ORIGINAL ARTICLE

Correlation Between Fasting Blood Glucose and Hba1c with Vitamin D in Diabetes Mellitus

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ABSTRACT

Background: Diabetes Mellitus (DM) is one of the largest health problems in the world. The prevalence of DM in human population has increased globally. Fasting blood glucose and HbA1c is one of parameters for diagnosing and monitoring DM. Vitamin D is a fat-soluble vitamin that has a role in glucose tolerance through its effect on insulin secretion and sensitivity in DM and the vitamin D deficiency condition sometime happened. Further more, the relation between fasting blood glucose and HbA1c with vitamin D in DM need to be investigated
Aim: To determine the correlation of fasting blood glucose and HbA1c with vitamin D in DM.
Methods: An observational analytic study with cross sectional approach in 46 subjects suitable with the inclusion and exclusion criterias. This study was conducted from April to September 2019 in *Rumah Sakit Nasional Diponegoro* (RSND) Semarang. Variables of this study were fasting blood glucose (FBG), HbA1c levels, and vitamin D (25(OH)D). Data were analyzed by Spearman and Pearson correlation.Test was significant if p<0,05.
Result: Mean±SDof fasting blood glucose, HbA1c and vitamin D (25(OH)D) were 168,78 ±86,21mg/dL, 8,46±2,20 %, and 15,85±8,75 ng/mL. The correlation between fasting blood glucose and vitamin D were not significant with p=0,193; r=0,195 and neither the correlation between HbA1c and vitamin D withp=0,153; r=0.214. **Conclusion:** Assessment of vitamin D deficiency base on the measurement of the vitamin D in diabetes melitus and this parameter don't have correlation with FBG and HbA1c levels.
Keywords: Fasting blood glucose, HbA1c, Vitamin D, Diabetes Mellitus

INTRODUCTION

Diabetes Mellitus (DM) is one of the largest problems in the world. In recent years,prevalence of DM in human population has been increased globally[1]. It has been reported in "*Riset Kesehatan Dasar*" that the prevalence of DM in Indonesia for population with aged ≥ 15 years has increasedfrom 6,9% in 2013 to 8,5& in 2018[2].

Diabetes mellitus is defined as a group of metabolic diseases characterized by chronic hyperglycemia caused by damage of insulin secretion, insulin action or both, causing abnormalities in the metabolism of carbohydrates, lipids, and proteins[3].

The condition of hyperglycemia in DM increases reactive oxygen species (ROS) which induces oxidative stress in pancreatic β cells. This oxidative stress increase the production and release of pro-inflammatory mediators (cytokines and chemokines) which activate CYP27B1 (1α-hydroxylase), an enzyme that cause 25 (OH) D to be converted to 1.25 (OH) D, thereby reducinglevel of 25 (OH) D OH) D and increasinglevel of 1,25 (OH) D[4,5].

Fasting blood glucose (FBG)was used as a parameter to distinguish diabetes mellitus patients from non-mellitus diabetes patients because fasting blood glucose has high specificity. World Health Organization also recommends measurement of HbA1c level to diagnose diabetes, HbA1c tends to be stable in the blood for a longer period and the examination can be done at any time without special preparation. According to Metcalf PA, *et al* (2017), HbA1c has correlation with macrovascular complications (cardiovascular disease and ischemic stroke) and microvascular (retinopathy, nephropathy and neuropathy)[6,7].

The latest guidance from scientific bodies around the world recommends measuring 25 (OH) D serum as the test of choice for assessing vitamin D status.[8]Serum 25 (OH) D levelis the best indicator for assessing vitamin D status because 25 (OH) D level reflects the production of skin vitamin D3 and vitamin D (D2 and D3) from food. 25 (OH) D also has a long half-life in circulation which is 3-4 weeks. Although the active metabolite of vitamin D is 1.25 (OH) 2D, measurement of serum 1.25 (OH) 2D level is not recommended to determine vitamin D status because the half-life in short circulation is 4-6 hours and its level in serum is very low when compared with a level of 25 (OH) D. When vitamin D deficiency occurs, parathyroid hormone secretion will increase as a compensatory response that will stimulate the kidneys to increase production of 1.25 (OH) D so that when vitamin D deficiency occurs, 25 (OH) D level are decreased, while level of 1.25 (OH) 2D is maintained at normal or even elevated level[9].

Until now then, research on the relationship of fasting blood glucose and HbA1c level with vitamin D (25 (OH) D) levels in diabetes mellitus especially in Indonesia is still limited, and also there were differences in previous studies between these variables. Therefore, it needs advanced investigations.

MATERIALS AND METHODS

An observational study with cross sectional approach was conducted in Rumah Sakit Nasional Diponegoro (RSND) Semarang on April to September 2019. The subjects of the

study were 46 diabetes mellitus patients who met inclusion and exclusion criterias by consecutive sampling. The incluson criterias were diabetic patients, >18 years old, normal body temperature, normal liver function test, and willing to be respondent, while the exclusion criterias were anemia, pregnant, smoker, consuming vitamin D supplements, patient with history of chronic liver, patient with history of chronic kidney disease, and stroke patient.

Data in this study were identity of the patients, weight, height, sport activity, blood pressure, percentage of body fat, hemoglobin levels, AST, ALT, FBG, HbA1c levels, and 25(OH)D levels. Blood sampling, blood presureand the percentage of body fat measurement weredone at laboratory of RSND. The measurement of hemoglobin levels, AST, ALT, FBG, HbA1c, and 25(OH)D was done at laboratory of RSND, GAKI laboratory faculty of medicine UNDIP, and laboratory of Prodia.

The percentageofbodyfatwasdonebyomron body composition monitor HBF-375. Fasting blood glucose were measured by GOD-PAP method on automatic clinical chemistry analyzer architech C-4000, normal level of FBG is ≤ 100 mg/dl. HbA1c levels were measured by *high performance liquid chromatography* (HPLC) on a D-10 system, normal level of HbA1c is less than 5,7%. 25(OH)D levels were measured by *Enzyme-Linked Immuno Sorbent Assay* (ELISA)method, normal level of 25(OH) is 30-100ng/mL.

Data analysis was performed by statistical programme computer. Normality test was *Saphiro-Wilk* and data that were not normally distributed carried out data transformation. *Pearson* correlation test was performed to test correlation of HbA1c levels with vitamin D (25(OH)D) levels and *Spearman* correlation was performed to test relation of fasting blood glucose with vitamin D (25(OH)D).*p*>0,05 was significant.

Ethical clearance was obtained from the Medical and Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Diponegoro University. Subjects were given a brief explanation of the purpose, benefits, research protocols, and possible side effects, and written informed consent was done.

RESULT

The population of this study were diabetes mellitus patients in RumahSakit Nasional Diponegoro (RSND) Semarang. This study was conducted from April to September 2019 in RSND Semarang and the samples were examined in laboratory of RSND Semarang. There were 79 subjects who were willing to be sampled, but only 46 subjects met the inclusion and exclusion criteria. Descriptive are shown in table 1.

The gender distribution in this study was 17 (36,96%) males and 29 (63,04%) females. The average age of respondents was 57.85 ± 11.58 years. The youngest age in this study was 34 years and the oldest age was 79 years. There were 16 (34.78%) subjects who routinely did sport activities and there were 30 (65.22%) subjects who did not routinely do sport activities.

Table 1. Characteristicsof subjects

Parameter	Mean± SD
Age (years)	57,85± 11,58
Gender (%)	
Male	36,96
Female	63,04
Sport activity (%)	
Yes	34,78
No	65,22
Blood pressure (mmHg)	
Sistol	131,89 ± 11,73
Diastol	82,83 ± 6,08
Percentage of body fat (%)	32,56 ± 6,48
Male	26,76 ± 6,77
Female	35,56 ± 5,03
Body weight (kilograms)	63,19 ± 11,54
Height (centimeters)	156,29 ± 7,87
Body Mass Index (kg/m^2)	25,72 ± 4,15
Hemoglobin levels (mg/dL)	13,18 ± 0,95
SGOT (mg/dL)	19,37 ± 5,2
SGPT (mg/dL)	18,65 ± 5,33
Fasting blood glucose (mg/dl)	168,78± 86,21
HbA1c levels (%)	8,46± 2,20
Vitamin D (25(OH)D) levels (ng/mL)	15,85± 8,75

The percentage of body fat in female is higher than male with BMI obtained in normal to overweight range. Fasting blood glucose levels in this study population ranged from normal to high, where the proportion of normal FBG level was less than those of high levels. There were 21 (45,65%) subjects with normal FBG and 25 (54,35%) subjects with increased FBG, while HbA1c levels in all subjects of this study were found to be increasing from normal. 25(OH)D levels in this study were found decreased based on normal values.

Table 2: Correlation test results

Variable	**Vitamin D (25(OH)D)**	
	r	***p***
HbA1c	0,214	0,153[a]
Fasting blood glucose	0,195	0,193[b]

[a]*Pearson* correlation test
[b]*Spearman* correlation test

Data was analyzed by parametric *Pearson* correlation test for HbA1c and vitamin D (25(OH)D) and non-parametric *Spearman* correlation test for fasting glucose test and vitamin D (25(OH)D). Based on the *Pearson* correlation test between HbA1c and vitamin D (25(OH)D), the result shows there was no significant correlation between HbA1c and vitamin D (25(OH)D). Based on the *Spearman* correlation test between fasting blood glucose and vitamin D (25(OH)D), the result shows there was no significant correlation between fasting blood glucose and vitamin D (25(OH)D) as shown in table 2.

DISCUSSION

The result of *Spearman* correlation test between fasting blood glucose with vitamin D (25(OH)D) showed that there was no significant correlation. The study conducted by Alkhatatbeh in 2018 found that there was no significant relationship between fasting blood glucose with vitamin D (25(OH)D) in diabetes mellitus[10]. Tandon in 2014 also stated there was no significant correlation between fasting

blood glucose with vitamin D (25(OH)D) in diabetes mellitus[11].

The result of this study differs from some previous studies. Study conducted by Pannu in 2017 found there was a negative relationship between fasting blood glucose and vitamin D (25(OH)D) in DM[12]. Another study in 2017 by Kanakaraju shows there was a negative relationship between vitamin D (25(OH)D) with blood glucose parameters[13]. The same result was also mentioned by Bhatt in 2018 there was a negative relationship between fasting blood glucose with vitamin D (25(OH)D in pre-diabetic population[14].

Insignificant relationship between fasting blood glucose and vitamin D (25(OH)D) can be caused by several factors. One of them is the percentage of body fat. Individuals with a high percentage of body fat can reduce level of vitamin D (25(OH)D) because excess fat tissue can store fat-soluble vitamin D thus it reduces vitamin D is released in the bloodstream and serum 25(OH)D level become low[15,16].

The use of drugs such as glucocorticoid drugs,anti-hypertension may affect vitamin D (25(OH)D) level, glucocorticoids may affect function of osteoblasts and osteoclasts thus it reduces vitamin D levels. Some glucocorticoids also increase degradation of 25(OH)D and 1,25(OH)D due activation of *pregnane X receptors*[17]. In addition, physical activity also affects plasma vitamin D concentrations, a study conducted by Fernandes in 2017 showed that the concentration plasma vitamin D increases with physical activity[18]. Research conducted by Sakungin 2018 showed that physical activity may increases insulin sensitivity and increases glucose uptake by body tissues thus it reduce blood glucose level[19].

The result of *Pearson* correlation test between HbA1c with vitamin D (25(OH)D) showed there was no significant correlation. The study conducted by Kumar in 2017 showed that diabetes mellitus could not be proven to have a significant relationship between HbA1c and vitamin D (25(OH)D) levels in people with diabetes mellitus[20]. Coskun in 2012 also stated there was no significant relationship between HbA1c with vitamin D (25(OH)D) levels in diabetes mellitus[21].

The result of this study differs from some previous studies. Study conducted by Al-Timimi in 2013 stated that patients with poor glycemic control (HbA1c) had lower serum 25(OH)D[22]. In another study in 2017 by Pannu shows that high levels serum 25(OH)D was associated with a low HbA1c levels[12]. The same result was also mentioned by Buhary in 2017 that there was a negative relationship between HbA1c and vitamin D (25(OH)D) in diabetes mellitus[23].

Insignificant relationship between HbA1c and vitamin D (25(OH)D) can be caused by several factors. One of themisexposure of sun's ultraviolet B (UV B) rays, UV B has an important role in the synthesis of vitamin D.UV B play a role in breaks B ring at 7-dehydrocholesterol into pre-D3 which is isominated into D3 by irradiation of UV B.Thus, the lack of exposure from UV B sunlight can interfere with the synthesis of vitamin D[24].

Gender can also affect the level of vitamin D (25 (OH) D) because men have outside activities more frequently thusthey are moreexposed to sunlight, usage of sunblock more frequent in women can also reduce vitamin D synthesis, and also women have a higher percentage of fat than men thus they have lower concentrations of vitamin D (25 (OH) D) than men. Furthermore, age also affects vitamin D level due to reduced production of vitamin D in the skin, lack of exposure to UV B sunlight, reduced food intake, reduced skin thickness, impaired absorption in the intestine, and reduced hydroxylation in the liver and kidneys.In the study conducted by Al-Horani in 2016 showed that there was a relationship between gender, age, and body mass index with vitamin D (25(OH)D) levels[25].

Another factors that can influence HbA1c level in this study is glycation factors which can be influenced by the levels of consumption of vitamin C, the levels of consumption of vitamin E, and alcoholism, as well as Yunika (2017)[9]. In the study conducted by Ardekani in 2007 showed that consumption of vitamin D decreases serum level of fasting blood glucose, LDL, and HbA1c significantly[26].

Limitations in this study are the current study subjects,they are not distinguished based on physical activity, gender and age. This study also did not distinguish DM subjects based on BMI or body fat percentage. Medicines were consumed by patients, where the use of several drugs such as anti-hypertensive drugs, glucocorticoids, vitamin C supplements, vitamin E supplements can influence the results of the study.

CONCLUSION

Relationship between FBG and HbA1c levels with vitamin D (25(OH)D) level in diabetes mellitus patients are not significant. Assessment of vitamin D deficiency base on the measurement of the vitamin D in diabetes melitus.The next study needs to be adjusted with interference factors related to variables detail that mention in limitation.

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