Clinical Research

Vitamin D levels and depression in type 2 diabetes mellitus patients: a cross-sectional study

Rudi Putranto, Kresna Adhiatma, Tri Juli Edi Tarigan, Cleopas Martin Rumende, Hamzah Shatri, Iris Rengganis, Pringgodigdo Nugroho, Ikhwan Rinaldi

pISSN: 0853-1773 • eISSN: 2252-8083
https://doi.org/10.13181/mji.oa.237005
Med J Indones. 2023;32:177–82

Received: June 09, 2023
Accepted: November 14, 2023
Published online: December 14, 2023

Authors' affiliations:
Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Corresponding author:
Rudi Putranto
Division of Psychosomatic and Palliative Medicine, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jalan Diponegoro No. 71, Central Jakarta 10430, DKI Jakarta, Indonesia
Tel/Fax: +62-21-3196052
E-mail: putranto.rudi09@gmail.com

ABSTRACT

BACKGROUND The prevalence of type 2 diabetes mellitus (T2DM) is increasing and commonly accompanied by comorbidities, such as depression. Vitamin D levels have been associated with T2DM and depression although the mechanism is uncertain. This study aimed to compare vitamin D levels between patients with T2DM with and without depression in the Indonesian community, where such research is rare.

METHODS This cross-sectional study was conducted at Cipto Mangunkusumo Hospital. The participants who met the inclusion criteria on an outpatient basis were screened for depression using the Beck Depression Inventory-II (BDI-II) questionnaire and then divided into 2 groups: patients with T2DM with (BDI-II ≥14) and without (BDI-II <14) depression. Both groups were examined for vitamin D levels using the ELISA method, and an analysis of the mean difference between both groups was performed.

RESULTS Of 60 patients, 23 (38%) experienced depression. The median vitamin D levels were 21.8 ng/ml (IQR 14.9–26.6) in the depression group and 26.5 ng/ml (IQR 23.96–34.08) in the non-depression group (p = 0.001). After performing multivariate analysis with confounding variables, the adjusted OR of variables (sex, sun exposure score, and body mass index) was 1.123 (95% CI: 1.003–1.259; p = 0.045).

CONCLUSIONS Vitamin D levels were significantly lower in patients with T2DM with depression. Future studies should be carried out to determine the benefits of vitamin D supplementation in patients with T2DM with depression and their pathophysiology.

KEYWORDS depression, type 2 diabetes mellitus, vitamin D level

Patients with type 2 diabetes mellitus (T2DM) are at risk for depression, with a higher prevalence rate (11–17.6%) than the general population (3–4%).[1,2] Furthermore, 41% of patients with T2DM experience depression.[2] Theoretically, depression could be exacerbated by diabetes treatment. Diabetes causes anatomical changes in the brain, including cerebral atrophy and lacunar infarctions, blood flow variations (hypoperfusion and hyperperfusion), and an increased risk of depression.[3] Depression in patients with T2DM greatly influences medication adherence, diet control, and blood glucose monitoring, thus increasing the treatment cost and lowering the quality of the prognosis of the disease course.[2–4] Despite the condition, using tricyclic antidepressants might impair glucose metabolism in patients with diabetes and increase their body weight.[5]

Vitamin D is a fat-soluble vitamin commonly involved in bone and calcium metabolism and known for its anti-inflammatory and immunomodulatory

properties. Various studies have shown that vitamin D deficiency correlates with various diseases, such as DM, cardiovascular diseases, cancer, autoimmune diseases, and depression.[6–8] Vitamin D plays a crucial role in regulating insulin levels and maintaining proper glucose metabolism, which is essential for the prevention and management of diabetes. Furthermore, individuals with depression tend to have higher blood sugar levels, indicating a potential connection between depression and T2DM. Therefore, addressing vitamin D deficiency could positively impact mental health and prevent T2DM.[6,7]

The association between vitamin D and depression has been reported in several studies, including a systematic review by Ju et al,[9] which reported that an increase in vitamin D levels by 10 ng/ml was associated with improved depressive symptoms and reduced depression risk. Lower levels of vitamin D have also been reported in patients with depression than in the controls.[10,11] It has been proposed that hypovitaminosis D may contribute to depression. Vitamin D metabolites protect neuronal integrity by upregulating neurotrophic factors (nerve growth factor, neurotrophin [NT]-3, and NT-4) in the hippocampus and neocortex. Furthermore, vitamin D affects inflammatory pathways (downregulating autoimmune processes, releasing proinflammatory cytokines, and increasing anti-inflammatory pathways through vitamin D receptor-mediated gene transcription), which are associated with depression.[10]

Notably, vitamin D levels have not been compared between patients with and without depression who have T2DM in Indonesia. To address this knowledge gap, the present study aimed to investigate the relationship between vitamin D levels and T2DM in patients with and without depression. This would provide a better understanding of the association between vitamin D deficiency and the co-occurrence of T2DM and depression.

METHODS

This cross-sectional study was conducted at the Metabolic Endocrine and Diabetes Clinic of the Department of Internal Medicine, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, between July and August 2022. This study analyzed data collected from interviews and laboratory tests of the included participants.

Selection and characteristics of the participants

Patients with T2DM aged ≥18 years (adult) who visited the clinic were enrolled in this study. The sample was obtained through consecutive sampling until the number of participants reached the required size. Patients with a known history of comorbidities, such as cancer, autoimmune disease, and stages 4 and 5 chronic kidney disease, and pregnant and lactating women were excluded from this study. Patients who received vitamin D supplementation, antidepressants, or immunosuppressant therapy and who declined to participate in this study were also excluded.

Study procedure

Eligible outpatients with T2DM were screened for depression by conducting an interview using the Beck Depression Inventory-II (BDI-II) questionnaire and weekly sun exposure scoring, as reported by Husna.[12] The skin area exposed to sunlight each day for a week was multiplied by the old score (length of exposure) to determine the sun exposure score. Subsequently, history-taking and physical examinations were conducted. Based on the BDI-II scoring results, the participants were divided into two groups: patients with T2DM with (BDI-II score ≥14) and without (BDI-II score <14) depression. The Indonesian version of the BDI-II questionnaire was validated by Ginting et al,[13] with good specificity and sensitivity. Patients were then prepared for serum vitamin D analysis using laboratory analysis. A 3 ml blood sample from a peripheral venipuncture was assessed for 25-hydroxyvitamin D (25[OH]D) serum at the Cipto Mangunkusumo Laboratory using the enzyme-linked immunosorbent assay (ELISA) method.[14] The procedure was performed only once without any therapeutic intervention or any other invasive procedure to minimize hemorrhage after blood puncture.

Laboratory analysis

Serum vitamin D tests were performed using a sandwich ELISA. Two antibodies were used to capture the target antigens. The test was performed using the DiaSino® 25(OH)D Total ELISA Kit (DiaSino Laboratories Co., Ltd, China). The microplate was then prepared for absorbance reading using a light wave of 450 nm in the microplate reader 30 min after the addition of the stop solution. The absorbance was extrapolated to a reference value based on the manufacturer's instructions.

Statistical analysis

Statistical analyses were performed using Microsoft Excel 2016 (Microsoft Corp., USA) and SPSS software version 20.0 (IBM Corp., USA). Categorical data are presented as frequencies and percentages, whereas numerical data are presented as mean (standard deviation [SD]) for normally distributed data or median (min–max) for data with non-normal distribution. Data normality was determined using the Kolmogorov–Smirnov test. The comparison or significant difference in the 25(OH)D of each independent and confounding variable was analyzed using bivariate analysis, utilizing an independent *t*-test for normally distributed data and the Mann–Whitney *U* test for data with non-normal distribution. Data are presented as mean, SD, and *p*-value using a 95% confidence interval [CI] (statistical significance was set at $p<0.05$). Confounding variables were analyzed using multivariate logistic regression analysis.

Ethical clearance

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital (No. KET-348/UN2.F1/ETIK/PPM.00.02/2022). The participants were informed of the study procedure and signed an informed consent form prior to data extraction.

RESULTS

Of the 93 patients enrolled in this study, 60 were finally included (Figure 1). Participants' baseline characteristics are presented in Table 1.

Age and body mass index (BMI) were similar between patients with T2DM with and without depression. However, those who had depression were predominantly females. Higher median sun exposure scores and lower vitamin D levels were observed in the depression group (Table 2).

The lower the vitamin D level, the higher the risk of depression (crude odds ratio [OR]: 1.107; 95% CI: 1.031–1.189; $p = 0.005$). This remained significant after adjusting for sex, sun exposure score, and BMI (adjusted OR: 1.123; 95% CI: 1.003–1.259; $p = 0.045$).

DISCUSSION

This study found a significantly increased risk of depression in patients with T2DM with vitamin D deficiency. Vitamin D levels were lower in the depression group than in the control group. In contrast, Westra et al[15] found no correlation between vitamin D deficiency and the risk of depression in patients with T2DM. Other studies have shown different vitamin D levels in patients with obesity experiencing depression compared with those without depression.[16] The results are consistent with other studies on depression in patients with several comorbidities, such as liver disease and perinatal or postpartum depression.[17–25] Furthermore, Wang et al[26] found a median vitamin D level of 10.2 ng/ml (interquartile range [IQR]: 7.6–15.2) among patients with T2DM with depression, compared with 14.6 ng/ml (IQR: 10.7–19.8) among those without depression. No significant associations were found between vitamin D levels and the duration of T2DM, therapy, or sociodemographic factors.

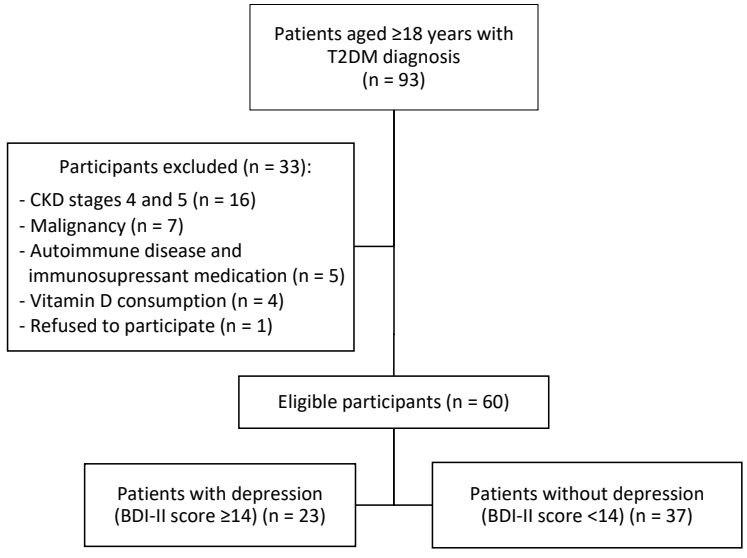

Figure 1. Participants' enrollment flowchart. BDI-II= Beck Depression Inventory-II; CKD=chronic kidney disease; T2DM=type 2 diabetes mellitus

Table 1. Baseline characteristics of the participants

Variables	N = 60
Male sex, n (%)	31 (52)
Age (years), median (min–max)	59 (52–63)
BMI (kg/m²), median (min–max)	26.9 (24.65–28.85)
Obese, n (%)	43 (72)
Depression, n (%)	23 (38)
Vitamin D levels (ng/ml), median (min–max)	24.95 (18.95–32.17)
Vitamin D level, n (%)	
Deficiency	15 (25)
Insufficiency	27 (45)
Normal	18 (30)
Sun exposure score, median (min–max)	16 (9–20)
GFR, median (IQR)	81.45 (57.25–92.7)
HbA1C, median (IQR)	7.9 (7.0–9.1)

BMI=body mass index; GFR=glomerular filtration rate; HbA1c=glycosylated hemoglobin; IQR=interquartile range

Regarding the confounding variables in the present study, there were no significant differences in age and BMI. However, significant differences were observed in sex and sun exposure. The depression group comprised females predominantly, which is consistent with the study of Salk et al,[22] in which a 3 times higher risk of depression was observed in females than in males, particularly in the teenage age group (12–16 years old). Females are more prone to depression because of higher stress, cognitive instability owing to hormonal imbalance, and a higher risk of comorbidities of anxiety and somatic symptoms, particularly during peripartum and postpartum periods.[23,24] However, Al Qusaibi et al[25] found an insignificant incidence between males and females.

Sun exposure is a significant confounding factor that increases serum vitamin D levels and lowers the proportion of vitamin D deficiency.[27,28] Notably, sun exposure might also affect depressive symptoms and other mental disorders because it has a dose-response effect, with lower exposure correlating with worsening cognitive status.[29] This finding is consistent with that of other reports on the efficacy of sun exposure in improving depressive symptoms and quality of life.[30,31] This phenomenon might be explained by an increase in anti-inflammatory cytokines, which might explain the improvement in mood progression. In addition, sun exposure is correlated with increased cortisol levels and circadian rhythm regulation, thereby improving mood and depressive symptoms.[32–34]

Diabetes is associated with vitamin D deficiency. The significance of vitamin D in sustaining accurate insulin release by pancreatic beta cells in patients with diabetes involves the establishment of insulin resistance. Beta cells can overcome this resistance by releasing more insulin, thus preventing hyperglycemia. However, when hyperactivity increases, the cells exhibit increased Ca^{2+} levels and reactive oxygen species signaling, leading to cell death and diabetes. Vitamin D deficiency contributes to initial insulin resistance and subsequent onset of diabetes caused by beta cell apoptosis. Vitamin D prevents inflammation, which is a major factor in insulin resistance.[35] The use of vitamin D supplementation has also been reported to positively impact mental health and depressive symptoms in patients, particularly those with insufficient vitamin D.[36–38] According to several studies, vitamin D supplementation may reduce depression in patients with T2DM.[39–42]

This study had several limitations. First, the study design did not cover the causes of depression or vitamin D deficiency. Second, this study did not

Table 2. Multivariate analysis of depression in patients with T2DM

Variables	Depression		*p*
	Yes	No	
Age (years), median (min–max)	59 (55–65)	59 (48–63)	0.342*
Male sex, n (%)	5 (16.1)	26 (83.9)	**<0.001†**
Sun exposure score, median (min–max)	9 (7–15)	18 (12–22)	**<0.001***
BMI (kg/m²), median (min–max)	26.3 (23.1–30.0)	27.1 (25.7–28.8)	0.186*
Vitamin D levels (ng/ml), median (min–max)	21.8 (14.9–26.6)	26.5 (23.96–34.08)	**0.001***

BMI=body mass index; T2DM=type 2 diabetes mellitus
*Mann–Whitney *U* test; †chi-square test

include the diet consumption variable despite the probable increase in vitamin D based on a suitable diet. However, several studies have reported non-significant differences owing to diet differences in vitamin D levels.[43,44]

In conclusion, this study reported significantly lower vitamin D levels in patients with T2DM with depression. Future studies should be conducted to determine the benefits of vitamin D supplementation in patients with T2DM with depression and their pathophysiology.

Conflict of Interest
The authors affirm no conflict of interest in this study.

Acknowledgment
None.

Funding Sources
None.

REFERENCES

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107843.
2. Auliana A, Yunir E, Putranto R, Nugroho P. [The effect of depression on infection improvement diabetic foot ulcers]. J Penyakit Dalam Indones. 2015;2(4):212–6. Indonesian.
3. Bădescu SV, Tătaru C, Kobylinska L, Georgescu EL, Zahiu DM, Zăgrean L. The association between diabetes mellitus and depression. J Med Life. 2016;9(2):120–5.
4. Maimaitituerxun R, Chen W, Xiang J, Kaminga AC, Wu XY, Chen L, et al. Prevalence of comorbid depression and associated factors among hospitalized patients with type 2 diabetes mellitus in Hunan, China. BMC Psychiatry. 2023;23(1):158.
5. Khaledi M, Haghighatdoost F, Feizi A, Aminorroaya A. The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies. Acta Diabetol. 2019;56(6):631–50.
6. Husain K, Sharma G, Rizvi A. Co-relation between vitamin D levels and Hamilton depression scores in patients with depression. J Med Sci Clin Res. 2017;5(7):25513–8.
7. Hsaini A. Association between vitamin D, and depression among diabetes patients. Clin Nutr. 2018;37(Suppl 1):S283.
8. Anglin RE, Samaan Z, Walter SD, McDonald SD. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br J Psychiatry. 2013;202:100–7.
9. Ju SY, Lee YJ, Jeong SN. Serum 25-hydroxyvitamin D levels and the risk of depression: a systematic review and meta-analysis. J Nutr Health Aging. 2013;17(5):447–55.
10. Milaneschi Y, Hoogendijk W, Lips P, Heijboer AC, Schoevers R, van Hemert AM, et al. The association between low vitamin D and depressive disorders. Mol Psychiatry. 2014;19(4):444–51.
11. Al-Timimi DJ, Ali AF. Serum 25(OH) D in diabetes mellitus type 2: relation to glycaemic control. J Clin Diagn Res. 2013;7(12):2686–8.
12. Husna K, Widajanti N, Sumarmi S, Firdaus H. [Correlation of sun exposure score and vitamin D intake with serum 25(OH)D levels in older women]. J Penyakit Dalam Indones. 2021;8(2):63–71. Indonesian.
13. Ginting H, Näring G, van der Veld WM, Srisayekti W, Becker ES. Validating the Beck Depression Inventory-II in Indonesia's general population and coronary heart disease patients. Int J Clin Health Psychol. 2013;13(3):235–42.
14. Jukic AM, Hoofnagle AN, Lutsey PL. Measurement of vitamin D for epidemiologic and clinical research: shining light on a complex decision. Am J Epidemiol. 2018;187(4):879–90.
15. Westra S, Simsek S, Rutters F, Krul-Poel YM, Stehouwer CD, Dekker JM, et al. Low vitamin D levels are not a contributing factor to higher prevalence of depressive symptoms in people with type 2 diabetes mellitus: the Hoorn study. Diabet Med. 2017;34(4):577–81.
16. Kamalzadeh L, Saghafi M, Mortazavi SS, Jolfaei AG. Vitamin D deficiency and depression in obese adults: a comparative observational study. BMC Psychiatry. 2021;21(1):599.
17. Stokes CS, Grünhage F, Baus C, Volmer DA, Wagenpfeil S, Riemenschneider M, et al. Vitamin D supplementation reduces depressive symptoms in patients with chronic liver disease. Clin Nutr. 2016;35(4):950–7.
18. Vaziri F, Nasiri S, Tavana Z, Dabbaghmanesh MH, Sharif F, Jafari P. A randomized controlled trial of vitamin D supplementation on perinatal depression: in Iranian pregnant mothers. BMC Pregnancy Childbirth. 2016;16:239.
19. Arathimos R, Ronaldson A, Howe LJ, Fabbri C, Hagenaars S, Hotopf M, et al. Vitamin D and the risk of treatment-resistant and atypical depression: a Mendelian randomization study. Transl Psychiatry, 2021;11(561).
20. Mozaffari-Khosravi H, Nabizade L, Yassini-Ardakani SM, Hadinedoushan H, Barzegar K. The effect of 2 different single injections of high dose of vitamin D on improving the depression in depressed patients with vitamin D deficiency: a randomized clinical trial. J Clin Psychopharmacol. 2013;33(3):378–85.
21. Okereke OI, Reynolds CF 3rd, Mischoulon D, Chang G, Vyas CM, Cook NR, et al. Effect of long-term vitamin D3 supplementation vs placebo on risk of depression or clinically relevant depressive symptoms and on change in mood scores: a randomized clinical trial. JAMA. 2020;324(5):471–80.
22. Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: meta-analyses of diagnoses and symptoms. Psychol Bull. 2017;143(8):783–822.
23. Eid RS, Gobinath AR, Galea LA. Sex differences in depression: insights from clinical and preclinical studies. Prog Neurobiol. 2019;176:86–102.
24. Zhao L, Han G, Zhao Y, Jin Y, Ge T, Yang W, et al. Gender differences in depression: evidence from genetics. Front Genet. 2020;11:562316.
25. Al Qusaibi B, Mosli H, Kattan W, Fadel H, Alariefy A, Almalki B, et al. Depression among patients with type 2 diabetes mellitus at King Abdulaziz University Hospital (KAUH): a cross-sectional study. Cureus. 2022;14(6):e25990.
26. Wang Y, Yang H, Meng P, Han Y. Association between low serum 25-hydroxyvitamin D and depression in a large sample of Chinese patients with type 2 diabetes mellitus. J Affect Disord. 2017;224:56–60.
27. Wacker M, Holick MF. Sunlight and vitamin D: a global perspective for health. Dermatoendocrinol. 2013;5(1):51–108.
28. Nimitphong H, Holick MF. Vitamin D status and sun exposure in southeast Asia. Dermatoendocrinol. 2013;5(1):34–7.
29. Komulainen K, Hakulinen C, Lipsanen J, Partonen T, Pulkki-Råback L, Kähönen M, et al. Long-term residential sunlight exposure associated with cognitive function among adults residing in Finland. Sci Rep. 2022;12(20818).
30. Cui Y, Gong Q, Huang C, Guo F, Li W, Wang Y, et al. The relationship between sunlight exposure duration and depressive symptoms: a cross-sectional study on elderly Chinese women. PLoS One. 2021;16(7):e0254856.
31. Xu Y, Qi J, Yang Y, Wen X. The contribution of lifestyle factors to depressive symptoms: a cross-sectional study in Chinese college

students. Psychiatry Res. 2016;245:243–9.
32. Veleva BI, van Bezooijen RL, Chel VG, Numans ME, Caljouw MA. Effect of ultraviolet light on mood, depressive disorders and well-being. Photodermatol Photoimmunol Photomed. 2018;34(5):288–97.
33. Køster B, Søndergaard J, Nielsen JB, Olsen A, Bentzen J. Reliability and consistency of a validated sun exposure questionnaire in a population-based Danish sample. Prev Med Rep. 2018;10:43–8.
34. Islam MR, Sohan M, Daria S, Al Masud A, Ahmed MU, Roy A, et al. Evaluation of inflammatory cytokines in drug-naïve major depressive disorder: a systematic review and meta-analysis. Int J Immunopathol Pharmacol. 2023;37.
35. Berridge MJ. Vitamin D deficiency and diabetes. Biochem J. 2017;474(8):1321–32.
36. Fallah M, Askari G, Asemi Z. Is vitamin D status associated with depression, anxiety and sleep quality in pregnancy: a systematic review. Adv Biomed Res. 2020;9:32.
37. Di Gessa G, Biddulph JP, Zaninotto P, de Oliveira C. Changes in vitamin D levels and depressive symptoms in later life in England. Sci Rep. 2021;11(1):7724.
38. Saji Parel N, Krishna PV, Gupta A, Uthayaseelan K, Uthayaseelan K, Kadari M, et al. Depression and vitamin D: a peculiar relationship. Cureus. 2022;14(4):e24363.
39. Omidian M, Mahmoudi M, Abshirini M, Eshraghian MR, Javanbakht MH, Zarei M, et al. Effects of vitamin D supplementation on depressive symptoms in type 2 diabetes mellitus patients: randomized placebo-controlled double-blind clinical trial. Diabetes Metab Syndr. 2019;13(4):2375–80.
40. Penckofer S, Ridosh M, Adams W, Grzesiak M, Woo J, Byrn M, et al. Vitamin D supplementation for the treatment of depressive symptoms in women with type 2 diabetes: a randomized clinical trial. J Diabetes Res. 2022;2022:4090807.
41. Fazelian S, Amani R, Paknahad Z, Kheiri S, Khajehali L. Effect of vitamin D supplement on mood status and inflammation in vitamin D deficient type 2 diabetic women with anxiety: a randomized clinical trial. Int J Prev Med. 2019;10:17.
42. Mirzavandi F, Babaie S, Rahimpour S, Razmpoosh E, Talenezhad N, Aghaei Zarch SM, et al. The effect of high dose of intramuscular vitamin D supplement injections on depression in patients with type 2 diabetes and vitamin D deficiency: a randomized controlled clinical trial. Obes Med. 2020;17:100192.
43. Carlberg C, Raczyk M, Zawrotna N. Vitamin D: a master example of nutrigenomics. Redox Biol. 2023;62:102695.
44. Santana KV, Oliver SL, Mendes MM, Lanham-New S, Charlton KE, Ribeiro H. Association between vitamin D status and lifestyle factors in Brazilian women: implications of sun exposure levels, diet, and health. EClinicalMedicine. 2022;47:101400.