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25-hydroxy vitamin D concentrations negatively correlated with HbA1c in type 2 diabetes mellitus patients: a cross-sectional study in Mampang, South Jakarta

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ABSTRACT

INTRODUCTION: Insulin resistance plays a central role in type 2 diabetes mellitus (T2DM). Another possible cause of T2DM is a deficiency of 25-hydroxy vitamin D [25(OH)D], although the underlying mechanism is not yet clearly understood. The most frequently used laboratory parameters for monitoring T2DM are fasting blood glucose (FBG) and HbA1c. Determining any association of vitamin D with HbA1c and FBG in T2DM.

METHODS: A cross-sectional study involving 100 T2DM patients with the following characteristics: 18-year and older persons of both genders, not having kidney and liver disease, not on insulin therapy, not pregnant or lactating, and not consuming vitamin D in the last three months. Spearman's correlation coefficient was used to test any association of 25(OH)D with HbA1c and fasting blood glucose (FBG) ($p<0.05$).

RESULTS: Subjects comprised 74 females and 26 males with a median age of 56 years. Median HbA1c, 25(OH)D, and FBG were 8.05%, 11.2 ng/mL, and 127 mg/dL, respectively. The Spearman correlation coefficient for vitamin D and HbA1c was $r=-0.217$ ($p=0.03$), and for vitamin D and FBG, it was $r=-0.153$ ($p=0.128$).

CONCLUSION: There was a significant negative correlation of vitamin D with HbA1c but not with FBG. Administration of vitamin D should be considered for additional treatment of T2DM.

Keywords: Type 2 Diabetes Mellitus, 25-hydroxy Vitamin D, Blood Glucose, HbA1c, Fasting Blood Glucose

INTRODUCTION

The metabolic disorder diabetes mellitus (DM) features high blood glucose levels due to defective insulin response. Insulin resistance in target tissues, particularly in the skeletal muscles and adipose tissue, is responsible for abnormalities in carbohydrate, fat and protein metabolism, which may result in diabetes. There are several types of DM. The 2022 American Diabetes Association guidelines categorize DM into type 1 diabetes due to autoimmune damage to the beta cells, type 2 diabetes due to insulin resistance; diabetes due to other causes such as monogenic diabetic syndrome, DM-causing drugs, exocrine pancreatic disease, and gestational diabetes [1,2].

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Type 2 diabetes mellitus (T2DM) comprises the highest number of patients globally and in Indonesia. The global prevalence of T2DM at age 20-79 years, according to the International Diabetes Federation (IDF) 2013 report, was 8.3% (382 million persons), with 14 million more men than women, generally aged 40-59 years. The global number of cases is projected to increase to 592 million in the year 2035. Changes in lifestyle and unhealthy food may presumably cause the increased incidence of T2DM at younger ages. Obesity is also responsible for the occurrence of T2DM [1].

Insulin resistance plays a central role in T2DM. Oxidative stress, proinflammatory activation, adipokines, and abnormal glucose and lipid metabolism can lead to insulin resistance [3]. Another possible cause of T2DM is a deficiency of vitamin D. Although the underlying mechanism is not yet clearly understood, low 25-hydroxyvitamin D [25(OH)D] level is connected with functional disorders of pancreatic islet Langerhans cells and insulin resistance causing changes in glucose homeostasis such as to result in the occurrence of T2DM [4].

Vitamin D may increase insulin secretion, skeletal muscle glucose, and lipid metabolism and reduce systemic inflammation. However, several studies found no influence of vitamin D supplementation on blood glucose in patients with T2DM, while other studies found inconsistencies in the connection of vitamin D with blood glucose [5].

Although low vitamin D level is correlated with higher glycosylated hemoglobin (HbA1c) and blood glucose levels in patients with T2DM, the relationship is as yet unclear as well as inconsistent, such that there is still a need for further research on the connection of vitamin D with blood glucose in T2DM patients. Our study aimed to explore the connection of vitamin D with HbA1c and blood glucose in T2DM patients.

METHODS

This cross-sectional study recruited 100 patients with T2DM at Mampang District Puskesmas, South Jakarta, from June to July 2022 through consecutive sampling. The size of the required research sample was obtained using the formula for the correlation sample size, with $Z\alpha=1.96$; $Z\beta=1.28$; and $r=-0.387$ [6].

The inclusion criteria were as follows: men and women older than 18 years, not on insulin therapy, not having kidney and liver disease, not being pregnant or lactating, and not consuming vitamin D in the last three months. All subjects were provided with information about this study, and all gave written agreement by signing the informed consent form.

A self-reported questionnaire was used with items on subjects' employment, education, sunbathing habits, use of covered clothing, consumption of vitamin D-rich foods, and T2DM condition.

After a 10-hour fast by the respondents, venous blood was drawn from each respondent and divided into aliquots of 3, 2, and 5 mL that were respectively placed into one EDTA anticoagulant tube for measuring HbA1c, one sodium fluoride (NaF) anticoagulant tube for measuring fasting blood glucose (FBG), and one tube without anticoagulant for 25(OH)D determination. The HbA1c level was measured by High-Performance Liquid Chromatography (HPLC), FBG by the hexokinase method, and 25(OH)D by Direct Competitive Chemiluminescent Microparticle Immunoassay (CMIA). Determination of HbA1c and FBG was performed directly on the day of blood specimen collection, whereas 25(OH)D was determined simultaneously after all specimens had been collected. The blood specimens were frozen at minus 200C prior to being examined.

For data analysis, the Statistical Package for Social Sciences (SPSS) program version 23 was used. The Kolmogorov-Smirnov test was used to determine whether or not the data were normally distributed. Because the data distribution was non-normal, the correlation of vitamin D with HbA1c and FBG was analyzed by the Spearman correlation test at $p < 0.05$.

Ethics approval was issued by the Faculty of Medicine Ethics Committee, Universitas Trisakti, under No. 037/KER/FK/V/2022.

RESULTS

The characteristics of the study subjects, comprised of 26 males and 74 females with median age of 56 years (35 -79 years) may be seen in Table 1. The educational level of 35% of the subjects was high school graduate, while the most frequent occupation was housewife (68%). The most frequent 25(OH)D status was deficiency in 86% of subjects. Seventy-seven percent of the subjects

Table 1. Characteristics of study subjects

Characteristic	N (%)
Gender	
Female	74 (74)
Male	26 (26)
Education	
No schooling	5 (5)
Elementary school	15 (15)
Junior high school	29 (29)
Senior high school	35 (35)
Academy	16 (16)
Employment history	
Housewife	68 (68)
Employed	25 (25)
Unemployed	7 (7)
Vitamin D status	
Deficient	86 (86)
Insufficient	12 (12)
Sufficient	2 (2)
Sunlight exposure (15-30 minutes)	
Yes	16 (16)
No	84 (84)
Wearing of long-sleeved clothing (12-24 hours)	
Yes	69 (69)
No	31 (31)
	Median (IQR)
Age (years)	56 (35-79)
Duration of DM (months)	12 (1-120)
25(OH)D concentration (ng/mL)	11.2 (2.4-31.1)
HbA1c (%)	8.05 (5.1-17.4)
Blood glucose (mg/dL)	127 (70-383)
Dietary vitamin D intake (µg/day)	1.76 (0.0-12.44)
	Mean (SD)
Height (m)	1.54 (0.07)
Weight (kg)	62.04 (11.06)
BMI (kg/m^2)	26.09 (4.52)

BMI: Body Mass Index, DM: Diabetes Mellitus, IQR: Interquartile, SD: Standard deviation, HbA1c: Hemoglobin A1c

Table 2. Concentrations of vitamin D, HbA1c, and blood glucose in female and male Subjects

Parameter	Concentration	P value
25(OH)D concentration (ng/mL)		
Females	10.2 (2.4-24.7)	0.001*
Males	14.7 (4.7-31.1)	
HbA1c (%)		
Females	8.3 (5.1-17.4)	0.389
Males	7.8 (5.4-12.5)	
Blood glucose (mg/dL)		
Females	125.5 (70-383)	0.804
Males	130.5 (83-248)	

**Statistically significant, HbA1c: Hemoglobin A1c*

had never consumed vitamin D-containing foods, 84% of the subjects had never sunbathed, and 69% wore long-sleeved clothing daily for 24 hours.

We found that the male and female subjects differed significantly in vitamin D levels but not in HbA1c and FBG levels (Table 2).
This study also found a significant but negative correlation of vitamin D concentration with HbA1c at r= - 0.217 (p= 0.03). However, no correlation of vitamin D with FBG was found at r= - 0.153 (p=0.128).

DISCUSSION

The patients with T2DM in this study were mostly females. The greater number of females who had diabetes is similar to that in the study of Mihardja, in that diabetes affects women more than men because of their higher body mass index. This is in contrast with Japan and China, where T2DM prevalence is higher in males, which may be caused by the differing diets and behaviors of males [7]. The study by Azlin et al. shows that there are more females with T2DM than males. According to the 2002 study of Brunner and Suddart, as cited by Azlin, there are more females with T2DM as compared to males because there is proportionately more body fat in the former than in the latter. Body fat deposit is one of the factors that may reduce insulin sensitivity in muscles and liver [8]. In the 2018 Basic Health Survey of Indonesia, the DM prevalence in females was higher than in males, at a ratio of 1.78% to 1.21%. The Basic Health Survey of Indonesia also found that in the last five years, the prevalence of T2DM in females showed a slight increase compared to males [9].
The participants in our research had a median age of 56 years. In third-world countries, most of the patients with T2DM are between 45 and 64 years old, whereas in first-world countries, the patients with T2DM are mostly older than 64 years [10]. The prevalence of diabetes also shows an increase with increasing age of the patients and peaks at age 55-64 years. In the Basic Health Survey of Indonesia 2018, there were also indications of an increase in age and, thus, a higher risk for diabetes [9]. Sharan and team [11] reported that recent onset T2DM accounted for 79.1% in the age range of 40-60 years. Older respondents are commonly more at risk of hyperglycemia due to decreased function of the pancreas [7].
The median 25(OH)D level in this study was 11.2 ng/mL, corresponding to vitamin D deficiency in 86% of patients. Vitamin D can be categorized as deficiency if 25(OH)D concentration < 20 ng/mL, insufficiency if 25(OH)D concentration = 21-29 ng/mL, sufficiency if 25(OH)D concentration ≥ 30 ng/mL and intoxication if 25(OH)D level ≥ 150 ng/mL [12]. The proportion of deficiency and insufficiency for vitamin D in Indonesia is relatively great, being 68.8% in Pusparini's study in South Jakarta [13] on women and men aged 55-65 years. In North Sumatra, however, Keumala [14] found that 95% of adult women had vitamin D deficiency and insufficiency. Arjana's team [15] in Yogyakarta found that in adult males aged 19-25 years, the proportion of deficiency of vitamin D was 43.3%,

whereas the proportion of insufficiency of vitamin D was 51.7%.

The causative factors of vitamin D deficiency are varied, among others, low exposure to sunlight, fewer vitamin D-containing foods in the diet, insufficient outdoor activity, a lifestyle that avoids sunlight, sunscreen usage, covered clothing or traditional clothing covering the whole body, and dark-colored skin. Skin color is an important factor in natural vitamin D production. Darker skins need more time to form vitamin D than fair skins. Sunscreens may absorb ultraviolet light (UVB-UVA) to inhibit UVB penetration into the skin [16,17]. Reduced physical activity is also a factor in vitamin D deficiency and T2DM because physical activity may improve the vitamin D status [18].

Our findings of reduced median vitamin D level and high vitamin D deficiency prevalence were probably caused by inadequate vitamin D intake from sunlight and the diet. This study found that the proportion of study subjects who had never been exposed to sunlight for 15-30 minutes was 84% because the majority of study subjects were housewives (68%) such that their activity was indoors. Our study also found that the median vitamin D intake was extremely low, at 1.76 µg/day. The average vitamin D intake recommended by the Institute of Medicine (IOM) for females and males aged 18-70 years is 15 µg/day [19]. Vitamin D-containing foods are among others egg yolk, salmon, mackerel, tuna, meat, mushrooms, cod liver oil, and fortified foods [14,19]. According to the study of Masood and Iqbal, as cited by Keumala et al. [14] the inability to buy vitamin D-containing foods results in the occurrence of vitamin D deficiency. Salmon and cod liver oil are highly expensive vitamin D-containing foods on the market. It should be noted that around 69% of our subjects wore covered or long-sleeved clothing for 12-24 hours, such as to prevent sunlight from penetrating the body through the skin's surface. According to Holick, adequate vitamin D can be obtained by twice weekly sunlight exposure of the arms and legs for 5-30 minutes between 10 AM and 3 PM (as determined by weather and skin color) [12]. Similar results were found between our study and Keumala's, in that deficiency of vitamin D correlates with indoor occupations and activities, less vitamin D-containing foods in the diet, and sunbathing of ≤ 1 hour daily [14].

Mahmodnia's team [20] reported a strong positive correlation of vitamin D and age. The age variable is a dominant factor that causes vitamin D deficiency, which is correlated with low outdoor activities, resulting in low exposure to sunlight. In addition, there are changes in the skin, namely a reduction in the content of 7-dehydroxycholesterol, the precursor of vitamin D3 [21]. The study of Jha et al. [22] also showed low vitamin D concentrations with increasing age. The reduced synthesis of vitamin D with increasing age, in addition to being due to reduced 7-dehydroxycholesterol concentrations, is also caused by reduced oral absorption of vitamin D.

In our study, an important difference was found in the vitamin D levels of men and women, This may have been the result of differences in physical activity and lifestyle between males and females, where the activities of the males were presumably carried out to a greater extent out of doors, in comparison to those of the females, such that the males were more frequently exposed to sunlight. Lifestyle, in this case, the style of clothing, also affects vitamin D concentrations. The majority of the female respondents in this study wore covered clothing (Muslim clothing with headscarves), causing a reduction in the exposure of the body to sunlight, such that vitamin D synthesis is reduced. Another factor that may have caused the contrasting vitamin D levels in men and women is the larger amount of body fat in women than in men. Vitamin D is soluble in fats, while body fat absorbs and stores vitamin D, which may reduce circulatory vitamin D concentrations in females [23,24].

As stated above, our study found that vitamin D had a strong negative relationship with HbA1c but not with FBG. This agrees with Mehta's report of a significant negative correlation (r = - 0.1205) of HbA1c with vitamin D, where decreased vitamin D level is connected with increased HbA1c level [25]. Our study also agrees with Jha et al. [22], which reported an inverse relationship between vitamin D and HbA1c. However, our study results differ from those of Suguna's group [26] from Bengaluru, showing no strong relationship of HbA1c with vitamin D concentrations in T2DM patients (r= -0.109 at p=0.05).

Research findings of Raumulfaro [24] revealed no association between vitamin D and HbA1c (r = 0.214, P=0.153) on the one hand and vitamin D and blood glucose (r =0.195, p=0.193) on the other. The non-significant correlation of FBG with vitamin D may have been among other causes due to body fat percentage. A person with a high body fat percentage may have reduced vitamin D concentrations, as a large amount of body fat retains vitamin D, thereby diminishing circulatory vitamin D, leading to low serum levels. Consumption of glucocorticoids and blood-pressure-lowering medications may also influence vitamin D concentrations. The use of glucocorticoids may interfere with osteoblastic and osteoclastic functions, such that it can reduce vitamin D concentrations. Furthermore, sport increases the level of this vitamin, as reported in the study by Fernandez [24,27–29]. The study conducted by Sakung [30] found that physical activity heightens tissue sensitivity to insulin and absorption of glucose, thereby reducing blood glucose concentrations.

One study showed that vitamin D is negatively correlated with HbA1c, but not with FBG, thereby showing that adequate vitamin D in T2DM patients improves HbA1c but not FBG. This may have been due to differences in the level of glycemic control of HbA1c and FBG, where HbA1c represents the mean glucose level over the last 60 to 90 days., whereas serum glucose concentration is determined after an overnight fast. The FBG level is determined by basal insulin secretion, whereas HbA1c is determined by basal and post-prandial insulin secretion. The significant connection of vitamin D with HbA1c was presumably due to the effect of vitamin D on post-prandial but not on basal insulin release. Post-prandial vitamin D increase is connected with calcium absorption, leading to increased intracellular calcium, which mediates post-prandial insulin release, thereby improving HbA1c concentrations without affecting FBG concentrations [31–33].

No significant differences were found in HbA1c and blood glucose parameters between males and females in this study. Vitamin D was also not strongly correlated with HbA1c or with blood glucose after adjustment for gender subgroups (data not shown), possibly because of the disproportionately larger number of females.

According to Kautzky-Willer et al. [34] the gender differences for HbA1c cannot be related to the makeup of the body, because there are various factors affecting HbA1c level, among others, genetic, age-related, ethnic, and environmental factors.

Fasting blood glucose is influenced mainly by the release of glucose in the liver [34,35]. Measurement of random glucose concentration, such as post-prandial glucose, may improve glycemic control in females, particularly when there are differences between HbA1c and fasting glucose [34,36].

The American Diabetes Association recommends HbA1c instead of FBG for the diagnosis of diabetes mellitus. HbA1c constitutes an invaluable monitor of blood glucose control because it represents the glucose level accumulated over the last 60 to 90 days. HbA1c is also highly correlated with the risk of diabetic sequelae over a prolonged period of time [32].

Vitamin D is important for glucose metabolism, stimulating insulin release from pancreatic beta cells and increasing intracellular calcium and insulin sensitivity in peripheral muscles and adipocytes [18]. Vitamin D also stimulates insulin receptor expression and peroxisome proliferator-activated receptor delta (PPAR-δ) activation involved in the metabolism of fatty acids and the transport of glucose in the muscles, where these compounds will be converted into ATP as an energy source. Vitamin D deficiency may affect calcium concentrations in cells that are sensitive to insulin, thus leading to peripheral insulin resistance that reduces glucose transport to the muscles. In addition, vitamin D deficiency indirectly influences insulin resistance via the renin-angiotensin-aldosterone system, where angiotensin blocks vascular and skeletal muscle insulin, thus interfering with energy needs [37].

Maintaining a normal vitamin D concentration may help glucose homeostasis, while in individuals with high HbA1c, screening for vitamin D may be performed [25].

The weak points of the present study were its cross-sectional study design, which prevented delving into the relationship of vitamin D versus HbA1c or glucose, and the fact that it did not use healthy individuals as controls; and thirdly, this study performed only single blood glucose determinations that did not reflect glycemic variability. Further studies need to be conducted on vitamin D supplementation in the form of a ` randomized, double-blind, placebo-controlled trial to determine the effects of vitamin D on HbA1c and FBG.

CONCLUSION

This study found a strong negative relationship of vitamin D with HbA1c, but not with FBG. Additional research is required using healthy controls and performing serial blood glucose determinations.

REFERENCES

1. Kharroubi, A.T.; Darwish, H.M. Diabetes mellitus: The epidemic of the century. World J Diabetes 2015, 6, 850-867, doi:10.4239/wjd.v6.i6.850.
2. American Diabetes Association Professional Practice Committee. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2022. Diabetes Care 2022, 45(Suppl 1), S17-S38, doi:10.2337/dc22-S002
3. Rehman, K.; Akash, M.S. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? J Biomed Sci 2016, 23, 87, doi: 10.1186/s12929-016-0303-y.
4. Das, G. Vitamin D and type 2 diabetes. Practical Diabetes 2017, 34, 19-24. URL: https://wileymicrositebuilder.com/practicaldiabetes/wp-content/uploads/sites/29/2017/01/Rev-Das-lsw.pdf
5. Yu, J.R.; Lee, S.A.; Lee, J.G.; Seong, G.M.; Ko, S.J.; Koh, G.; et al. Serum vitamin d status and its relationship to metabolic parameters in patients with type 2 diabetes mellitus. Chonnam Med J 2012, 48, 108-115, doi: 10.4068/cmj.2012.48.2.108.
6. Aaty, T.A.A.; Magallaa, M.H.Z.; Moneim, H.A.; Ismail, H.M.; Genena, D.M.; Frugina, R. Serum vitamin D level in type 2 diabetic subjects: Relation to glycemic control, insulin resistance and proinflammatory markers. Journal of High Institute of Public Health 2017, 47, 62-68, doi:10.21608/JHIPH.2017.19966.
7. Mihardja, L.; Soetrisno, U.; Soegondo, S. Prevalence and clinical profile of diabetes mellitus in productive aged urban Indonesians. J Diabetes Investig 2014, 5, 507-512, doi: 10.1111/jdi.12177.
8. Azlin, A.; Ganie, R.A.; Syafril, S. The difference of vitamin D levels between controlled and uncontrolled type 2 diabetes mellitus patients. Indonesian Journal of Clinical Pathology and Medical Laboratory 2019, 26, 18-22, doi:10.24293/ijcpml.v26i1.1407.
9. Tetap produktif, cegah dan atasi DM melitus. Pusat Data dan Informasi Kementrian Kesehatan Republik Indonesia 2020. ISSN 2442-7659. URL: https://www.kemkes.go.id/downloads/resources/download/pusdatin/infodatin/Infodatin%202020%20Diabetes%20Melitus.pdf
10. Wild, S.; Roglic, G.; Green, A.; Sicree, R.; King, H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004, 27, 1047-1053, doi: 10.2337/diacare.27.5.1047.
11. Sharan, A.; Mukhopadhyay, S.; Majumdar, J.; Ghosh, B.; Sengupta, S. A study of prevalence of vitamin D deficiency in new onset type 2 diabetes mellitus in a tertiary care hospital of Eastern India. JIACM 2018, 19, 106-111. URL: https://www.jiacm.in/journals/2018/april_june_2018/Journal%2070%20Page%20106-111%20Original%20Article.pdf
12. Holick, M.F. Vitamin D deficiency. N Engl J Med 2007, 357, 266-281, doi: 10.1056/NEJMra070553.
13. Pusparini.; Meriyanti, L.T.; Sudharma, N.I. Increased matrix metalloproteinase-9 in male elderly with low 25-hydroxy-vitamin D. Univ Med 2016, 35, 171-180, doi:10.18051/UnivMed.2016.v35.171-180.
14. Keumala, D.; Alrasyid, H.; NurIndrawaty, L.; Zulkifli, L. Occurence of vitamin D deficiency among women in North Sumatera, Indonesia. Mal J Nutr 2014, 20, 63-70. URL: https://www.researchgate.net/publication/285524669_Occurrence_of_vitamin_D_deficiency_among_women_in_North_Sumatera_Indonesia#fullTextFileContent
15. Arjana, A.Z.; Devita, N.; Nurmasitoh, T.; Fidianingsih, I.; Dewi, M.; Khoiriyah, U. High proportion of vitamin D deficiency in male adolescents in Yogyakarta Indonesia. In Proocedings of the 4th International Conference on Sustainable Innovation 2020–Health Science and Nursing (ICoSIHSN 2020), March 2021; Atlantis Press B.V, 2021; volume 33, pp. 54-58, doi:10.2991/ahsr.k.210115.011.
16. Pusparini. Defisiensi vitamin D terhadap penyakit. Indonesian Journal Of Clinical Pathology and Medical Laboratory 2014, 21, 90-95, doi:10.24293/ijcpml.v21i1.1265.
17. Rimahardika, R.; Subagio, H.W.; Wijayanti, H.S. Asupan vitamin D dan paparan sinar matahari pada orang yang bekerja di dalam ruangan dan di luar ruangan. Journal Of Nutrition College 2017, 6, 333-342, doi:10.14710/jnc.v6i4.18785.
18. Asegaonkar, S.B. Vitamin D and type 2 diabetes mellitus: Indian perspectives. J Diabetic Complications Med 2016, 1, 1-4, doi:10.4172/2475-3211.1000110.
19. Holick, M.F.; Binkley, N.C.; Bischoff-Ferrari, H.A.; Gordon, C.M.; Hanley, D.A.; Heaney, R.P.; et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical

practice guideline. J Clin Endocrinol Metab 2011, 96, 1911-1930, doi: 10.1210/jc.2011-0385.
20. Mahmodnia, L.; Tamadon, M.R.; Sadoughi, M.; Beigrezaei, S. Vitamin D status and its relationship with age in type 2 diabetic patients. Journal of Parathyroid Disease 2017, 5, 45-48, doi:10.15171/jpd.2017.05.
21. Hidayat, R.; Setiati, S.; Soewondo, P. The association between vitamin D deficiency and type 2 diabetes mellitus in elderly patients. Acta Med Indones 2010, 42, 123-129. URL: https://pubmed.ncbi.nlm.nih.gov/20724765/
22. Jha, S.C.; Kumar, H.; Faisal, S.Y. Correlation between vitamin D and HbA1c in type 2 diabetic patients. Academia Journal of Medicine 2020, 3, 4-10, doi:10.47008/ajm.2020.3.1.2.
23. Al-Horani, H.; Dayyih, W.A.; Mallah, E.; Hamad, M.; Mima, M.; Awad, R.; et al. Nationality, gender, age, and body mass index influences on vitamin D concentration among elderly patients and young Iraqi and Jordanian in Jordan. Biochem Res Int 2016, 2016, 1-8, doi: 10.1155/2016/8920503.
24. Akbar, A.R.; Kurnia, E.; Hendrianingtyas, M.; Nugroho, H. Correlation between fasting blood glucose and Hba1c with vitamin D in diabetes mellitus. Pakistan Journal of Medical Health Sciences 2019, 13, 1093-1096. URL: https://pjmhsonline.com/2019/oct_dec/pdf/1093.pdf
25. Mehta, N.; Shah, S.; Shah, P.P.; Prajapati, V. Correlation between vitamin D and HbA1c in type 2 diabetic patients. GCSMC J Med Sci 2016, 5, 42-46. URL: https://gcsmc.org/assets/pdf/journal/journal-1227/original-article/correlation-between-vitamin-d-and-hba1c-in-type-2-diabetic-patients201810051242459072370.pdf
26. Suguna, S.; Kusumadevi, M.S. Relationship between vitamin D and HbA1c levels in patients with type 2 diabetes mellitus of Bengaluru City. International Journal of Physiology 2019, 7, 104-108, doi:10.5958/2320-608x.2019.00149.5.
27. Zhang, M.; Li, P.; Zhu, Y.; Chang, H.; Wang, X.; Liu, W.; et al. Higher visceral fat area increases the risk of vitamin D insufficiency and deficiency in Chinese adults. Nutr Metab (Lond) 2015, 12, 50, doi: 10.1186/s12986-015-0046-x.
28. Fernandes, M.R.; Barreto, W.D.R.J. Association between physical activity and vitamin D: A narrative literature review. Rev Assoc Med Bras 2017, 63, 550-556, doi: 10.1590/1806-9282.63.06.550.
29. Grober, U.; Kisters, K. Influence of drugs on vitamin D and calcium metabolism. Dermatoendocrinol 2012, 4, 158-166, doi: 10.4161/derm.20731.
30. Sakung, J.M.; Sirajuddin, S.; Zulkifli, A.; Rahman, S.A.; Sudargo, T. Physical activity is associated with lower blood glucose level in high school teachers in Palu, Indonesia. Int J Community Med Public Health 2018, 5, 3176-3179, doi:10.18203/2394-6040.ijcmph20183047.
31. Alkhatatbeh, M.J.; Abdul-Razzak, K.K. Association between serum 25-hydroxyvitamin D, hemoglobin A1c and fasting blood glucose levels in adults with diabetes mellitus. Biomed Rep 2018, 9, 523-530, doi: 10.3892/br.2018.1159.
32. Sherwani, S.I.; Khan, H.A.; Ekhzaimy, A.; Masood, A.; Sakharkar, M.K. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. Biomark Insights 2016, 11, 95-104, doi: 10.4137/BMI.S38440.
33. Monnier, L.; Colette, C. Contributions of fasting and post-prandial glucose to hemoglobin A1c. Endocr Pract 2006, 12 Suppl 1, 42-46, doi: 10.4158/EP.12.S1.42.
34. Kautzky-Willer, A.; Kosi, L.; Lin, J.; Mihaljevic, R. Gender-based differences in glycaemic control and hypoglycaemia prevalence in patients with type 2 diabetes: results from patient-level pooled data of six randomized controlled trials. Diabetes Obes Metab 2015, 17, 533-540, doi: 10.1111/dom.12449.
35. Tabak, A.G.; Herder, C.; Rathmann, W.; Brunner, E.J.; Kivimaki, M. Prediabetes: a high-risk state for diabetes development. Lancet 2012, 379, 2279-2290, doi: 10.1016/S0140-6736(12)60283-9.
36. Ehrhardt, N.M.; Chellappa, M.; Walker, M.S.; Fonda, S.J.; Vigersky, R.A. The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. J Diabetes Sci Technol 2011, 5, 668-675, doi: 10.1177/193229681100500320.
37. Sanda, A.; Bahrun, U.; Pakasi, R.D.N.; Aman, A.M. Analysis of vitamin D in patients with type 2 diabetes mellitus. Indonesian Journal of Clinical Pathology and Medical Laboratory 2019, 25, 150-154, doi: 10.24293/ijcpml.v25i2.1360.

25-hydroxy vitamin D concentrations negatively correlated with HbA1c in type 2 diabetes mellitus patients: a cross-sectional study in Mampang, South Jakarta

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25-hydroxy vitamin D concentrations negatively correlated with HbA1c in type 2 diabetes mellitus patients: a cross-sectional study in Mampang, South Jakarta

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ABSTRACT

INTRODUCTION: Insulin resistance plays a central role in type 2 diabetes mellitus (T2DM). Another possible cause of T2DM is a deficiency of 25-hydroxy vitamin D [25(OH)D], although the underlying mechanism is not yet clearly understood. The most frequently used laboratory parameters for monitoring T2DM are fasting blood glucose (FBG) and HbA1c. Determining any association of vitamin D with HbA1c and FBG in T2DM.

METHODS: A cross-sectional study involving 100 T2DM patients with the following characteristics: 18-year and older persons of both genders, not having kidney and liver disease, not on insulin therapy, not pregnant or lactating, and not consuming vitamin D in the last three months. Spearman's correlation coefficient was used to test any association of 25(OH)D with HbA1c and fasting blood glucose (FBG) ($p<0.05$).

RESULTS: Subjects comprised 74 females and 26 males with a median age of 56 years. Median HbA1c, 25(OH)D, and FBG were 8.05%, 11.2 ng/mL, and 127 mg/dL, respectively. The Spearman correlation coefficient for vitamin D and HbA1c was $r=-0.217$ ($p=0.03$), and for vitamin D and FBG, it was $r=-0.153$ ($p=0.128$).

CONCLUSION: There was a significant negative correlation of vitamin D with HbA1c but not with FBG. Administration of vitamin D should be considered for additional treatment of T2DM.

Keywords: Type 2 Diabetes Mellitus, 25-hydroxy Vitamin D, Blood Glucose, HbA1c, Fasting Blood Glucose

INTRODUCTION

The metabolic disorder diabetes mellitus (DM) features high blood glucose levels due to defective insulin response. Insulin resistance in target tissues, particularly in the skeletal muscles and adipose tissue, is responsible for abnormalities in carbohydrate, fat and protein metabolism, which may result in diabetes. There are several types of DM. The 2022 American Diabetes Association guidelines categorize DM into type 1 diabetes due to autoimmune damage to the beta cells, type 2 diabetes due to insulin resistance; diabetes due to other causes such as monogenic diabetic syndrome, DM-causing drugs, exocrine pancreatic disease, and gestational diabetes [1,2].

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Type 2 diabetes mellitus (T2DM) comprises the highest number of patients globally and in Indonesia. The global prevalence of T2DM at age 20-79 years, according to the International Diabetes Federation (IDF) 2013 report, was 8.3% (382 million persons), with 14 million more men than women, generally aged 40-59 years. The global number of cases is projected to increase to 592 million in the year 2035. Changes in lifestyle and unhealthy food may presumably cause the increased incidence of T2DM at younger ages. Obesity is also responsible for the occurrence of T2DM [1].

Insulin resistance plays a central role in T2DM. Oxidative stress, proinflammatory activation, adipokines, and abnormal glucose and lipid metabolism can lead to insulin resistance [3]. Another possible cause of T2DM is a deficiency of vitamin D. Although the underlying mechanism is not yet clearly understood, low 25-hydroxyvitamin D [25(OH)D] level is connected with functional disorders of pancreatic islet Langerhans cells and insulin resistance causing changes in glucose homeostasis such as to result in the occurrence of T2DM [4].

Vitamin D may increase insulin secretion, skeletal muscle glucose, and lipid metabolism and reduce systemic inflammation. However, several studies found no influence of vitamin D supplementation on blood glucose in patients with T2DM, while other studies found inconsistencies in the connection of vitamin D with blood glucose [5].

Although low vitamin D level is correlated with higher glycosylated hemoglobin (HbA1c) and blood glucose levels in patients with T2DM, the relationship is as yet unclear as well as inconsistent, such that there is still a need for further research on the connection of vitamin D with blood glucose in T2DM patients. Our study aimed to explore the connection of vitamin D with HbA1c and blood glucose in T2DM patients.

METHODS

This cross-sectional study recruited 100 patients with T2DM at Mampang District Puskesmas, South Jakarta, from June to July 2022 through consecutive sampling. The size of the required research sample was obtained using the formula for the correlation sample size, with $Z\alpha=1.96$; $Z\beta=1.28$; and $r=-0.387$ [6].

The inclusion criteria were as follows: men and women older than 18 years, not on insulin therapy, not having kidney and liver disease, not being pregnant or lactating, and not consuming vitamin D in the last three months. All subjects were provided with information about this study, and all gave written agreement by signing the informed consent form.

A self-reported questionnaire was used with items on subjects' employment, education, sunbathing habits, use of covered clothing, consumption of vitamin D-rich foods, and T2DM condition.

After a 10-hour fast by the respondents, venous blood was drawn from each respondent and divided into aliquots of 3, 2, and 5 mL that were respectively placed into one EDTA anticoagulant tube for measuring HbA1c, one sodium fluoride (NaF) anticoagulant tube for measuring fasting blood glucose (FBG), and one tube without anticoagulant for 25(OH)D determination. The HbA1c level was measured by High-Performance Liquid Chromatography (HPLC), FBG by the hexokinase method, and 25(OH)D by Direct Competitive Chemiluminescent Microparticle Immunoassay (CMIA). Determination of HbA1c and FBG was performed directly on the day of blood specimen collection, whereas 25(OH)D was determined simultaneously after all specimens had been collected. The blood specimens were frozen at minus 200C prior to being examined.

For data analysis, the Statistical Package for Social Sciences (SPSS) program version 23 was used. The Kolmogorov-Smirnov test was used to determine whether or not the data were normally distributed. Because the data distribution was non-normal, the correlation of vitamin D with HbA1c and FBG was analyzed by the Spearman correlation test at $p < 0.05$.

Ethics approval was issued by the Faculty of Medicine Ethics Committee, Universitas Trisakti, under No. 037/KER/FK/V/2022.

RESULTS

The characteristics of the study subjects, comprised of 26 males and 74 females with median age of 56 years (35 -79 years) may be seen in Table 1. The educational level of 35% of the subjects was high school graduate, while the most frequent occupation was housewife (68%). The most frequent 25(OH)D status was deficiency in 86% of subjects. Seventy-seven percent of the subjects

Table 1. Characteristics of study subjects

Characteristic	N (%)
Gender	
Female	74 (74)
Male	26 (26)
Education	
No schooling	5 (5)
Elementary school	15 (15)
Junior high school	29 (29)
Senior high school	35 (35)
Academy	16 (16)
Employment history	
Housewife	68 (68)
Employed	25 (25)
Unemployed	7 (7)
Vitamin D status	
Deficient	86 (86)
Insufficient	12 (12)
Sufficient	2 (2)
Sunlight exposure (15-30 minutes)	
Yes	16 (16)
No	84 (84)
Wearing of long-sleeved clothing (12-24 hours)	
Yes	69 (69)
No	31 (31)
	Median (IQR)
Age (years)	56 (35-79)
Duration of DM (months)	12 (1-120)
25(OH)D concentration (ng/mL)	11.2 (2.4-31.1)
HbA1c (%)	8.05 (5.1-17.4)
Blood glucose (mg/dL)	127 (70-383)
Dietary vitamin D intake (µg/day)	1.76 (0.0-12.44)
	Mean (SD)
Height (m)	1.54 (0.07)
Weight (kg)	62.04 (11.06)
BMI (kg/m^2)	26.09 (4.52)

BMI: Body Mass Index, DM: Diabetes Mellitus, IQR: Interquartile, SD: Standard deviation, HbA1c: Hemoglobin A1c

Table 2. Concentrations of vitamin D, HbA1c, and blood glucose in female and male Subjects

Parameter	Concentration	P value
25(OH)D concentration (ng/mL)		
Females	10.2 (2.4-24.7)	0.001*
Males	14.7 (4.7-31.1)	
HbA1c (%)		
Females	8.3 (5.1-17.4)	0.389
Males	7.8 (5.4-12.5)	
Blood glucose (mg/dL)		
Females	125.5 (70-383)	0.804
Males	130.5 (83-248)	

**Statistically significant, HbA1c: Hemoglobin A1c*

had never consumed vitamin D-containing foods, 84% of the subjects had never sunbathed, and 69% wore long-sleeved clothing daily for 24 hours.

We found that the male and female subjects differed significantly in vitamin D levels but not in HbA1c and FBG levels (Table 2).
This study also found a significant but negative correlation of vitamin D concentration with HbA1c at r= - 0.217 (p= 0.03). However, no correlation of vitamin D with FBG was found at r= - 0.153 (p=0.128).

DISCUSSION

The patients with T2DM in this study were mostly females. The greater number of females who had diabetes is similar to that in the study of Mihardja, in that diabetes affects women more than men because of their higher body mass index. This is in contrast with Japan and China, where T2DM prevalence is higher in males, which may be caused by the differing diets and behaviors of males [7]. The study by Azlin et al. shows that there are more females with T2DM than males. According to the 2002 study of Brunner and Suddart, as cited by Azlin, there are more females with T2DM as compared to males because there is proportionately more body fat in the former than in the latter. Body fat deposit is one of the factors that may reduce insulin sensitivity in muscles and liver [8]. In the 2018 Basic Health Survey of Indonesia, the DM prevalence in females was higher than in males, at a ratio of 1.78% to 1.21%. The Basic Health Survey of Indonesia also found that in the last five years, the prevalence of T2DM in females showed a slight increase compared to males [9].
The participants in our research had a median age of 56 years. In third-world countries, most of the patients with T2DM are between 45 and 64 years old, whereas in first-world countries, the patients with T2DM are mostly older than 64 years [10]. The prevalence of diabetes also shows an increase with increasing age of the patients and peaks at age 55-64 years. In the Basic Health Survey of Indonesia 2018, there were also indications of an increase in age and, thus, a higher risk for diabetes [9]. Sharan and team [11] reported that recent onset T2DM accounted for 79.1% in the age range of 40-60 years. Older respondents are commonly more at risk of hyperglycemia due to decreased function of the pancreas [7].
The median 25(OH)D level in this study was 11.2 ng/mL, corresponding to vitamin D deficiency in 86% of patients. Vitamin D can be categorized as deficiency if 25(OH)D concentration < 20 ng/mL, insufficiency if 25(OH)D concentration = 21-29 ng/mL, sufficiency if 25(OH)D concentration ≥ 30 ng/mL and intoxication if 25(OH)D level ≥ 150 ng/mL [12]. The proportion of deficiency and insufficiency for vitamin D in Indonesia is relatively great, being 68.8% in Pusparini's study in South Jakarta [13] on women and men aged 55-65 years. In North Sumatra, however, Keumala [14] found that 95% of adult women had vitamin D deficiency and insufficiency. Arjana's team [15] in Yogyakarta found that in adult males aged 19-25 years, the proportion of deficiency of vitamin D was 43.3%,

whereas the proportion of insufficiency of vitamin D was 51.7%.

The causative factors of vitamin D deficiency are varied, among others, low exposure to sunlight, fewer vitamin D-containing foods in the diet, insufficient outdoor activity, a lifestyle that avoids sunlight, sunscreen usage, covered clothing or traditional clothing covering the whole body, and dark-colored skin. Skin color is an important factor in natural vitamin D production. Darker skins need more time to form vitamin D than fair skins. Sunscreens may absorb ultraviolet light (UVB-UVA) to inhibit UVB penetration into the skin [16,17]. Reduced physical activity is also a factor in vitamin D deficiency and T2DM because physical activity may improve the vitamin D status [18].

Our findings of reduced median vitamin D level and high vitamin D deficiency prevalence were probably caused by inadequate vitamin D intake from sunlight and the diet. This study found that the proportion of study subjects who had never been exposed to sunlight for 15-30 minutes was 84% because the majority of study subjects were housewives (68%) such that their activity was indoors. Our study also found that the median vitamin D intake was extremely low, at 1.76 µg/day. The average vitamin D intake recommended by the Institute of Medicine (IOM) for females and males aged 18-70 years is 15 µg/day [19]. Vitamin D-containing foods are among others egg yolk, salmon, mackerel, tuna, meat, mushrooms, cod liver oil, and fortified foods [14,19]. According to the study of Masood and Iqbal, as cited by Keumala et al. [14] the inability to buy vitamin D-containing foods results in the occurrence of vitamin D deficiency. Salmon and cod liver oil are highly expensive vitamin D-containing foods on the market. It should be noted that around 69% of our subjects wore covered or long-sleeved clothing for 12-24 hours, such as to prevent sunlight from penetrating the body through the skin's surface. According to Holick, adequate vitamin D can be obtained by twice weekly sunlight exposure of the arms and legs for 5-30 minutes between 10 AM and 3 PM (as determined by weather and skin color) [12]. Similar results were found between our study and Keumala's, in that deficiency of vitamin D correlates with indoor occupations and activities, less vitamin D-containing foods in the diet, and sunbathing of ≤ 1 hour daily [14].

Mahmodnia's team [20] reported a strong positive correlation of vitamin D and age. The age variable is a dominant factor that causes vitamin D deficiency, which is correlated with low outdoor activities, resulting in low exposure to sunlight. In addition, there are changes in the skin, namely a reduction in the content of 7-dehydroxycholesterol, the precursor of vitamin D3 [21]. The study of Jha et al. [22] also showed low vitamin D concentrations with increasing age. The reduced synthesis of vitamin D with increasing age, in addition to being due to reduced 7-dehydroxycholesterol concentrations, is also caused by reduced oral absorption of vitamin D.

In our study, an important difference was found in the vitamin D levels of men and women, This may have been the result of differences in physical activity and lifestyle between males and females, where the activities of the males were presumably carried out to a greater extent out of doors, in comparison to those of the females, such that the males were more frequently exposed to sunlight. Lifestyle, in this case, the style of clothing, also affects vitamin D concentrations. The majority of the female respondents in this study wore covered clothing (Muslim clothing with headscarves), causing a reduction in the exposure of the body to sunlight, such that vitamin D synthesis is reduced. Another factor that may have caused the contrasting vitamin D levels in men and women is the larger amount of body fat in women than in men. Vitamin D is soluble in fats, while body fat absorbs and stores vitamin D, which may reduce circulatory vitamin D concentrations in females [23,24].

As stated above, our study found that vitamin D had a strong negative relationship with HbA1c but not with FBG. This agrees with Mehta's report of a significant negative correlation ($r = - 0.1205$) of HbA1c with vitamin D, where decreased vitamin D level is connected with increased HbA1c level [25]. Our study also agrees with Jha et al. [22], which reported an inverse relationship between vitamin D and HbA1c. However, our study results differ from those of Suguna's group [26] from Bengaluru, showing no strong relationship of HbA1c with vitamin D concentrations in T2DM patients ($r= -0.109$ at $p=0.05$).

Research findings of Raumulfaro [24] revealed no association between vitamin D and HbA1c ($r = 0.214$, $P=0.153$) on the one hand and vitamin D and blood glucose ($r =0.195$, $p=0.193$) on the other. The non-significant correlation of FBG with vitamin D may have been among other causes due to body fat percentage. A person with a high body fat percentage may have reduced vitamin D concentrations, as a large amount of body fat retains vitamin D, thereby diminishing circulatory vitamin D, leading to low serum levels. Consumption of glucocorticoids and blood-pressure-lowering medications may also influence vitamin D concentrations. The use of glucocorticoids may interfere with osteoblastic and osteoclastic functions, such that it can reduce vitamin D concentrations. Furthermore, sport increases the level of this vitamin, as reported in the study by Fernandez [24,27–29]. The study conducted by Sakung [30] found that physical activity heightens tissue sensitivity to insulin and absorption of glucose, thereby reducing blood glucose concentrations.

One study showed that vitamin D is negatively correlated with HbA1c, but not with FBG, thereby showing that adequate vitamin D in T2DM patients improves HbA1c but not FBG. This may have been due to differences in the level of glycemic control of HbA1c and FBG, where HbA1c represents the mean glucose level over the last 60 to 90 days., whereas serum glucose concentration is determined after an overnight fast. The FBG level is determined by basal insulin secretion, whereas HbA1c is determined by basal and post-prandial insulin secretion. The significant connection of vitamin D with HbA1c was presumably due to the effect of vitamin D on post-prandial but not on basal insulin release. Post-prandial vitamin D increase is connected with calcium absorption, leading to increased intracellular calcium, which mediates post-prandial insulin release, thereby improving HbA1c concentrations without affecting FBG concentrations [31–33].

No significant differences were found in HbA1c and blood glucose parameters between males and females in this study. Vitamin D was also not strongly correlated with HbA1c or with blood glucose after adjustment for gender subgroups (data not shown), possibly because of the disproportionately larger number of females.

According to Kautzky-Willer et al. [34] the gender differences for HbA1c cannot be related to the makeup of the body, because there are various factors affecting HbA1c level, among others, genetic, age-related, ethnic, and environmental factors.

Fasting blood glucose is influenced mainly by the release of glucose in the liver [34,35]. Measurement of random glucose concentration, such as post-prandial glucose, may improve glycemic control in females, particularly when there are differences between HbA1c and fasting glucose [34,36].

The American Diabetes Association recommends HbA1c instead of FBG for the diagnosis of diabetes mellitus. HbA1c constitutes an invaluable monitor of blood glucose control because it represents the glucose level accumulated over the last 60 to 90 days. HbA1c is also highly correlated with the risk of diabetic sequelae over a prolonged period of time [32].

Vitamin D is important for glucose metabolism, stimulating insulin release from pancreatic beta cells and increasing intracellular calcium and insulin sensitivity in peripheral muscles and adipocytes [18]. Vitamin D also stimulates insulin receptor expression and peroxisome proliferator-activated receptor delta (PPAR-δ) activation involved in the metabolism of fatty acids and the transport of glucose in the muscles, where these compounds will be converted into ATP as an energy source. Vitamin D deficiency may affect calcium concentrations in cells that are sensitive to insulin, thus leading to peripheral insulin resistance that reduces glucose transport to the muscles. In addition, vitamin D deficiency indirectly influences insulin resistance via the renin-angiotensin-aldosterone system, where angiotensin blocks vascular and skeletal muscle insulin, thus interfering with energy needs [37].

Maintaining a normal vitamin D concentration may help glucose homeostasis, while in individuals with high HbA1c, screening for vitamin D may be performed [25].

The weak points of the present study were its cross-sectional study design, which prevented delving into the relationship of vitamin D versus HbA1c or glucose, and the fact that it did not use healthy individuals as controls; and thirdly, this study performed only single blood glucose determinations that did not reflect glycemic variability. Further studies need to be conducted on vitamin D supplementation in the form of a ` randomized, double-blind, placebo-controlled trial to determine the effects of vitamin D on HbA1c and FBG.

CONCLUSION

This study found a strong negative relationship of vitamin D with HbA1c, but not with FBG. Additional research is required using healthy controls and performing serial blood glucose determinations.

REFERENCES

1. Kharroubi, A.T.; Darwish, H.M. Diabetes mellitus: The epidemic of the century. World J Diabetes 2015, 6, 850-867, doi:10.4239/wjd.v6.i6.850.
2. American Diabetes Association Professional Practice Committee. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2022. Diabetes Care 2022, 45(Suppl 1), S17-S38, doi:10.2337/dc22-S002
3. Rehman, K.; Akash, M.S. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? J Biomed Sci 2016, 23, 87, doi: 10.1186/s12929-016-0303-y.
4. Das, G. Vitamin D and type 2 diabetes. Practical Diabetes 2017, 34, 19-24. URL: https://wileymicrositebuilder.com/practicaldiabetes/wp-content/uploads/sites/29/2017/01/Rev-Das-lsw.pdf
5. Yu, J.R.; Lee, S.A.; Lee, J.G.; Seong, G.M.; Ko, S.J.; Koh, G.; et al. Serum vitamin d status and its relationship to metabolic parameters in patients with type 2 diabetes mellitus. Chonnam Med J 2012, 48, 108-115, doi: 10.4068/cmj.2012.48.2.108.
6. Aaty, T.A.A.; Magallaa, M.H.Z.; Moneim, H.A.; Ismail, H.M.; Genena, D.M.; Frugina, R. Serum vitamin D level in type 2 diabetic subjects: Relation to glycemic control, insulin resistance and proinflammatory markers. Journal of High Institute of Public Health 2017, 47, 62-68, doi:10.21608/JHIPH.2017.19966.
7. Mihardja, L.; Soetrisno, U.; Soegondo, S. Prevalence and clinical profile of diabetes mellitus in productive aged urban Indonesians. J Diabetes Investig 2014, 5, 507-512, doi: 10.1111/jdi.12177.
8. Azlin, A.; Ganie, R.A.; Syafril, S. The difference of vitamin D levels between controlled and uncontrolled type 2 diabetes mellitus patients. Indonesian Journal of Clinical Pathology and Medical Laboratory 2019, 26, 18-22, doi:10.24293/ijcpml.v26i1.1407.
9. Tetap produktif, cegah dan atasi DM melitus. Pusat Data dan Informasi Kementrian Kesehatan Republik Indonesia 2020. ISSN 2442-7659. URL: https://www.kemkes.go.id/downloads/resources/download/pusdatin/infodatin/Infodatin%202020%20Diabetes%20Melitus.pdf
10. Wild, S.; Roglic, G.; Green, A.; Sicree, R.; King, H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004, 27, 1047-1053, doi: 10.2337/diacare.27.5.1047.
11. Sharan, A.; Mukhopadhyay, S.; Majumdar, J.; Ghosh, B.; Sengupta, S. A study of prevalence of vitamin D deficiency in new onset type 2 diabetes mellitus in a tertiary care hospital of Eastern India. JIACM 2018, 19, 106-111. URL: https://www.jiacm.in/journals/2018/april_june_2018/Journal%2070%20Page%20106-111%20Original%20Article.pdf
12. Holick, M.F. Vitamin D deficiency. N Engl J Med 2007, 357, 266-281, doi: 10.1056/NEJMra070553.
13. Pusparini.; Meriyanti, L.T.; Sudharma, N.I. Increased matrix metalloproteinase-9 in male elderly with low 25-hydroxy-vitamin D. Univ Med 2016, 35, 171-180, doi:10.18051/UnivMed.2016.v35.171-180.
14. Keumala, D.; Alrasyid, H.; NurIndrawaty, L.; Zulkifli, L. Occurence of vitamin D deficiency among women in North Sumatera, Indonesia. Mal J Nutr 2014, 20, 63-70. URL: https://www.researchgate.net/publication/285524669_Occurrence_of_vitamin_D_deficiency_among_women_in_North_Sumatera_Indonesia#fullTextFileContent
15. Arjana, A.Z.; Devita, N.; Nurmasitoh, T.; Fidianingsih, I.; Dewi, M.; Khoiriyah, U. High proportion of vitamin D deficiency in male adolescents in Yogyakarta Indonesia. In Proocedings of the 4th International Conference on Sustainable Innovation 2020–Health Science and Nursing (ICoSIHSN 2020), March 2021; Atlantis Press B.V, 2021; volume 33, pp. 54-58, doi:10.2991/ahsr.k.210115.011.
16. Pusparini. Defisiensi vitamin D terhadap penyakit. Indonesian Journal Of Clinical Pathology and Medical Laboratory 2014, 21, 90-95, doi:10.24293/ijcpml.v21i1.1265.
17. Rimahardika, R.; Subagio, H.W.; Wijayanti, H.S. Asupan vitamin D dan paparan sinar matahari pada orang yang bekerja di dalam ruangan dan di luar ruangan. Journal Of Nutrition College 2017, 6, 333-342, doi:10.14710/jnc.v6i4.18785.
18. Asegaonkar, S.B. Vitamin D and type 2 diabetes mellitus: Indian perspectives. J Diabetic Complications Med 2016, 1, 1-4, doi:10.4172/2475-3211.1000110.
19. Holick, M.F.; Binkley, N.C.; Bischoff-Ferrari, H.A.; Gordon, C.M.; Hanley, D.A.; Heaney, R.P.; et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical

practice guideline. J Clin Endocrinol Metab 2011, 96, 1911-1930, doi: 10.1210/jc.2011-0385.
20. Mahmodnia, L.; Tamadon, M.R.; Sadoughi, M.; Beigrezaei, S. Vitamin D status and its relationship with age in type 2 diabetic patients. Journal of Parathyroid Disease 2017, 5, 45-48, doi:10.15171/jpd.2017.05.
21. Hidayat, R.; Setiati, S.; Soewondo, P. The association between vitamin D deficiency and type 2 diabetes mellitus in elderly patients. Acta Med Indones 2010, 42, 123-129. URL: https://pubmed.ncbi.nlm.nih.gov/20724765/
22. Jha, S.C.; Kumar, H.; Faisal, S.Y. Correlation between vitamin D and HbA1c in type 2 diabetic patients. Academia Journal of Medicine 2020, 3, 4-10, doi:10.47008/ajm.2020.3.1.2.
23. Al-Horani, H.; Dayyih, W.A.; Mallah, E.; Hamad, M.; Mima, M.; Awad, R.; et al. Nationality, gender, age, and body mass index influences on vitamin D concentration among elderly patients and young Iraqi and Jordanian in Jordan. Biochem Res Int 2016, 2016, 1-8, doi: 10.1155/2016/8920503.
24. Akbar, A.R.; Kurnia, E.; Hendrianingtyas, M.; Nugroho, H. Correlation between fasting blood glucose and Hba1c with vitamin D in diabetes mellitus. Pakistan Journal of Medical Health Sciences 2019, 13, 1093-1096. URL: https://pjmhsonline.com/2019/oct_dec/pdf/1093.pdf
25. Mehta, N.; Shah, S.; Shah, P.P.; Prajapati, V. Correlation between vitamin D and HbA1c in type 2 diabetic patients. GCSMC J Med Sci 2016, 5, 42-46. URL: https://gcsmc.org/assets/pdf/journal/journal-1227/original-article/correlation-between-vitamin-d-and-hba1c-in-type-2-diabetic-patients20181005124245907 2370.pdf
26. Suguna, S.; Kusumadevi, M.S. Relationship between vitamin D and HbA1c levels in patients with type 2 diabetes mellitus of Bengaluru City. International Journal of Physiology 2019, 7, 104-108, doi:10.5958/2320-608x.2019.00149.5.
27. Zhang, M.; Li, P.; Zhu, Y.; Chang, H.; Wang, X.; Liu, W.; et al. Higher visceral fat area increases the risk of vitamin D insufficiency and deficiency in Chinese adults. Nutr Metab (Lond) 2015, 12, 50, doi: 10.1186/s12986-015-0046-x.
28. Fernandes, M.R.; Barreto, W.D.R.J. Association between physical activity and vitamin D: A narrative literature review. Rev Assoc Med Bras 2017, 63, 550-556, doi: 10.1590/1806-9282.63.06.550.
29. Grober, U.; Kisters, K. Influence of drugs on vitamin D and calcium metabolism. Dermatoendocrinol 2012, 4, 158-166, doi: 10.4161/derm.20731.
30. Sakung, J.M.; Sirajuddin, S.; Zulkifli, A.; Rahman, S.A.; Sudargo, T. Physical activity is associated with lower blood glucose level in high school teachers in Palu, Indonesia. Int J Community Med Public Health 2018, 5, 3176-3179, doi:10.18203/2394-6040.ijcmph20183047.
31. Alkhatatbeh, M.J.; Abdul-Razzak, K.K. Association between serum 25-hydroxyvitamin D, hemoglobin A1c and fasting blood glucose levels in adults with diabetes mellitus. Biomed Rep 2018, 9, 523-530, doi: 10.3892/br.2018.1159.
32. Sherwani, S.I.; Khan, H.A.; Ekhzaimy, A.; Masood, A.; Sakharkar, M.K. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. Biomark Insights 2016, 11, 95-104, doi: 10.4137/BMI.S38440.
33. Monnier, L.; Colette, C. Contributions of fasting and post-prandial glucose to hemoglobin A1c. Endocr Pract 2006, 12 Suppl 1, 42-46, doi: 10.4158/EP.12.S1.42.
34. Kautzky-Willer, A.; Kosi, L.; Lin, J.; Mihaljevic, R. Gender-based differences in glycaemic control and hypoglycaemia prevalence in patients with type 2 diabetes: results from patient-level pooled data of six randomized controlled trials. Diabetes Obes Metab 2015, 17, 533-540, doi: 10.1111/dom.12449.
35. Tabak, A.G.; Herder, C.; Rathmann, W.; Brunner, E.J.; Kivimaki, M. Prediabetes: a high-risk state for diabetes development. Lancet 2012, 379, 2279-2290, doi: 10.1016/S0140-6736(12)60283-9.
36. Ehrhardt, N.M.; Chellappa, M.; Walker, M.S.; Fonda, S.J.; Vigersky, R.A. The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. J Diabetes Sci Technol 2011, 5, 668-675, doi: 10.1177/193229681100500320.
37. Sanda, A.; Bahrun, U.; Pakasi, R.D.N.; Aman, A.M. Analysis of vitamin D in patients with type 2 diabetes mellitus. Indonesian Journal of Clinical Pathology and Medical Laboratory 2019, 25, 150-154, doi: 10.24293/ijcpml.v25i2.1360.

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