

# Cigarette Smoking and Hyperglycaemia in Diabetic Patients

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## Abstract

**Citation:** Sari MI, Sari N, Darlan DM, Prasetya RJ. Cigarette Smoking and Hyperglycaemia in Diabetic Patients. Open Access Maced J Med Sci. 2018 Apr 15; 6(4):634-637. https://doi.org/10.3889/oamjms.2018.140

**Keywords:** Smoking; Nicotine; Diabetes mellitus; Blood glucose; HbA1c

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**Received:** 05-Nov-2017; **Revised:** 20-Feb-2018; **Accepted:** 28-Feb-2018; **Online first:** 05-Apr-2018

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**Funding:** This research is supported by Institutions of Research, Universitas of Sumatera Utara (USU), as Talenta Research USU of the Year 2017 with contract no. 5338/UNS.1.R/RPM/2017, May 22nd, 2017

**Competing Interests:** The authors have declared that no competing interests exist

**BACKGROUND:** The incidence rate of diabetes mellitus has increased throughout the year. Various studies indicate that smoking may affect glucose metabolism and cause hyperglycemia in diabetes mellitus. This study aimed to compare the blood glucose and HbA1c level in diabetic smoking patients and non-smoking diabetic patients.

**METHODS:** This study used the cross-sectional approach. The study population consisted of 30 diabetic smoking patients and 30 non-smoking diabetic patients. The diabetes history and the smoking status of the study population obtained by questionnaire-based interview, the blood glucose and HbA1c level were measured by hexokinase and immunoturbidimetry method using cobas 6000 analyser module c501 (Roche Diagnostics, Switzerland).

**RESULTS:** The result in this study showed the fasting blood glucose, postprandial blood glucose, and HbA1c were higher by 23.64 mg/dl ( $p = 0.325$ ), 58.00 mg/dl ( $p = 0.016$ ), 0.39% ( $p = 0.412$ ) in smoking diabetic patients compared to non-smoking diabetic patients. After statistical analysis, there was a significant difference ( $p < 0.05$ ) of postprandial glucose level between smokers group and non-smokers group, but the non-significant difference of fasting blood glucose and HbA1c

**CONCLUSIONS:** This study concluded that there was a significant difference in postprandial glucose level between smokers group and non-smokers group but the non-significant difference of fasting blood glucose and HbA1c.

## Introduction

The incidence rate of Diabetes Mellitus (DM) has been increasing in every year in the worldwide. International Diabetes Federation estimates in 2015 that 8.5% (equivalent to 78.3 million people) of the adult population in South-East Asia suffers from diabetes. In Indonesia, an increase in diabetes incidence has been noted, from 1.1% in 2007 to 2.1% in 2013 [1] [2]. Diabetes is a metabolic disorder characterised by the presence of chronic hyperglycemia. Hyperglycemia may be caused by insulin resistance syndrome, insulin deficiency, or both [3]. Diabetes can be diagnosed by biomarker of hyperglycemia, i.e. the random blood glucose test,

fasting blood glucose test, or postprandial glucose test. Many factors are known to affect blood glucose in the diabetic patient, including lifestyle factors such as smoking [4].

Cigarette smoking is independently associated with the incidence of diabetes mellitus [5][6]. Smoking-induced oxidative stress might have some effect on blood glucose as well as directly alter blood glucose homeostasis and cause insulin resistance. The exact biological pathway of this theory has not been fully elucidated, but it is suspected that high concentration of circulating epinephrine and norepinephrine due to smoking may contribute to hyperglycemia by increasing the rate of hepatic gluconeogenesis and glycogenolysis [5] [6] [7].

Another method used to assess blood

glucose over a longer period is by analysing the concentration of glycated haemoglobin (HbA1c). HbA1c is a result of non-enzymatic attachment of a hexose molecule to the haemoglobin molecule. This process occurs continually over the entire lifespan of the erythrocyte and is dependent on blood glucose concentration and the duration of erythrocyte exposure to blood glucose [8]. Therefore, the HbA1c reflects the mean glucose concentration over the previous period. The international expert committee stated that HbA1c could be used as a diagnostic test for diabetes [9]. Smoking might alter glucose homeostasis; it might be as well affecting HbA1c concentration [10].

This experiment was conducted to assess the difference of blood glucose concentration and HbA1c among diabetic smoking patient and non-smoking diabetic patients.

## Methods

The protocol of the study was approved by the Research Ethics Committee of Faculty of Medicine of University of Sumatera Utara (NO: 198/TGL/KEPK FK USU-RSUP HAM/2017). This study used the cross-sectional approach. The study population included diabetic patients attending Endocrine Clinic University of Sumatera Utara Hospital from June to September 2017. The study population consisted of thirty diabetic smoking patients and thirty non-smoking diabetic patients. To avoid confounding factors, the diabetic patients included in this study was in 50-60 years age range and has been diagnosed with diabetes for the past 5 to 10 years. The exclusion criteria were: (1) history of using any antioxidant supplement; (2) history of current acute or chronic infection; (3) history of malignancy; (3) History of red blood cell membrane disorder or anaemia.

To obtain data on age, duration of diabetes, and history of smoking (duration of smoking and cigarette per day), a questionnaire-based interview was used. The biomarker of hyperglycemia is, i.e. fasting blood glucose, postprandial blood glucose, and the HbA1c level was measured by hexokinase and immunoturbidimetry method using Cobas 6000 analyser module c501 (Roche Diagnostics, Switzerland). Diabetes patients with HbA1c higher than 6.5% were categorised as uncontrolled diabetes. All data were processed using the statistical package for social science (SPSS). The differences among groups were tested by using Mann-Whitney, and *p*-values of < 0.05 were considered significant.

## Results

This study was carried out among 60 diabetic patients attending the endocrine clinic in North Sumatera University Hospital from June to September 2017. The characteristic of the study population is shown in Table 1 below.

**Table 1: Characteristics of the study population**

	Smoking Status		Total
	Non-Smokers	Smokers	
Sex			
Male	13 (43.33%)	26 (86.67%)	39 (65%)
Female	17 (56.67%)	4 (13.33%)	21 (35%)
Age	57.7 (± 6)	57 (± 9.9)	-
Duration of Diabetes	7.76 (± 9.26)	7.03 (± 6.76)	-
Diabetes Criteria			
Controlled Diabetes	6 (20%)	2 (6.67%)	8 (13.33%)
Uncontrolled	24 (± 80%)	28 (93.33%)	52 (86.67%)
Diabetes			
Duration of Smoking	-	29.7 (± 10.92)	
Cigarettes Per Day	-	15.93 (± 10.24)	

Table 1 shows that the study population consists of 39 male diabetic patients and 21 female diabetic patients. Among 39 male diabetic patients, 26 were smokers while the other 13 were not. As for female patients, 4 were smokers, and 17 were non-smokers. The mean age of the participant in this study is 57.7 for the control group and 57 for the study group. Among 60 diabetic patients in this study, 36 of them were diagnosed with diabetes during the past 5 years. Diabetic patients with HbA1c higher than 6.5% were categorised as uncontrolled diabetes. Table 1 showed 52 diabetic patients have uncontrolled diabetes. Among the 52 diabetic patients, 24 were a non-smoker, and the other 28 were smokers. For the smokers group, the average duration of smoking was 29.7 (± 10.92) years, with average cigarettes per day were 15.93 or equivalent to almost 1 pack of cigarettes per day.

The comparison between fasting blood glucose, postprandial blood glucose, and HbA1c in each study group is shown in Table 2.

**Table 2: Blood glucose level and HbA1c in the studied group**

		Non-smokers	Smokers	<i>p</i>
FBG	Min.	94	93	
	Max.	307	486	
	Median	155	177	
	Mean ± SD	170.36 (± 54.74)	194 (± 83.95)	0.325
PBG	Min.	117	130	
	Max.	407	611	
	Median	242	294	
	Mean ± SD	249.67 (± 76.07)	307.67 (± 97.22)	0.016
HbA1c	Min.	5	7	
	Max.	13	12	
	Median	9	9	
	Mean ± SD	8.65 (± 1.91)	9.04 (± 1.53)	0.412

A Higher level of fasting blood glucose was observed in the study group compared to the control group. The mean difference between groups was 23.64 mg/dl. The Mann-Whitney test showed *p*-value 0.325. There was 58.0 mg/dl difference in postprandial glucose between study and control group. The Mann-Whitney test showed *p*-value 0.016. HbA1c was 0.39 mmol/mol higher in the study group

compared to the control group with  $p$ -value 0.412.

## Discussion

All three chemical biomarkers were higher in the smokers group compared to the non-smokers group after adjustment for a possible confounding variables such as age, diet, physical activity, and types of medication used. There was no significant difference in fasting blood glucose levels between study and control groups. There was also no significant difference of HbA1c among the group as the independent t-test shows the  $p$ -value  $> 0.05$ . For postprandial glucose, the independent t-test showed  $p$ -value  $< 0.05$  which means there was a significant difference in postprandial glucose between both groups.

The postprandial blood glucose test is used to evaluate the ability to regulate glucose metabolism. The postprandial glucose test also provides an insight on insulin sensitivity. Compared with fasting blood glucose and HbA1c cut points, the postprandial glucose test value diagnoses more people with diabetes [9]. Various studies have demonstrated that insulin resistance is dose-dependently related to smoking. The level of basal insulin secretion and insulin resistance (evaluated by HOMA-IR protocol) were higher in smoking compared to non-smoking patients [5] [6] [11] [12].

The prevalence of type 2 diabetes increases with age, and it is also well documented that ageing is associated with a decline in insulin action as well as pancreas function. Normally, pancreatic beta cells have a long lifespan with low proliferation rate; however, during increased metabolic demand or after injury, adult pancreas could be able to produce new cells. As we age, this proliferative capability of pancreas declines [13] [14]. Smoking causes oxidative stress due to an increase in ROS that found in smokers body [12] [15]. This condition causes oxidative damage such as lipid peroxidation, protein oxidation, and DNA damage. The island of the pancreas is particularly vulnerable to damage caused by ROS accompanied by a lack of antioxidant enzymes in the cells. ROS will induce the activation of Poly-ADP-Ribose-Polymerase (PARP) that causes NAD depletion. This will result in the apoptosis of insulin-producing cells [12].

There is a clear, dose-dependent relation between diabetes or glucose intolerance and both active and passive cigarette exposure. Adiponectin concentration seems to partially mediate the effect of smoking on glucose homeostasis [5] [17] [18].

High level of ROS generated by smoking will inhibit phosphatidylinositol-3-kinase activity, thus

decreasing the secretion of adiponectin from adipose tissue. This lower concentration of adiponectin is a common finding in obese or diabetic patients [18]. Adiponectin stimulates the phosphorylation and activation of 5'-adenosine monophosphate-activated protein kinase in the liver and skeletal muscles, thereby directly affecting glucose homeostasis and insulin sensitivity [5].

Another experiment showed how nicotine alters glucose metabolism in animal models. The dose of nicotine used in this experiment was chosen to mirror the average cigarette smokers peak blood level of cotinine. Acute nicotine treatment for 30 minutes, caused hyperglycemia and glucose intolerance. The hyperglycemic effect of acute nicotine treatment was mediated by the activation of certain nAChR subunit because the hyperglycemia was abolished by CSM (nAChR inhibitor). This acute nicotine treatment also increases both basal insulin secretion, glucose-stimulated insulin secretion, and decreases insulin sensitivity [7]. Furthermore, smokers have been shown to have higher fasting plasma cortisol concentrations than non-smokers. Higher cortisol concentrations may be a consequence of the stimulation of sympathetic nervous system activity that is induced by smoking, and higher cortisol may lead to hyperinsulinemia [11] [17].

For HbA1c variable, the result in this study was in contrast with a previous study that shows HbA1c was higher by 0.08% in smokers compared to non-smokers [19]. Glycated haemoglobin provides a better indication of long-term glycemic control than blood glucose levels. During the lifespan of erythrocyte, they are constantly exposed to glucose and result in non-enzymatic attachment of glucose to the haemoglobin molecule within the erythrocyte. Due to the longer lifespan of erythrocyte, haemoglobin reflects the mean blood glucose over previous periods (approximately 3 months, as the average lifespan of the erythrocyte is 120 days). The rate of HbA1c formation is directly proportional to the mean of blood glucose during the lifespan of the erythrocyte. Due to its properties, HbA1c is often used to monitor blood glucose in the diabetic patient and also used to monitor patient response toward diabetes therapy [9] [10]. Many studies have reported the unfavorable effects of smoking for diabetes mellitus. Smoking increases the risk of developing diabetes, and aggravates the micro-and macro-vascular complications of diabetes mellitus [6] [9]. Diabetic patients are also more likely to develop various oral health problems that may be aggravated by smoking [20].

The result in this study did not represent the entire smoking and non-smoking diabetic patients due to the cross-sectional design and relatively very small study population. Future studies are needed to analyse the exact biological effect of various factors

such as types of medication used, physical activity and lifestyle that can affect blood glucose and HbA1c, since a substantial portion of HbA1c and blood glucose concentration may be determined by these non-glycemic factors [10] [15] [21].

This study concluded that postprandial glucose levels were different in smoking compared to non-smoking diabetic patients. Smoking may contribute to the development of insulin resistance as there were higher postprandial glucose levels in smoking diabetic patients compared to the non-smoking diabetic patients. Although further studies are needed for this specific population regarding the impact of smoking on glucose metabolism and insulin resistance, smoking cessation programs should be offered to the diabetic population.

## Acknowledgement

We gratefully acknowledge that this research is supported by Institutions of Research, Universitas Sumatera Utara (USU), as Talenta Research USU of Year 2017 with contract no. 5338/UN5.1.R/RPM/2017, May 22nd 2017. We also would like to show our gratitude to the Dean of Medical Faculty of Universitas Sumatera Utara and the Head Director of Universitas Sumatera University Hospital for the general administrative support provided.

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