

THE DIFFERENCE OF VITAMIN D LEVELS BETWEEN CONTROLLED AND UNCONTROLLED TYPE 2 DIABETES MELLITUS PATIENTS

Adhisti Azlin¹, Santi Syafril², Ratna Akbari Ganie¹

¹ Department of Clinical Pathology, Faculty of Medicine, University of North Sumatera/ Adam Malik Hospital Medan, Indonesia. E-mail: adhistiazlin@gmail.com

² Department of Internal Medicine, Faculty of Medicine, University of North Sumatera/Adam Malik Hospital Medan, Indonesia

ABSTRACT

Vitamin D as an immunomodulator plays an important role in controlling glycemic levels and decreasing diabetic complications. HbA1c is a marker of glycemic control which is known to have a correlation with vitamin D. This study aimed to determine the differences of serum vitamin D levels and glycemic index in patients with type 2 DM. The design of this study was a cross-sectional study and was performed in the Adam Malik Hospital from December 2017 until March 2018. Type 2 diabetes mellitus patients were classified based on HbA1c levels into controlled (HbA1c <7%) and uncontrolled diabetes mellitus (HbA1c ≥ 7%). Serum vitamin D levels were measured using the Enzyme-Linked Fluorescent Assay (ELFA) method. Differences of vitamin D levels among controlled and uncontrolled type 2 diabetes mellitus were statistically analyzed using an independent t-test, and the differences of HbA1c levels were analyzed using the Mann-Whitney-U test. Forty-five patients with type 2 DM were divided into controlled (HbA1c <7%) and uncontrolled diabetes (HbA1c ≥ 7%). There was no difference of vitamin D serum levels between controlled and uncontrolled Type 2 DM patients (p=0.310).

Key words: Type 2 diabetes mellitus, vitamin D, HbA1c

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia which occurs due to abnormalities in insulin secretion, insulin action or both.¹

Globally, the World Health Organization (WHO) estimated that 422 million adults suffered from Diabetes Mellitus (DM) in 2014. The global prevalence of DM has almost doubled since 1980, rising from 4.7% to 8.5% in the adult population. Diabetes mellitus alone caused 1.5 million deaths in 2012. Uncontrolled conditions of hyperglycemia also caused additional 2.2 million deaths by increasing the risk of cardiovascular disease and other diseases. Forty-three percent of these 3.7 million deaths occurred before the age of 70.²

Similar data was also reported by the International Diabetes Federation (IDF) in 2015, showing 415 million people with diabetes age 20-79 years worldwide and predicted to increase to 642 million people by 2040. Diabetes mellitus also led to a large economic loss of countries and national health systems. Most countries spend approximately 5-20% of their total health spending on DM cases.³ In Indonesia, the 2013 Basic Health Research (Riskesdas) reported the prevalence of DM in

patients > 15 years was 6.9%.⁴

Diabetes is one of the commonly underdiagnosed. Approximately 30% of diabetics patients were frequently unaware of the disease and at the time of diagnosis, around 25% of them were reported to have suffered from microvascular complications. The average delay from onset to diagnosis is estimated to be around 7 years, suggesting a need of earlier identification of in a more efficient way. HemoglobinA1c (HbA1c) test is considered as an examination for screening and diagnosis of diabetes.⁵

Benefits of HbA1c are known for assessing the quality of long-term glycemic control and the effectiveness of the therapy. However, several recent studies support greater use of HbA1c, not only for monitoring but also for diagnosing or screening of type 2 diabetes mellitus.⁵

Clinical manifestations in DM patients emerge in the form of macrovascular complications that develop into heart disease, hypertension, stroke, or impaired kidney function. While microvascular complications can include neuropathy and retinopathy.⁶

Because of its tendency to be a global problem, it is necessary to control DM, to identify, and early manage the existence of chronic complications

through control of blood glucose levels by laboratory test of HbA1c (glycohemoglobin).

Measurement of HbA1c levels is one way to monitor blood glucose control.⁷ This test provides an average amount of blood glucose levels during the previous 2-3 months.⁸ HbA1c as a non-enzymatic reaction product from blood glucose can be used as a parameter of DM status because of its strong relationship with blood glucose during the lifespan of red blood cells. Therefore, an improved DM condition will be indicated by the show decreased HbA1c levels.⁹

Several factors seem to play a role in the development of DM including genetics, lifestyle, environment and nutritional conditions. Among nutritional factors, vitamin D tends to have an important role both in glycemic control or reduction of diabetes complications. Vitamin D has diverse functions. Many epidemiological studies have shown that vitamin D deficiency is associated with an increased risk of chronic diseases such as cancer, heart disease, type 2 diabetes, autoimmune disease, and multiple sclerosis. Calcitriol (vitamin D3) has been reported to alter glycemic control and with some studies pointed its role in the development of DM.¹⁰

The role and mechanism of vitamin D in influencing blood sugar levels is still unknown. The most likely mechanisms by vitamin D are regulating the insulin synthesis and secretion of pancreatic β cells, increasing uptake of peripheral and hepatic glucose and inhibiting inflammation that frequently occurs in obesity. The role of vitamin D in glucose metabolism is known due to the presence of specific vitamin D receptors (VDR) and the expression of the 1- α -hydroxylase enzyme in pancreatic β cells and peripheral tissues that are sensitive to insulin such as muscle and fatty tissues.¹¹

METHODS

This research was a cross-sectional study performed at the Adam Malik Hospital Medan from December 2017 until March 2018. The subjects were typed 2 DM patients without any infection. Patients with pregnancy, fracture, and treatment with vitamin D supplements were excluded. Subjects were classified based on HbA1c levels (<7% and \geq 7%.) Vitamin D levels were measured from the serum of patients using Enzyme-Linked Fluorescent Assay (ELFA) method with MINI VIDAS. HbA1c (glycated hemoglobin) levels were measured using the Turbidimetric Inhibition Immunoassay (TINIA) method with INDIKO devices. ALT/AST, ureum, and

creatinine levels were measured using a photometric examination method with an automatic ARCHITECT Plus analyzer. Ethical clearance of this research was approved by the Research Committee of Health in the Faculty of Medicine, University of North Sumatra, Medan with No:64/TGL/KEPK FK USU-RSUP HAM/2018. Informed consents were obtained handwritten by the research subjects as a statement of willingness to participate in the study after getting an explanation of the purpose and objectives of the study.

RESULTS AND DISCUSSION

Statistical analysis was performed using a computerized program. The patient characteristics and laboratory parameters were described in the form of tabulations. Differences of vitamin D levels among controlled and uncontrolled type 2 diabetes mellitus patients were determined by using an independent t-test, while the differences of HbA1c levels were determined using the Mann-Whitney-U test. The test results would be stated as significant if $p < 0.05$ was obtained.

Subjects consisted of 45 patients with type 2 diabetes mellitus which were further classified into controlled and uncontrolled diabetes based on HbA1c levels. Twenty-one patients were categorized as controlled type 2 DM patients (HbA1c <7) and 24 of them were categorized as uncontrolled type 2 DM patients (HbA1c \geq 7). The characteristics of the study subjects were shown in Table 1.

From table 1 it can be seen that most research subjects (25 patients) were females, of with 11 and 14 of them were controlled and uncontrolled type 2 DM, respectively. Twenty males were consisting of 10 subjects with controlled type 2 DM and 10 subjects with uncontrolled type 2 DM, there were no significant gender differences between controlled and uncontrolled type 2 DM with $p = 0.688$.

From Table 1 it can be seen that the average age of patients with controlled and uncontrolled type 2 DM was 59.33 ± 11.23 and 56.79 ± 7.80 , respectively, with a p-value of 0.378. Therefore, there was no significant age difference between controlled and uncontrolled type 2 DM patients.

Meanwhile, based on the occupation, the subject characteristics predominantly consisted of 6 housewives (2.7%) with controlled DM and 12 people (0.4%) with uncontrolled.

Based on levels of 25 (OH) vitamin D, among subjects with controlled DM there were 8 with 25 (OH) vitamin D levels of <20 ng/mL, 11 (28.9%) with 25 (OH) vitamin D levels between 20-29.9 ng/mL, 2 (6.7%) with

Table 1. General characteristics of patients with type 2 diabetes

Variable		Controlled Type 2 Diabetes (HbA1c <7)	Poorly controlled Type 2 Diabetes (HbA1c = 7)	P
Gender	Male	10 (22.22 %)	10 (22.22%)	0.688
	Female	11 (24.44%)	14 (31.11%)	
Age (Mean±SD)		59.33 ± 11.23	56.79 ± 7.80	0.378
Occupation	Construction workers	0 (0)	1 (0.45%)	0.001*
	Housewife	6 (2.7%)	12 (5.4%)	
	Merchant	2 (0.9%)	2 (0.9%)	
	Retiree	5 (2.25%)	3 (1.35%)	
	Farmer	2 (0.9%)	2 (0.9%)	
	Civil servants	2 (0.9%)	1 (0.45%)	
	Private workers	3 (1.35%)	1 (0.45%)	
	Unemployed	1 (0.45%)	4 (1.8%)	
Length of suffering	<5 Years	1	1	0.001*
	> 5 Years	20	23	
HbA1C (median (min-max))		(6.30) (5.00-6.90)	(9.25) (7.00-13.80)	0.001*
Urea median (min-max)		30 (11-49)	21 (12-56)	0.299
Creatinine median (min-max)		0.79 (0.54-10.30)	0.805 (0.47-1.58)	0.946
ALT mean±SD		21.19±5.134	22.33±7.476	0.820
AST mean±SD		21.9±4.636	24.63±9.527	0.254

*Mann-Whitney U Test

25 (OH) vitamin D levels ranging from 30-100 ng/mL and no subject with 25 (OH) vitamins D levels of >100 ng/mL. In addition, among subjects with uncontrolled DM there were 9 with 25 (OH) vitamin D levels of <20 ng/mL, 13 with 25 (OH) vitamin D levels between 20-29.9 ng/mL, 2 with 25 (OH) vitamin D levels between 30-100 ng/mL and no subject with 25 (OH) vitamin D levels of > 100 ng/mL.

Based on the length of suffering, among subjects with controlled type 2 DM, there was one patient with length of suffering <5 years and 20 patients with length of suffering > 5 years. Besides, among subjects with uncontrolled type 2 DM, there was one patient with length of suffering <5 years and 23 patients with length of suffering > 5 years.

Based on the urea levels, among subjects with controlled type 2 DM, there were 30 patients with urea levels of 11-49 and among subjects with uncontrolled type 2 DM, there were 21 patients with urea levels of 12-56 (p=0.299).

Based on creatinine levels, subjects with controlled type 2 DM showed creatinine levels of 0.79 (0.54-10.30) while subjects with uncontrolled type 2 DM showed creatinine levels of 0.805 (0.47-1.58) with p-value of 0.946.

Based on ALT levels, subjects with controlled type 2 DM showed ALT levels of 21.19±5.134 and subjects with uncontrolled type 2 DM showed ALT levels of 22.33±7.476 with p=0.820.

Based on AST levels, subjects with controlled type 2 DM showed AST levels of 21.9±4.636 and subjects with uncontrolled type 2 DM showed AST levels of 24.63±9.527 with p=0.254.

Urea and creatinine levels were analyzed in this study as the process of vitamin D formation in the circulation is bound by vitamin D binding protein (DBP) which is then transported to the liver. Vitamin D liver undergoes hydroxylation by the 25-hydroxylase enzyme to 25 hydroxyvitamin D (25 (OH) D. 25 (OH) D is the main form of biologically

Table 2. Differences of vitamin D and HbA1c levels in type 2 diabetes patients

Variable	Uncontrolled Type 2 Diabetes HbA1c <7	Uncontrolled Type 2 Diabetes HbA1c ≥7	p
Vitamin D (Mean±SD)	22.94±6.18	20.99±6.47	0.310 *

*: Independent T-test

inactive vitamin D and is an indicator of vitamin D status. After that vitamin D will experience further hydroxylation in the kidneys by 1 α hydroxylase to 1.25 dihydroxyvitamin D active form (1.25 (OH)₂D or calcitriol. Vitamin D deficiency can be caused by changes in the function of organs involved in the synthesis of 25 (OH) D such as the liver and kidneys. In this study, there was no difference of vitamin D levels between controlled and uncontrolled diabetes mellitus due to changes in the function of the liver and kidneys.¹²

Based on Table 2, despite the tendency of higher vitamin D levels in controlled type 2 DM patients (22.94±6.18) compared to uncontrolled type 2 DM (20.99±6.47), there were no significant differences with p-value of 0.310.

This study found that there were more females type 2 DM patients than males. This finding was in accordance with a study by Brunner and Suddart in 2002 which showed that females suffered from diabetes more than males due to the higher percentage of body fat deposits found in females than males. Body fat deposits were one of the factors with the ability to reduce sensitivity to the activity of insulin in the muscles and liver.¹³ Other studies in accordance with the results of Riskesdas 2013 also showed that the prevalence of type 2 DM was higher in females (2.3%) compared to males (2.0%).⁴

Based on the mean age of patients in this study, there were no significant differences of age between controlled type 2 DM (59.33±11.23) and uncontrolled type 2 DM (56.79±7.80) patients. This situation was similar to Perdatin 2014 which showed that the age of the sufferer in each group varied from the 4th to the 5th decade. Based on the WHO, after a person reaches the age of 30 years, there will be an increase of GDP level of 1-2% per year and 2-hour postprandial blood glucose of 5.6-13 mg%. The prevalence of subjects whose history of type 2 diabetes tended to increase along with the increased age due to the aging of the pancreas and the decrease of insulin release.¹¹

In this study, there was no significant difference of vitamin D levels between controlled and uncontrolled type 2 DM patients. Vitamin D levels in controlled type 2 DM were (22.94±6.18) higher than

uncontrolled type 2 DM (20.99±6.47) patients with p-value of 0.310. Other studies also reported that there was no significant difference between HbA1c and Vitamin D levels, and normal vitamin D levels were not initially affected by increases or decreases of HbA1C levels in type 2 diabetes mellitus patients.¹⁴

To date, it is still questionable whether vitamin D has an important role in type 2 DM although some previous research data showed that there was no correlation between low vitamin D levels, metabolic syndrome and glycemia in type 2 DM. The clinical impact on metabolic control in type 2 DM and correction of vitamin D deficiency will not have great clinical benefit as a therapeutic agent in diabetic patients.¹⁵

However, there are several factors known to harm vitamin D status, especially in patients with type 2 diabetes. Both glycemic control and duration of type 2 DM are considered factors that can cause a negative effect between the relationship of vitamin D to HbA1c levels. Patients with poor glycemic control (HbA1c levels) had lower levels of serum 25 (OH) D when compared to good glycemic control.¹⁶

Glycemic control may affect serum 25 (OH) D levels by different mechanisms. Poor glycemic control is associated with poor dietary habits and/or less exposure to sunlight. However, someone whose chronic glycemic control can adversely affect vitamin D metabolism. The relationship between vitamin D status and chronic hyperglycemia seems to reflect diabetic complications that cause low vitamin D status. Chronic hyperglycemia is known to play a role in diabetic nephropathy by decreasing the level of hydroxylation of vitamin D3 in the kidney which supports a decrease of the synthesis of this vitamin.¹⁷

Recent evidence has shown that people with type 2 DM with Vitamin D hypovitaminosis were more likely to have an increased HbA1c levels compared with people without DM. Vitamin D is associated with glucose metabolism and the development of type 2 DM.¹⁸ Vitamin D deficiency is an important contributor to insulin resistance, which is a pathogenic mechanism of type 2 DM. Conversely, higher vitamin D intake can increase diet-induced thermogenesis and fat oxidation and reduce spontaneous energy intake.¹⁹

Vitamin D affects the secretion and sensitivity of insulin so that the level will affect the appearance and duration of type 2 DM but does not significantly affect HbA1c levels as a marker of glycemic control.¹³ This is consistent with the data from this study which showed that there was no significant difference of vitamin D levels between patients with controlled and uncontrolled type 2 diabetes. The relationship between vitamin D levels and the effect of glycemic control in patients with type 2 DM could not be confirmed in this study.

The limitations in this study were no elimination of the factors that can affect changes of vitamin D and HbA1c levels such as diet, sun exposure, and type 2 DM.

CONCLUSION AND SUGGESTION

In this study, there was no significant correlation between vitamin D levels and HbA1c levels in controlled and uncontrolled type 2 DM patients.

Based on the results of this study it was suggested that further research should be conducted to determine the correlation between vitamin D and HbA1c levels using better research methods. Furthermore, further research with a parameter of 1.25 (OH) 2D was additionally needed to ensure the effectiveness of vitamin D on metabolic processes in type 2 DM patients.

REFERENCES

- American Diabetes Association. Classification and diagnosis of diabetes. *Diabetes Care*, 2015; 38(1):S8-S16.
- World Health Organization. Global report on diabetes. 1st Ed., Geneva, World Health Organization, 2016; 21-31.
- International Diabetes Federation. IDF diabetes atlas. 7th Ed., Brussels, International Diabetes Federation, 2015; 50-53.
- Kementerian Kesehatan Republik Indonesia. Riset kesehatan dasar. 1st Ed., Jakarta, Badan Penelitian dan Pengembangan Kesehatan, Kementerian Kesehatan RI, 2013; 87-94.
- International Diabetes Federation. The global burden. <http://www.idf.org/diabetesatlas/5e/the-global-burden>. (accessed 15 August 2017)
- Ruslianti. Pengobatan diabetes melalui pola makan. Jakarta, Kawan Pustaka, 2008; 2-3.
- Andi W. Pemeriksaan laboratorium untuk diagnosa dan pengelolaan diabetes melitus. *Forum Diagnosticum Prodia*, 2009; 1-8.
- Sunia GM, Tjokroprawiro A, Martono H. Efek dioxifenfluramine pada penderita DM-TI-obesitas. *Acta Medica Indonesia*, 2006; XXVIII(3): 690.
- Acharya A, Halemani S. Role of vitamin D in diabetes mellitus. *International Journal of Pharmaceutical Sciences and Research*, 2016; 7(5): 1881-1888.
- Haryati, Geria. Hubungan faktor resiko umur, jenis kelamin, kegemukan dan hipertensi dengan kejadian diabetes melitus tipe 2 di wilayah kerja Puskesmas Mataram. *Media Bina Ilmiah*, 2014; 8: 1978-3787.
- Dunstan DW, Zimmet PZ, Welborn TA, De Courten MP, Cameron AJ, Sicree RA. The rising prevalence of diabetes and impaired glucose tolerance: The Australian diabetes, obesity and lifestyle study. *Diabetes Care*, 2002; 57(2):119-129.
- Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, *et al.* Evaluation, treatment and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2011; 96(7): 1911-30.
- Brunner, Suddarth. Buku Ajar Keperawatan Medikal Bedah. Ed 8., Volume 1. Jakarta, EGC, 2013; 394-98.
- Jorde R, Figenschau Y. Supplementation with cholecalciferol does not improve glycaemic control in diabetic subjects with normal serum 25-hydroxyvitamin D levels. *Eur J Nutr*, 2009; 48(6): 349-54.
- Luo C, Wong J, Brown M, Hooper M, Molyneaux, Yue DK. Hypovitaminosis D in Chinese type 2 diabetes: Lack of impact on clinical metabolic status and biomarkers of cellular inflammation. *Diabetes and Vascular Disease Research*, 2009; 6(3): 197.
- Dhia J, Al Timimi, Ardawan F. Serum 25 (OH) D in diabetes mellitus type 2: Relation to glycaemic control. *Journal of Clinical and Diagnostic Research*, 2013; 7(12): 2686-2688.
- Palomer X, Gonzales Clemente J, Blanco-Vaca F. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. *Diabetes Obes Metab*, 2008; 10: 185-197.
- Zhang FF, Al Hooti S, Al Zenki S. Vitamin D deficiency is associated with high prevalence of diabetes in Kuwaiti adults: Results from a national survey. *BMC Public Health*, 2016; 16(1): 100.
- Mitri J, Pittas AG. Vitamin D and type 2 diabetes: A systematic review. *Eur J Clin Nutr*, 2011; 65(9): 1005-15.