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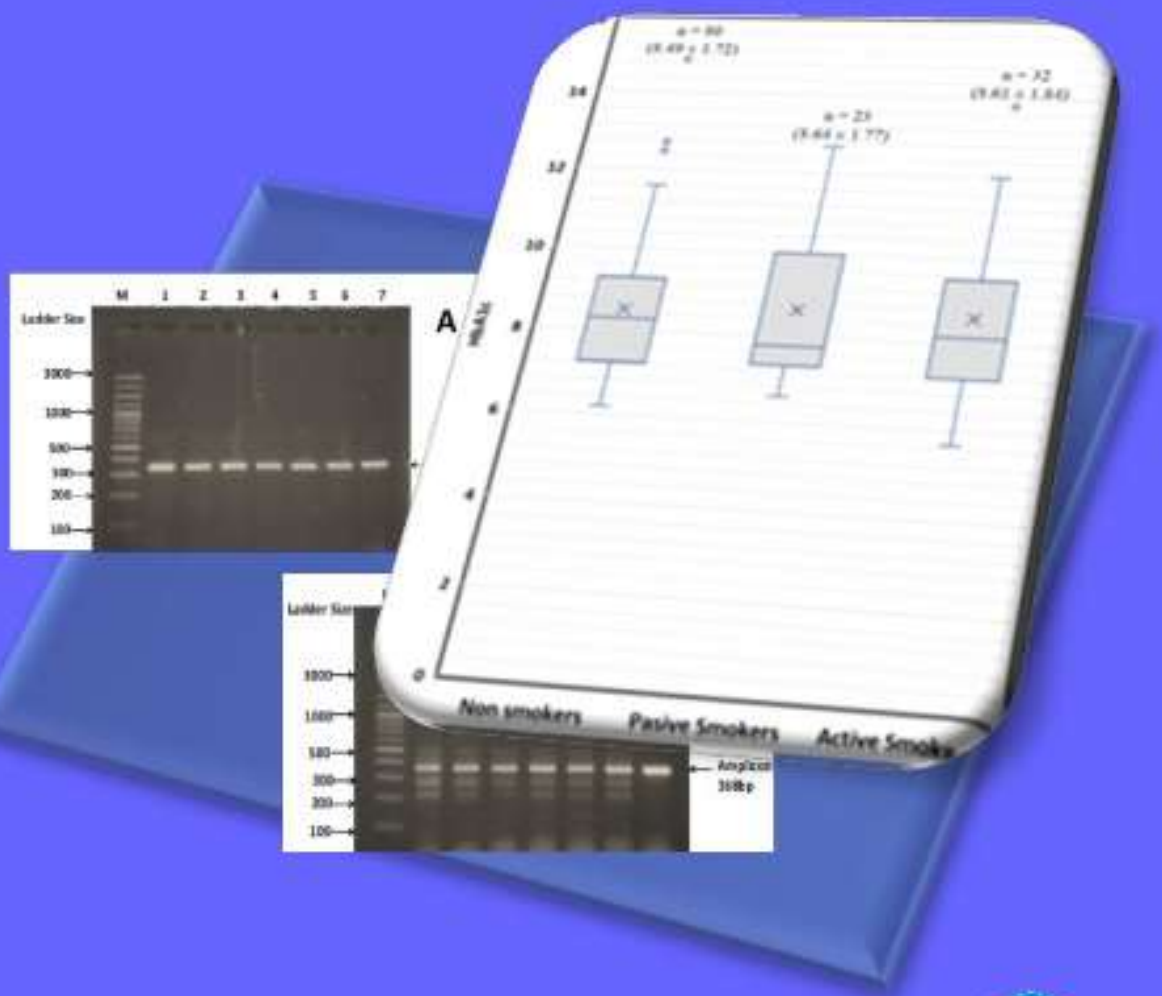
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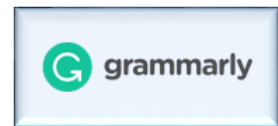
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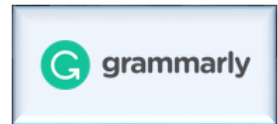
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High Frequency of *CYP2A6**4, *CYP2A6**7, and *CYP2A6**9 Alleles Detected Among Patients with Type 2 Diabetic: Genetic Study in The Private Hospital in Yogyakarta

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ABSTRACT

Smoking is a risk factor for type 2 diabetic (T2DM), since the nicotine in cigarettes can cause insulin resistance and increase lipolysis. Both of these can worsen the condition of patients with T2DM and increase treatment failure. Nicotine is metabolized to cotinine by the *CYP2A6* enzyme encoded by the *CYP2A6* gene. This gene is highly polymorphic, with several inactive alleles, which are *CYP2A6* *4, *CYP2A6* *7, and *CYP2A6* *9. Someone who has an inactive gene will experience being a slow or poor metabolizer. Therefore, the nicotine metabolism will decrease, nicotine blood levels will increase, causing therapy failure among patients with T2DM. This study aims to determine the distribution of *CYP2A6**4, *CYP2A6**7, and *CYP2A6**9 among patients with T2DM who have been routinely treated using oral antidiabetics. We also investigated whether HbA1c levels is a predictor for the success of the treatment. This observational study was conducted with a cross-sectional design. Polymerase chain reaction was used to analyze the three inactive alleles with specific primers. Based on our study, there is a high frequency of the inactive alleles, i.e., *CYP2A6**4, *CYP2A6**7, and *CYP2A6**9, among the patients with T2DM. The presence of these inactive alleles will worsen and reduce the effectiveness of the therapy. Smoking cessation programs are needed to increase the effectiveness of the anti-diabetic therapy.

INTRODUCTION

Diabetic Mellitus (DM), a chronic disease, is the third leading cause of death in Indonesia, with a percentage of 6.7%, after stroke (21.1%), and coronary heart disease (12.9%). General DM prevalence has increased significantly from 6.9% in 2013 to 8.5% in 2018 (Kementrian Kesehatan RI, 2018). Other data estimated that there are approximately 30% of Indonesia's population (30 million people) with diabetic who remain undiagnosed (Infodatin, 2020). Accordingly, if DM is not managed appropriately, then the incidence in Indonesia will increase dramatically. The International Diabetic Federation (IDF) has even estimated that the incidence of diabetic in

Indonesia will raise drastically to 212 million people in 2030 (IDF, 2021).

Type 2 Diabetic Mellitus (T2DM) is the most common DM in adults and accounts for more than 90% of all cases. In the past, T2DM was known to be a disease that primarily occurred in adults and acquired later in life. However, in recent years, there has been an increase in the incidence of T2DM in children and adolescents. Riskesdas (2018) reported that the prevalence of DM in the Daerah Istimewa Yogyakarta (DIY) Province is second in all provinces in Indonesia (Kementrian Kesehatan RI, 2018). In DIY, 74,668 people have been diagnosed with diabetic, but only 55,190 patients have received standard health services, which is

equivalent to 73.9% (DIY Health Profile, 2019). There are several risk factors for T2DM, including age, ethnicity, obesity, family history, and cigarette smoking (Zhao *et al.*, 2017).

Several studies have suggested that poor smoking behavior is associated with chronic complications of T2DM compared to nonsmokers (Hong, 2015; Kowall, 2010; Liu, 2018). Some other studies have reported that smoking can increase glycohemoglobin (HbA1c) blood levels (Nilsson *et al.*, 2004; Vlassopoulos *et al.*, 2013). This HbA1c value can accurately reflect glucose control 2-3 months ago. According to the American Diabetic Association (ADA) (2011), HbA1c levels are normal if <5.7%, prediabetic when 5.7-6.4%, while confirmed diabetic is identified as ≥6.5%. Nicotine, the main compound in cigarettes, is considered most responsible for increasing blood sugar levels due to insulin resistance (Bajaj, 2012; Borowitz and Isom, 2008; Xie *et al.*, 2009).

Nicotine is primarily metabolized by the liver enzyme CYP2A6 to cotinine and excreted in the urine (Hukanen, 2005). The CYP2A6 enzyme encoded by the *CYP2A6* gene is a polymorphic gene. The active allele gene is *CYP2A6*1*, and the inactive alleles are *CYP2A6*4*, *CYP2A6*7*, and *CYP2A6*9*. A person having these inactive allele genes is associated with being a slow or poor metabolizer. Furthermore, according to Liu *et al.* (2011), reduced metabolism function of CYP2A6 in smokers appears to be associated with a higher risk of developing T2DM.

In the preliminary study, we found a high-frequency of the *CYP2A6*4* allele gene among smokers and non-smokers in Javanese Indonesians (Patramurti *et al.*, 2015). In line with another study, we have also reported that

smoking can increase the risk factors for diabetic. Prediabetic was found in smokers who had smoked for at least 25 years with 25 cigarettes smoked per day (Patramurti, 2020). Accordingly, in this research, we evaluated the effect of *CYP2A6*4*, *CYP2A6*7*, and *CYP2A6*9* allele genes on glycohemoglobine levels among Javanese Indonesian patients with T2DM.

METHODS

This observational study was conducted with a cross-sectional design to describe the *CYP2A6* polymorphisms, especially *CYP2A6*4*, *CYP2A6*7*, and *CYP2A6*9*, among Indonesian patients with T2DM. Patients were enrolled in July 2021. A preliminary survey was directed to find patients who smoked using a self-reported smoking questionnaire adopted from the Fagerström Test for Nicotine Dependence (FTND) questionnaire (Heatherton, 1991). The participants had to meet the inclusion criteria study, i.e., T2DM patient who is routinely treated by oral antidiabetic, aged 20-75 years, bodyweight between 46 s/d -75 kg, with a varying height between 150-170 cm. All participants had agreed to participate in this study indicated by signing the informed consent form. The study had been approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

As much as 3 mL of blood was sampled from a cubital vein in all participants who had met the inclusion and exclusion criteria. Blood samples were collected in a vacutainer containing EDTA (1.8 mg / mL blood) and immediately stored in the refrigerator at +4°C.

Table 1. Primer used in the present study

| Alele Gen | Sequence | |
|-----------|-------------------------------------|--------------------------------------|
| | Forward Primer | Reverse Primer |
| CYP2A*4 | 5' CCT CAT CAC ACA CAA CTT CCT C 3' | 5' TGC AGG TAC TGG GTG CTT GGT AG 3' |
| CYP2A*7 | 5'-CTC CCA GTC ACC TAA GGA CAC-3' | 5'-AAA ATG GGC ATG AAC GCC C-3' |
| CYP2A*9 | 5'-GAT TCC TCT CCC CTG GAA C-3' | 5'-GGC TGG GGT GGT TTG CCT TTC-3' |

Table 2. PCR condition used in the present study

| PCR Condition | Allele Gene | | |
|----------------------|-------------|---------------|-------------|
| | CYP2A*4 | CYP2A*7 | CYP2A*9 |
| Initial denaturation | 95 °C (5') | 95 °C (5') | 94 °C (3') |
| Denaturation | 98 °C (20") | 95 °C (20") | 94 °C (30") |
| Annealing | 64 °C (15") | 56,5 °C (30") | 60 °C (30") |
| Extention | 72 °C (30") | 72 °C (30") | 70 °C (25") |
| Cycle | 30 | 35 | 35 |
| Final extention | 72°C (5') | 72°C (5') | 72°C (5') |

Table 3. The Respondent Characteristics

| Characteristic | Smoking Status | | | Total |
|--------------------|----------------|----------------|--------------|--------------|
| | Active Smoker | Passive Smoker | Non-Smoker | |
| Number (%) | 14 (11,97) | 23 (19,66) | 80 (68,38) | 100% |
| Age | 59.12 ± 9.60 | 58 ± 8,40 | 61.33 ± 7.55 | 60.23 ± 8.27 |
| Mean ± SD | 36 - 74 | 45 - 75 | 43 - 81 | 36 - 81 |
| Range | | | | |
| First Age Smoking: | | | | |
| Mean ± SD | 19.50 ± 11.27 | - | - | - |
| Range | 10 - 50 | | | |
| Smoking duration: | | | | |
| Mean ± SD | 31.11 ± 12.36 | - | - | - |
| Range | 15 - 53 | | | |
| CPD | | | | |
| Mean ± SD | 14 ± 5 | - | - | - |
| Range | 10 - 21 | | | |

Table 4. CYP2A6*4, CYP2A6*, and CYP2A6*9 Allele Frequency among The Patients

| Allele | Frequency | | Total |
|----------|----------------|-------------|-------|
| | Active Smokers | Non-Smokers | |
| CYP2A6*4 | 7.9% | 25.4% | 33.3% |
| CYP2A6*7 | 7.9% | 25.4% | 33.3% |
| CYP2A6*9 | 7.9% | 25.4% | 33.3% |

A TTAB tetradecyl trimethyl ammonium bromide Method using Indiko™ Clinical Chemistry Analyzer, which was calibrated using Diabetic Control and Complications Trial (DCCT) standards with the coefficient of variation <2.5% was used to analyze the total HbA1c in the Clinical Pathology Laboratory, Bethesda Hospital Yogyakarta.

DNA was extracted using the Cell DNA Mini Kit obtained from Bioron GmbH (Germany). The CYP2A6 *4, *7, and *9 allele genes were analyzed using the Polymerase Chain Reaction (PCR) methods. The forward and reverse primers used in this study are presented in Table 1.

The PCR mixture contained 12.5 µL Promega Go Taq Green Master Mix, 1.25 µL forward primer, 1.25 µL reverse primer, 5.0 µL genomic DNA with approximately 5 ng genomic DNA, and 5.0 µL nuclease-free water in a final volume of 25 µL. This mixture was run through a thermal cycler (Perkin Elmer 2400) to amplify the genomic DNA. The PCR conditions used are documented in Table 2.

The PCR products consisting of 350bp, 349bp, and 368bp fragments DNA were analyzed using electrophoresis with 1.5% agarose and evaluated using an ultraviolet (UV) transilluminator. These PCR products are documented using a Polaroid camera.

Statistical analyses

We used statistical software Microsoft Excel 2016 to describe the characteristics of the patients participating in this study. All values are expressed as mean ± standard deviation (SD) or median numbers with percentages (%). ANOVA test was used for all statistical analyses with a *p*-value < 0.05, indicating a significant difference. The box plot analysis was used to describe the HbA1c values among the patients.

RESULTS AND DISCUSSION

The patients participating in this study were patients with T2DM at a private hospital in Yogyakarta who routinely received oral antidiabetics. All test subjects received an oral antidiabetic for minimum six months. Based on their smoking habits, there were 11.97% active smokers among the patients, the rest were passive smokers and non-smokers (88.38%). Riset Kesehatan Dasar (Riskesdas) 2018 reported that smoking prevalence in Indonesia is very high, indicating that 62.9% are male, and 4.8% are women. This report also showed that as many as 96 million Indonesians are passive smokers. The number of passive smokers was dominated by women and children (R.I., 2018). Based on these data, the high percentage of patients who have no smoking history in this study may also be due to being passive smokers.

Table 1 below shows the respondents characteristics participating in this study.

Based on Table 1 above, 93.5% of patients are more than 40 years old, and only 6.5% of patients are less than 40 years old. Several studies have shown that the risk of diabetic increases with age, especially >40 years old (Alva *et al.*, 2017; Berenson, 2012; Gudbjornsdottir, 2019; Kirkman *et al.*, 2012). According to Riskesdas 2018, persons generally suffering T2DM are in the age of 55-74 years. Diabetic tends to be an underdiagnosed disease. Approximately 30% of diabetics often do not realize their disorder. Therefore, they often find out too late if they have T2DM. The average delay from onset to diagnosis is estimated to be about seven years (Buell *et al.*, 2007). This study has also supported the report issued by Riskesdas 2018, that indicated only about 25% of diabetics in Indonesia know that they have diabetic.

Based on Table 3 above, 11.97% of the patients are smokers. All of these patients had smoked for at least 17 years, indicating that they have been exposed to nicotine for a long time. Some of the patients had started smoking at the age of under ten years. Several factors influence smoking behavior among children and adolescents, including easy access to cigarettes, family and peer environment, and also cigarette promotion/advertising. Meanwhile, based on the number of cigarettes per day (CPD), the average of the CPD smoked by patients was only 14 cigarettes per day. Riskesdas (2018) reported that the average of CPD by Indonesian adults was 13 cigarettes or the equivalent of one pack (R.I., 2018). Several studies have proven that cigarette dependence can trigger the occurrence of T2DM. Compared to non-smokers, active smokers have a 76% higher risk of developing T2DM (Maddatu *et al.*, 2017; Sarah and Shilliday, 2006; Spijkerman *et al.*, 2014; Stadler *et al.*, 2014). Nicotine in cigarette smoke is responsible for the association between smoking and the development of T2DM (Bajaj, 2012; Borowitz and Isom, 2008; Xie *et al.*, 2009). Nicotine in cigarettes causes insulin resistance and reduced insulin secretion (Bajaj, 2012; Houston *et al.*, 2006; Liu *et al.*, 2013; Willi *et al.*, 2007). Xie *et al.* (2009) revealed that nicotine exposure in the long term will decrease insulin secretion through the activation of nAChRs present in pancreatic cells. Furthermore, Xie *et al.* (2009) also mentioned that nicotine exposure for a short period (24 hours) will inhibit insulin release from the pancreas. Other studies have shown that nicotine exposure can cause pancreatic cell dysfunction, increased cell apoptosis, and cell

loss (Morimoto *et al.*, 2013; Somm *et al.*, 2008). In addition, nicotine can also increase the lipolysis pathway, causing increased levels of fatty acids and triggering triglyceride synthesis and VLDL secretion (Devaranavadgi and Aski, 2012; Koda *et al.*, 2016; Papathanasiou *et al.*, 2014; Singh, 2016). Eventually, it will cause an increase in blood glucose levels and other T2DM risk factors, both in active and passive smokers.

As much as 70 to 90% of nicotine entering into the body will be metabolized into cotinine by cytochrome P450 2A6 (CYP2A6) enzyme coded the *CYP2A6* gene (Hukkanen *et al.*, 2005). This gene is highly polymorphic. These polymorphic genes can lead to conversion, deletion, duplication, and single nucleotide polymorphisms (SNPs). Furthermore, it causes decreasing, increasing, or even eliminating the CYP2A6 enzyme activity (Raunio and Rahnasto-Rilla, 2012). In addition, another factor that can increase the T2DM risk in a smoker is the *CYP2A6* polymorphism genes. There are three *CYP2A6* inactive allele genes that have been identified in this study, namely *CYP2A6**4, *7, and *9. The *CYP2A6**4, a whole gene deletion, is due to the unequal crossover junction with *CYP2A7*. *CYP2A6**7 occurs due to the SNPs in the 8454th nucleotide base sequence (T>C). The *CYP2A6**9 allele forms due to the SNPs in the TATA BOX in the *CYP2A6* promoter region at the -48T>G point (Raunio and Rahnasto-Rilla, 2012). Figure 1 presents the PCR products for *CYP2A6**4, *7, and *9.

The presence of these allele genes will decrease the CYP2A6 enzyme activity, making the person either an intermediate, slow, or poor metabolizer. Smokers with slow or poor metabolism are more susceptible to suffering T2DM than fast metabolizers (Liu *et al.*, 2011). Table 4 shows the allele frequency analysis among the patients.

Table 4 shows that all of the subjects participating in this study have the *CYP2A6**4, *CYP2A6**7, and *CYP2A6**9. The *CYP2A6* inactive allele frequencies found in this study are high. It is consistent with our previous studies that among Javanese and Chinese Indonesians, both smokers and non-smokers, there is a high frequency of the *CYP2A6* inactive alleles (Patramurti *et al.*, 2019; Patramurti, 2019; Patramurti *et al.*, 2015). These allele genes will decrease the CYP2A6 enzyme activity (Raunio and Rahnasto-Rilla, 2012). Several studies have revealed that smokers with the inactive alleles would slow the metabolize of nicotine compared to the active allele. Consequently, when the nicotine blood levels becomes higher, then the

CPD and the nicotine dependence becomes lower (Ando *et al.*, 2003; Chenoweth *et al.*, 2013; O'Loughlin, 2004; Schoedel *et al.*, 2004). Liu (2011) reported that slow metabolizer smokers would have a higher risk of developing T2DM compared to fast metabolizer smokers.

In this study, the patients participating in this study had received oral antidiabetic treatment. These antidiabetics could improve insulin receptor sensitivity, reduce free fatty acid levels and increase glucose transport in the blood (Bösenberg and Van Zyl, 2008; Lorenzati *et al.*, 2010). The parameter used to monitor blood sugar levels in this study was using HbA1c. Several studies have used the HbA1c parameter to control the blood sugar levels (Buell *et al.*, 2007; Nair *et al.*, 2011; Prajapati *et al.*, 2014; Saudek *et al.*, 2006; Soraya Soulimane, 2011). According to Soelistijo *et al.*, (2015), the normal range for the HbA1c level is lower than 5.6%. People with HbA1c levels between 5.7% and 6.4% have prediabetic and a higher chance of getting diabetic. The diabetic condition is established if the HbA1c levels are higher than 6.5%. Sargeant *et al.*, (2001) reported a positive correlation between cigarette dependence and

HbA1c values in smokers. Several other studies also revealed that compared to non-smokers, smokers have higher HbA1c levels and 30-40% higher risk of T2DM (Cho *et al.*, 2009; Hong *et al.*, 2018).

The box plot presented in Figure 2 describes the HbA1c distribution among the patients. For both active smokers, passive smokers, and non-smokers, the average HbA1c value is 8.5. Statistically, the HbA1c data between these three groups of patients did not differ significantly (p -value 0.915, >0.005). HbA1c data among patients was dominated by a value above 6.5. There are only six patients whose HbA1c values are below 6.5. It shows that oral antidiabetic treatment to the patients did not provide effective results. Chang (2012) had reported that smoking behavior, both in active and passive smokers, can worsen the condition of patients with T2DM and reduce the effectiveness of the treatment given. The presence of the CYP2A6 inactive allele among patients participating in this study will decrease the given oral diabetic treatment causing ineffectiveness, especially in active smokers.

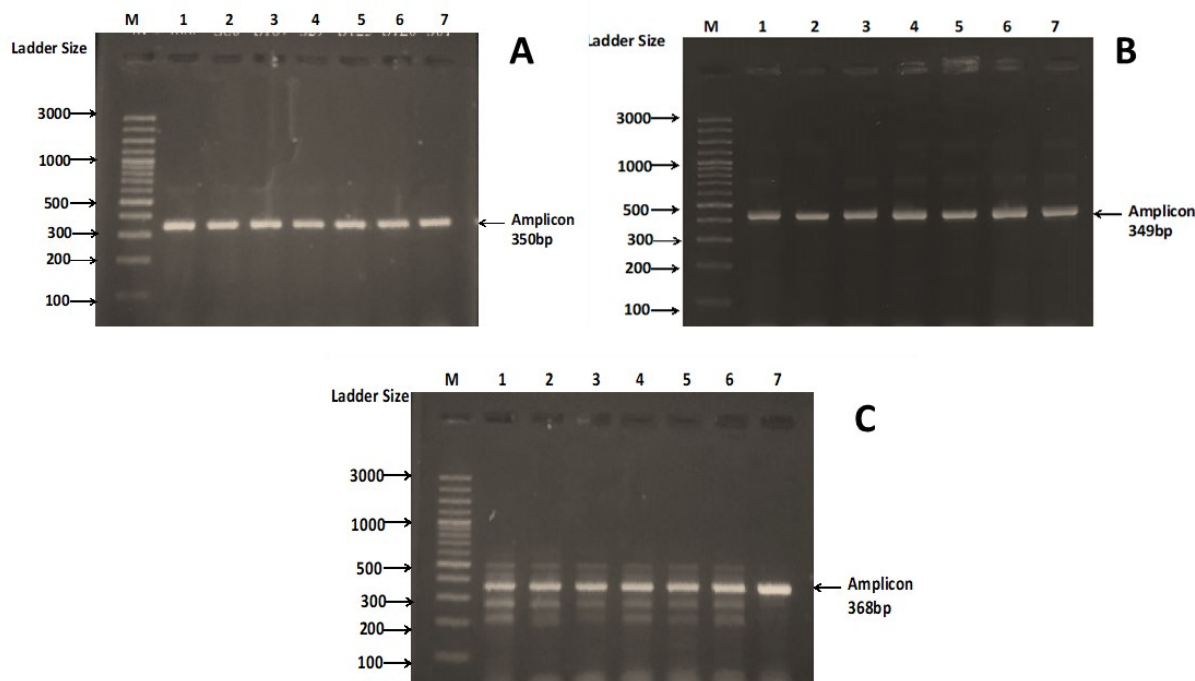


Figure 1. Electrophoregram PCR product identification of CYP2A6*4 (A), CYP2A6*7 (B), and CYP2A6*9 (C) allele gene among the respondents. M1: Marker DNA Ladder. 1-7: Amplicon obtained among the respondents

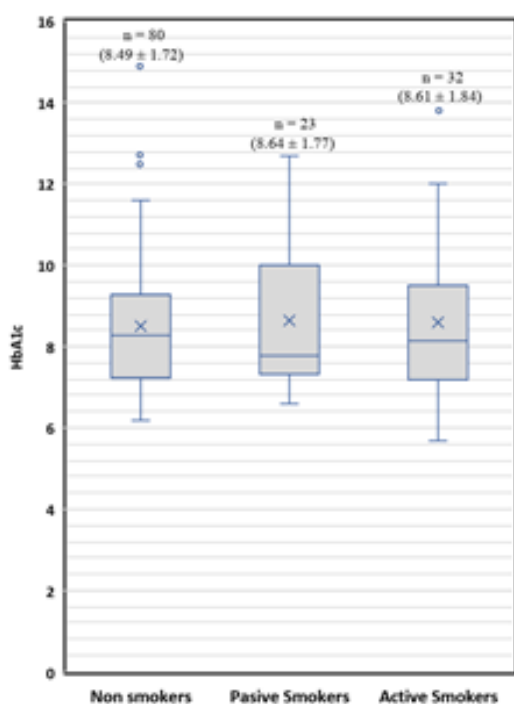


Figure 2. The HbA1c Distribution among Respondent according to their CPD.

○ : Outliyer value of HbA1c Levels
X : Avarage of HbA1c Levels

The increasing of lipid profiles, both levels of triglycerides, cholesterol, and high-density lipoproteins (HDL), due to nicotine exposure will worsen the condition of patients with T2DM2 so that the given treatment becomes ineffective. As a result, T2DM smoker patients who have the inactive alleles, i.e., *CYP2A6*4*, *CYP2A6*7*, or *CYP2A6*9*, and continue to smoke, their lipid profile levels will remain uncontrolled due to the high level of nicotine blood levels, leading to treatment failure.

Padmawati *et al.* (2009) reported that 65% of patients with T2DM in Yogyakarta had a smoking history before they were diagnosed with T2DM. As a matter of fact, some T2DM patients still smoked regardless of the smoking risk. It is due to the absence of an integrated effort from related parties to pursue a smoking cessation program. Several studies conducted on adult smokers have shown that smokers who have the *CYP2A6* inactive allele will have less CPD and a lower tendency to cigarette dependence when compared to smokers who have an active allele (*CYP2A6*1*) (Chenoweth *et al.*, 2013; O'Loughlin, 2004; Schoedel *et al.*, 2004). Another study reported that smokers with slow or poor metabolism would tend to be easier to quit smoking (Ando *et al.*, 2003; Fujieda *et al.*, 2004; Minematsu *et al.*, 2006). The high number of

smokers in Indonesia was one of the risk factors for serious health problems. Therefore, smoking cessation programs are needed to resolve these problems. The presence of the inactive allele of the *CYP2A6* gene among the Indonesian people will accelerate the accomplishment of smoking cessation programs in Indonesia.

There are some limitations to our study. First, we did not measure obesity and information about the diet of the patients. According to Binh and Nhung (2015), in addition, obesity, and the wrong diet will affect the DM therapy success. Second, we also did not conduct evaluations related to the therapy period of the patients. Third, we also did not obtain information about the HbA1c value the first time the patient was on treatment.

CONCLUSIONS

Based on our study, it is concluded that there is a high frequency of the three inactive main *CYP2A* alleles among the patients, i.e., *CYP2A6*4*, *CYP2A6*7*, and *CYP2A6*9*, which are considered to worsen the condition of patients with T2DM and tend to increase the given treatment failure. It is crucial for physicians who care for the T2DM patients, particularly those who are still smoking, to encourage them to stop their smoking habits. *CYP2A6* genotype identification may be the crucial practical step for smoking cessation programs.

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