non-communicable diseases with a high prevalence rate in Indonesia compared to many other countries. In 2021, the International Diabetes Federation (IDF) reported that Indonesia ranked fifth globally in the number of people with diabetes, with approximately 19.5 million cases [1]. According to the 2023 Indonesian Health Survey (Survei Kesehatan Indonesia, SKI) released by the Ministry of Health, the prevalence of diabetes among individuals aged 15 years and older reached 11.7%, an increase from 10.9% in 2018, indicating a sharp rise in the diabetic population [2]. Furthermore, Wahidin et al. (2024) projected that the prevalence of diabetes in Indonesia will increase from 9.19% in 2020 (18.69 million cases) to 16.09% in 2045 (40.7 million cases). The increasing prevalence of diabetes is closely associated with sedentary lifestyles, obesity, unhealthy dietary habits, and rapid urbanization [3].

Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes worldwide, affecting millions of individuals globally, and accounting for nearly 90% of all diagnosed diabetes cases[4]. Consistent with this global trend, the Indonesian Health Survey (SKI) reported that T2DM is widespread in Indonesia, with 50.2% of diabetic patients diagnosed with this condition [2]. Insulin resistance drives dyslipidemia by both boosting triglyceride production in the liver and hindering HDL metabolism, which in turn raises cardiovascular risk [5]. Due to its severe complications, T2DM is recognized as a leading cause of mortality, and dyslipidemia plays a significantly contributory role. Dyslipidemia refers to abnormalities in lipid metabolism, including TG, TC (total cholesterol), LDL, and HDL. The most prevalent dyslipidemia in diabetic patients is the elevation of TG and LDL-C levels. This condition not only increases the risk of cardiovascular disease but also exacerbates other diabetic complications, creating a vicious cycle that significantly worsens patient outcomes [6]. T2DM accompanied by dyslipidemia may lead to both microvascular and macrovascular complications, such as retinopathy, nephropathy, neuropathy, hypertension, stroke, and peripheral artery disease [7], [8]. Among these, cardiovascular complications, particularly coronary heart disease, remain the primary cause of mortality in diabetic patients [9], [10].

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One of the main contributory factors to type 2 diabetes mellitus (T2DM) is an unhealthy lifestyle, including a poor diet, physical inactivity, obesity, and smoking [11], [12], [13]. As a modifiable lifestyle factor, smoking is exceptionally detrimental because it has multifaceted adverse effects on both glucose and lipid metabolism. However, there is a notable lack of studies examining the link between smoking and dyslipidemia specifically among T2DM patients in Indonesia, particularly within Yogyakarta. Our previous study revealed that smoking could elevate HbA1c levels among Javanese Indonesian smokers who consumed at least 20 cigarettes per day and had smoked for a minimum of 25 years [14]. Other studies conducted in Indonesia have also reported that poor smoking habits may lead to elevated lipid profile levels in both non-diabetic and diabetic individuals [15], [16], [17]. Moreover, several studies have demonstrated that cigarette smoking is not only associated with the development of diabetes but also exacerbates its progression through increases in lipid profiles [18], [19], [20], [21], [22], [23]. In addition, recent meta-analyses by Momayyezi et al. (2024) and van der Plas (2023) reported that active smokers had significantly higher triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) levels compared to non-smokers [24], [25]. Nicotine activates adrenergic receptors, increasing catecholamine release and free fatty acid levels, thereby contributing to hypertriglyceridemia and insulin resistance [26]. Additionally, an increase in lipolysis leads to the synthesis of more free fatty acids due to the hydrolysis of triglycerides and very low-density lipoprotein (VLDL) [27].

Epidemiological data from the 2023 Indonesian Health Survey (SKI) indicated that the prevalence of diabetes mellitus (DM) in Yogyakarta City in 2020 was 4.9%, which was higher than the national prevalence of 2.4%[2]. Meanwhile, data from the Statistics Agency (BPS) of the Special Region of Yogyakarta (DIY) in 2023 reported that 26.2% of males aged 15 years and older in Yogyakarta were smokers, making it the second-highest smoking rate in the region [28]. Several factors may contribute to this persistently high prevalence of smoking, including the social acceptance of smoking in public spaces, cultural beliefs that associate smoking with masculinity, and the affordability and easy accessibility of tobacco products [29]. On average, smokers in the city consume 10.6 cigarettes per day [28]. In addition to active smokers, there is also a substantial population of passive smokers. According to the Data and Information Center of the Indonesian Ministry of Health (2022), there are approximately 96.9 million passive smokers in Indonesia, consisting of 66.7 million females and 30.2 million males[28] . Previous studies have reported that passive smokers are also at increased risk of developing type 2 diabetes mellitus (T2DM), similar to active smokers [30], [31], [32], [33]. Furthermore, several studies have shown that dyslipidemia occurs in both passive and active smoker [34], [35], [36]. This study aims to determine the association between smoking status and dyslipidemia among T2DM patients in Yogyakarta, Indonesia, to elucidate the metabolic impact of smoking in diabetic populations. We hope that the findings of this research will inform strategies or preventive measures for various diseases linked to cigarette smoke, particularly T2DM.

▪ MATERIALS AND METHODS

Materials

This study employed the Fagerström Test for Nicotine Dependence (FTND) questionnaire developed by Heatherton to determine the smoking status of the participants [37]. Venous blood samples (3 mL) were collected from outcare patients with type 2 diabetes mellitus at a private hospital in Yogyakarta using a 3 mL Terumo syringe and an EDTA vacutainer tube (Capes Medical, 3.0 mL). The blood samples were taken from outcare T2DM patients in a private hospital in Yogyakarta. The lipid profile, including TG, TC, LDL-C, and HDL-C levels, was measured using an enzymatic colorimetric method with reagent kits from Diasys Diagnostics (German) on a Beckman Coulter AU2700 autoanalyzer. The assays were performed according to the manufacturer's standard protocol to ensure analytical accuracy and precision.

Methods

This study employed an observational, cross-sectional design, conducted from July to August 2024, using a purposive sampling approach. The subjects were patients with type 2 diabetes mellitus (T2DM), both smokers and non-smokers, who had received regular treatment and care at a private hospital in Yogyakarta for at least six months. Participants who were taking medications that could affect lipid profiles, such as hypolipidemic agents (statins, gemfibrozil, niacin, or phytosterols), were excluded. Before joining the study, all participants got a full explanation of the purpose and procedures of the study, after which they signed the

informed consent. The levels of nicotine dependence and smoking behavior were assessed using the Fagerström Test for Nicotine Dependence (FTND) questionnaire developed by Heatherton [37]. The research protocol was approved by the Health Research Ethics Commission, Faculty of Medicine, Universitas Duta Wacana Yogyakarta (Protocol Number: 1637/C.16/FK/2024).

After an overnight fast (8–10 hours), venous blood samples were collected from each participant by professional healthcare personnel using vacutainer tubes. Each tube was left in an upright position for 30 minutes to allow coagulation. The serum was then separated by centrifugation at 3000 rpm for 10 minutes at room temperature (22–25 °C). Levels of TG, total cholesterol, LDL-C, and HDL-C were analyzed using the enzymatic colorimetric method in the hospital's clinical laboratory where the participants routinely received care.

Data analysis

Data analysis was performed using Microsoft Excel 2017. Descriptive statistics were expressed as mean ± standard deviation (SD). The Fagerström Test for Nicotine Dependence (FTND) questionnaire was used to determine the smoking status of the participants. The association between smoking status and dyslipidemia levels was evaluated using the chi-square test.

▪ RESULTS

Participant characteristics

This study involved 107 adult participants with diabetes, consisting of 41 males and 66 females. Participants were categorized based on their smoking status into three groups: active smokers, passive smokers, and non-smokers. Active smokers were individuals who currently inhaled mainstream cigarette smoke, while those who were regularly exposed to cigarette smoke from others were considered passive smokers. Non-smokers were individuals who had never smoked or been exposed to cigarette smoke. Notably, all participants identified as smokers in this study were men, whereas both passive smokers and non-smokers included both males and females. Table 1 presents the participant's general characteristics, including TG and LDL-C levels, based on their smoking status. Table 1 presents the participants' general characteristics, including HbA1c, TG, total cholesterol, LDL-C, and HDL-C levels, according to their smoking status.

Table 1. General characteristic and lipid profile of participants.

Characteristics	Smoking Status						P-value
	Active smokers		Pasive Smokers		Non Smokers		
	Male	Female	Male	Female	Male	Female	
Gender n (%)	19 (17.76)	-	7 (6.54)	24 (22.43)	15 (14.02)	42 (39.25)	
Age (year)							
Mean	56.58	-	62.92	57.29	61.29	60.93	0.216
SD	9.55		7.80	9.18	7.91	6.75	
Range	36 - 68		54 - 81	45 - 71	51 - 71	45 - 75	
First smoking (year)							
Mean	18.63	-	-	-	-	-	-
SD	9.88						
Range	10 - 50						
Smoking duration (years)	35	-	-	-	-	-	-
Mean	10.91						
SD	17-53						
Range							
Cigarette per-day (CPD)							
Mean	13.4	-	-	-	-	-	-
SD	8.55						
Range	1-30						
HbA1c (%)							
Mean	8.96	-	7.46	7.46	7.68	8.49	0.030
SD	2.09		1.04	1.07	1.02	1.87	
Range	6.8-13.8		6.2-9.5	6.6-10.5	5.7-9.9	6.2-14.9	
Trigliserida levels (mg/dL)							
Mean	199.32	-	189.43	197.17	169.73	214.77	0.218
SD	34.93		48.56	25.53	34.39	44.64	
Range	145-287		99-242	150-266	115-236	127-337	
Cholesterol Total levels (mg/dL)							
Mean	195.47	-	142.43	152.92	112.93	149.27	0.051
SD	136.16		65.89	53.59	50.69	118.63	
Range	70-572		90-274	75-263	54-239	58-779	
LDL-C levels (mg/dL)							
Mean	132.53	-	123.86	128.00	124.2	143.14	0.683
SD	33.873		45.95	46.75	45.84	66.16	
Range	89-189		48-191	81-314	62-219	44-350	
HDL-C levels (mg/dL)							
Mean	42.79	-	42.14	50.25	43.60	58.14	0.016
SD	10.29		10.65	12.07	14.92	15.88	
Range	31-74		31-55	28-73	24-81	26-89	

Participant's smoking status

As shown in Table 1, there were no statistically significant differences between the groups in terms of mean (±SD) age (years), HbA1c levels, TG, and LDL-C (p-value> 0.05). All participants in this study were aged 36-81 years. T2DM is a non-communicable disease most commonly found in adults with age ≥45 years [38]. Riskesdas DIY (2018) shows that individuals identified and diagnosed with diabetes who lived in Yogyakarta have the highest prevalence at age ≥45 years [39]. The T2DM prevalence shows an increase with increasing age of patients and reaches its peak at 55-65 years. Therefore, we classified the participants into two groups, one group ≥45 years and the other >45 years. The following table is a crosstabulation for the number of test subjects based on their age group.

Table 2. The Crosstabulation of the test subjects due to their ages and smoking status.

Smoking Status	Age (Years)		Total
	≤ 45	> 45	
Active Smokers n (%)	3 (2.8)	16 (15)	19 (17.8)
Pasive Smokers n (%)	0 (0)	31 (29.97)	31 (29)
Non-smokers n (%)	0 (0)	57 (53.3)	57 (53.3)
Total	3 (2.8)	104 (97.3)	107 (00)

The Guidelines for the Management and Prevention of Type 2 Diabetes Mellitus (T2DM) in Indonesia (2021) recommended that individuals with diabetes undergo a lipid profile examination at least once a year, or more frequently if necessary, to monitor the risk of dyslipidemia. The threshold limits for each lipid level are defined as follows: triglycerides (TG) should be less than 150 mg/dL, total cholesterol should be less than 200 mg/dL, low-density lipoprotein cholesterol (LDL-C) should be less than 130 mg/dL, and high-density lipoprotein cholesterol (HDL-C) should be higher than 40 mg/dL [40]. As shown in Table 1, TG levels in all participants exceeded the normal range. In contrast, the mean total cholesterol, LDL-C, and HDL-C levels were within expected limits. This finding is consistent with information from PERKENI (2021), which states that the typical characteristics of diabetic dyslipidemia include elevated TG levels and low HDL-C levels, while LDL-C levels are usually normal or only slightly elevated. However, the lipid profile, (TG, total cholesterol, LDL-C, and HDL-C) ranged from below to above normal values, indicating that some of the participants had dyslipidemia. In this study, a total of 60 participants were identified as having dyslipidemia, as presented in the following table:

Participant's lipid profile

Table 3. Dyslipidemia among the participants due to their lipid profile.

Profil lipid	Frekuency n (%)
High TG (only)	9 (15)
High LDL-C (only)	10 (16.7)
Low HDL-C (only)	19 (31.7)
High CH & high TG	1 (1.7)
High TG & low HDL-C	4 (6.7)
High CH & high LDL-C	4 (6.7)
High TG & high LDL-C	1 (1.7)
High LDL-C & low HDL-C	7 (11.7)
High CH & high TG & high LDL-C	3 (5)
High CH & high TG & low HDL-C	1 (1.7)
High CH & high TG & high LDL-C & low HDL-C	1 (1.7)
Total	60 (100)

Based on their lipid profiles, the following table presents the impact of smoking status on dyslipidemia among the participants:

Table 4. Dyslipidemia among participants due to their smoking status.

Risk Factor	Dyslipidemia		χ2 (P-value)
	Yes n (%)	No	
Smoking status			
Aktif smoker	17 (15.9)	2 (1.9)	13.463 (0.001)
Pasive smoker	19 (17.8)	12 (11.2)	
Non-smoker	24 (22.4)	33 (30.8)	

DISCUSSION

We found that the number of female participants in this study was higher than that of males, as shown in Table 1. Consistent with our findings, a review article titled "Sex Differences in Type 2 Diabetes" reported that females may be more susceptible to T2DM than males [41]. Several studies have suggested that women generally have a higher percentage of body fat than men, and excess adiposity, particularly visceral fat, is strongly associated with an increased risk of insulin resistance [42]-[44]. As indicated in Table 1, all female participants in this study were menopausal, a physiological condition characterized by hormonal changes that can reduce insulin sensitivity [45],[46]. In addition, lifestyle factors such as poor diet and physical inactivity have also been identified as major contributors to the increased risk of diabetes among females [47]-[49].

Furthermore, based on their smoking status shown in Table 1, it should be noted that all female participants in this study were passive or non-smokers, while all active smokers were male. According to Infodatin (2015), the prevalence of active smoking in Yogyakarta among individuals aged 10 years and older was substantially higher in men (54.2%) than in women (0.6%) [50]. The active male smokers began smoking between the ages of 10 and 50 years, with smoking durations ranging from 17 to 53 years, and consumed 1 to 30 cigarettes per day. It suggests that many of the active male smokers might have developed T2DM prior to diagnosis but continued smoking thereafter. Among the passive smokers, the number of female participants (n=24) exceeded that of males (n=7). According to Riskesdas (2018), approximately 96 million Indonesians were exposed to secondhand smoke, with women and children being the most affected. The same report indicated that in Yogyakarta, exposure to cigarette smoke reached 73.9% in enclosed public areas and 66.9% within households. Ironically, the household, expected to provide protection, has become one of the primary sources of secondhand smoke exposure [39]. Although passive smokers are often perceived as having a lower risk compared to active smokers, several studies have demonstrated that exposure to secondhand smoke may induce similar metabolic disturbances. Chronic exposure to cigarette smoke, even at low concentrations, increases oxidative stress, triggers systemic inflammation, and impairs insulin signaling pathways, thereby promoting glucose intolerance and dyslipidemia[31],[33]. Epidemiological evidence indicates that non-smoking individuals exposed to environmental tobacco smoke have a 20–30% higher risk of developing T2DM compared to those unexposed [48],[49]. Moreover, passive smoking in women has been associated with elevated fasting glucose levels and altered lipid profiles, suggesting that continuous exposure, especially in domestic environments, may substantially contribute to the pathogenesis of T2DM. Therefore, the impact of passive smoking should not be underestimated, as its biological effects may parallel those observed in active smokers, particularly in individuals with predisposing metabolic conditions [32].

As shown in Table 2, 95.3% of the participants were over 45 years old, while the remaining participants, who were under 45, were all smokers. None of the individuals under 45 were passive smokers or non-smokers. The participants in this study were patients who regularly received antidiabetic treatment. Therefore, to evaluate the effectiveness of T2DM therapy, we examined the HbA1c levels among the participants. Based on Table 1, the mean HbA1c levels among the participants were > 6.5, indicating that the treatment failed to meet the target therapy. However, the HbA1c range was 5.7–14.9%, suggesting that several participants had achieved the therapeutic target (HbA1c was <6.5). Only four participants had HbA1c levels below 6.5%, consisting of one passive smoker and three non-smokers. None of the active smokers achieved an HbA1c value below 6.5%. Our previous study reported that smoking adversely affected HbA1c levels in T2DM patients [13]. Consistent with our findings, several studies have also demonstrated that smoking worsens glycemic control in diabetic patients by increasing HbA1c levels and reducing treatment efficacy [51]-[53]. Furthermore, as shown in Table 1 above, four participants had HbA1c values <6.5, consisting of one passive smoker and three non-smokers. The passive smokers reported inhaling cigarette smoke in the same amount or even more than active smokers [34], [54], [55]. Our previous study revealed a high frequency of *cyp2a6* polymorphism, particularly *cyp26*4*, among both smokers and non-smoker with T2DM in the Javanese population [56]. The presence of the *cyp26*4* may contribute to elevated HbA1c levels in T2DM patients. The *cyp2a6* encodes the CYP2A6 enzyme, which plays a crucial role in nicotine metabolism. The *cyp2a6*4* allele produces an inactive enzyme, leading to higher nicotine accumulation in the blood and, consequently, lipid disorders among T2DM patients [57]-[59].

According to Table 4, the prevalence of diabetic dyslipidemia among the participants was 56.1%, while 43.9% exhibited a desirable lipid profile, the majority of whom were non-smokers. Previous studies have

consistently reported that diabetic dyslipidemia is characterized by elevated total cholesterol (TC) and reduced HDL-C levels [60]-[62]. Since insulin plays a crucial role in lipid metabolism, insulin resistance and insufficient insulin production in individuals with type 2 diabetes mellitus (T2DM) can contribute to dyslipidemia. Moreover, diabetic dyslipidemia has also been associated with the activity of adipocytokines such as resistin and adiponectin [6],[60],[63]. The independent chi-square analysis revealed a significant association between smoking status and the presence of dyslipidemia among the participants (χ^2 = 13.463, p-value of 0.001). This finding aligns with several studies conducted in other populations, which also demonstrated an association between smoking and abnormal lipid profiles among diabetic patients [64], [65]. People with diabetes who smoke generally exhibit a less favorable lipid profile compared to non-smokers [66], [67]. Nicotine, a primary compound of cigarette smoke, may alter lipid metabolism by enhancing lipolysis and increasing circulating free fatty acids, which in turn promote triglyceride synthesis and insulin resistance, ultimately leading to dysregulation of serum lipid levels [68]. Raddam and Zeidan (2020) similarly reported that smokers tend to have lower serum lipase activity, predisposing them to an unfavorable lipid profile compared with non-smokers [68]. Furthermore, smoking behavior among individuals with diabetes has been shown to increase the risk of developing cardiovascular diseases (CVDs) [69]. A separate study indicated that inadequate smoking behaviors in individuals with diabetes increase the risk of developing cardiovascular disease (CVD) [70].

The Handbook for Dyslipidemia Management in Indonesia (2021) states that dyslipidemia plays a principal role in the pathogenesis of atherosclerosis and in triggering cardiovascular disease (CVD) and stroke, which remain the leading causes of death globally, accounting for approximately 17.3 million of the 54 million total deaths each year [71]. Collaborative efforts among healthcare professionals, diabetic patients, and their families are urgently needed to prevent and reduce the prevalence of diabetes mellitus and its related complications in Indonesia. In response, the Indonesian Government (2014) established the Chronic Disease Management Program (Program Pengelolaan Penyakit Kronis—PROLANIS), an integrated health initiative involving patient communities, healthcare professionals, healthcare facilities, and the national health insurance system (BPJS). The program is implemented at the primary healthcare level to monitor clinical parameters, including HbA1c, TG, total cholesterol, LDL-C, and HDL-C levels. Its primary goals are to prevent complications and improve patients' quality of life. However, a preliminary study involving 43 PROLANIS participants reported that the program appeared less effective in controlling diabetes mellitus and preventing its complications, primarily due to participants' noncompliance with attending PROLANIS activities [72].

High cigarette consumption in Indonesia remains a principal public health concern, particularly in the management of diabetes mellitus. Despite the well-documented adverse effects of smoking, many individuals with diabetes continue to smoke, thereby increasing their risk of developing severe complications and contributing to higher mortality rates. Understanding the influence of smoking on diabetes management is essential for effective disease control. In Indonesia, smoking cessation programs are often not integrated into diabetes care services. Although the "Kawasan Tanpa Rokok" (KTR, or Smoke-Free Zone) policy was implemented in the Province of Yogyakarta Special Region in 2009, the prevalence of non-communicable diseases, including diabetes, cardiovascular diseases, and cancer, remains high, partly due to persistent exposure to cigarette smoke [29]. The present study provides evidence that may support the government's efforts to reduce cigarette smoke exposure through community-based smoking cessation initiatives. Strengthening collaboration between healthcare providers and public health authorities could be a key strategy to improve health outcomes among diabetic patients who smoke.

Although this study presents several research findings, it is crucial to acknowledge its limitations. First, the use of a cross-sectional design restricts the study's ability to establish a causal relationship between smoking status and the risk of dyslipidemia, as it only reveals correlations. Second, smoking status information was gathered through interviews, which depended on the respondents' honesty, thus introducing the potential for information bias or underreporting. Third, the participants were drawn solely from one hospital in Yogyakarta, which limits the generalizability of the results to a broader population or other areas with different demographic characteristics. Lastly, this study did not explicitly control for additional confounding factors that could influence the risk of dyslipidemia, such as dietary habits, physical activity levels, and genetic predispositions.

CONCLUSION

This study demonstrates a significant association between smoking habits and an increased risk of dyslipidemia among individuals with type 2 diabetes mellitus (T2DM). Smokers tend to exhibit greater abnormalities in lipid profiles, including elevated TG, total cholesterol, and LDL-C levels, along with reduced HDL-C levels, compared to passive and non-smokers. These findings highlight the urgent need for targeted educational and behavioral interventions to reduce smoking among patients with T2DM. Addressing smoking behavior is essential to mitigate metabolic complications such as dyslipidemia and to improve overall disease management and patient quality of life. Implementing these initiatives is crucial for both the physiological well-being of patients and the enhancement of their overall quality of life.

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