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Correlation of vitamin D with glucose-lipid metabolism and nutritional status in patients with newly diagnosed type 2 diabetes mellitus

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Abstract: Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases worldwide, with no cure at present. Vitamin D (VD) is a fat-soluble vitamin, which has been recognized as one of the major influencing factors of T2DM. However, the specific relationship between T2DM and VD remains elusive. In this study, we analyzed the correlation of VD with glucose-lipid metabolism and nutritional status in patients with newly diagnosed T2DM, so as to understand the role of VD in T2DM more comprehensively. First, we compared the differences in VD (vitamin D3), glucose-lipid metabolism and nutrient proteins between patients with T2DM and the healthy population and our patients with T2DM had lower VD and nutrient proteins and higher glucose and lipids ($P<0.05$). By receiver operating characteristic (ROC) curve analysis, it was seen that VD demonstrated an excellent assessment of the occurrence of T2DM as well as prognostic progression. In addition, we found that VD was negatively correlated with fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), triglyceride (TG) and total cholesterol (TC) in patients with T2DM ($P<0.05$), whereas it was negatively correlated with nutrient protein were all positively correlated ($P<0.05$). These results suggest that we can monitor the VD levels of T2DM patients in future clinical practice to assess their pathologic progression, so as to intervene in a timely manner to ensure the health of the patients.

Keywords: Glucose-lipid metabolism, nutritional status, prognosis, type 2 diabetes mellitus, vitamin D.

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INTRODUCTION

Diabetes mellitus (DM) remains one of the most common chronic diseases worldwide, with an average incidence of 0.9 percent and 1 in 10 individuals (Harreiter & Roden, 2023). DM is a systemic metabolic disease characterized by chronic hyperglycemia, typically presenting with glucose-lipid metabolism disturbances, islet β cell dysfunction and insulin resistance (Lovic *et al.*, 2020). Type 2 DM (T2DM) is the predominant type of DM, accounting for approximately 95 percent (Tinajero & Malik, 2021). At present, there is no clinical cure for T2DM. After the occurrence of the disease, the human body will be in a state of hyperglycemia for a long time, causing a series of organ diseases, which will eventually lead to various critical complications and endanger the life safety of patients (Yan *et al.*, 2022). As the global aging issue becomes increasingly serious, the incidence of T2DM is rising year by year. A thorough understanding of the pathological mechanism of T2DM is still the key to its future treatment.

Vitamin D (VD) is a fat-soluble vitamin that mainly participates in calcium and phosphorus regulation and promotes bone mineralization and remodeling, which is closely related to bone metabolism. In recent years, many studies have found that VD also has immunological functions such as regulating immunity, relieving inflammation and preventing tumors (Pittas *et al.*, 2023). In T2DM-associated research, clinical findings have shown that insulin-resistant and obese individuals have lower levels of VD compared to non-insulin resistant and obese individuals (Manousaki *et al.*, 2021), suggesting that maintaining a normal level of VD may be beneficial for preventing T2DM. Meanwhile, VD is an important nutrient element in the human body, which is closely related to the absorption and metabolism of nutritional proteins (Bopape *et al.*, 2023). Malnutrition, as one of the recognized risk factors for T2DM, is not only involved in the occurrence of T2DM, but also an inducement to promote various complications of T2DM (Naik *et al.*, 2023). At present, some studies believe that VD supplementation in the treatment of gestational T2DM can improve the nutritional status of pregnant women and newborns (Bouillon *et al.*, 2022). Nonetheless, the exact relationship between VD and T2DM has not yet been fully demonstrated and neither VD supplementation therapy nor VD testing regarding T2DM patients has received clinical attention. We believe that an in-depth understanding of the relationship between VD and T2DM has important implications for both the diagnosis and treatment of T2DM in the future.

Therefore, this study will analyze the correlation of VD with glucose-lipid metabolism and nutritional status in patients with T2DM, so as to understand the role of VD in T2DM more comprehensively and provide new reference and guidance for future diagnosis and treatment of T2DM.

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MATERIALS AND METHODS

Study participants

G*Power software was used to calculate the sample size needed for this study. Calculated with independent samples t-test, set parameters tail=one, effect size=0.5, α err prob=0.05, power=0.8, ratio=1 and output=61. That is, a minimum of 61 subjects were needed for this study. Subsequently, T2DM patients who were hospitalized in Shaoyang Central Hospital from September 2022 to August 2023 were selected for retrospective analysis, and after screening by inclusion and exclusion criteria, 64 T2DM patients were finally included. These T2DM patients were used as the research group, their basic information (e.g., age, gender, etc.) was counted and the control group was screened by case-control matching using SPSS software. We obtained a list of 64 healthy people and after screening by inclusion exclusion criteria, 52 healthy medical check-ups were finally identified as the control group. This study strictly followed *the Declaration of Helsinki*, the Central Hospital of Shaoyang Ethics Committee's approved the conduct of this study (NO.2022-235).

Eligibility and exclusion criteria

Research group: newly diagnosed T2DM (NDT2DM) (American Diabetes, 2011) patients by clinical diagnosis, who completed VD and glucose-lipid metabolism tests in our hospital, with complete medical records, were selected. Patients with acute infection, acute complications, a history of mental illness, or malignancy and VD supplemental therapy present during the 3 months prior to admission and during the 6 months after admission were excluded. Control group: Those who had a physical examination in our hospital, with no major medical history in the past and normal physical examination results were included. The exclusion criteria were the same as the research group.

Methods

All subjects had 3mL of fasting venous blood collected in a procoagulant tube on admission to the hospital, and the serum was obtained by centrifugation (3000 rpm/min) for 10 min after standing for 30 min at room temperature. Subsequently, the serum was divided into 3 portions and the VD (vitamin D3) levels by a chemiluminescence analyzer (BKI1100 Automatic Chemiluminescent Immunoassay Analyzer, BIOBASE), the measurement of glucose-lipid metabolism indexes (fasting blood glucose [FBG], glycosylated hemoglobin [HbA1c], triglyceride [TG], total cholesterol [TC] and high/low-density lipoprotein cholesterol [HDL-C/LDL-C]) with an automatic biochemical analyzer (BS-2000M Automatic Biochemistry Analyzer, Myriad) and the quantification of nutritional proteins (albumin [ALB], transferrin [TRF], prealbumin [PA] and total protein [TP]) by colorimetry (M5 Multifunction Enzyme Labeler, Spectra Max).

Prognostic follow-up

All NDT2DM patients were followed up for 6 months, with regular reviews and telephone follow-ups to record disease progression. During the follow-up period, any T2DM-related complications are defined as disease progression.

STATISTICAL ANALYSIS

SPSS24.0 software was used for statistical analysis. Baseline data (gender, family history of disease, etc.) were expressed as [n (%)] and chi-square tests were carried out for between-group comparisons; The test results of glycolipid metabolism and nutritional proteins were expressed in the form of ($\chi \pm s$), and independent sample t-tests were used for comparisons between groups. The diagnostic value is analyzed using the Receiver operating characteristic (ROC) curve and the cut-off value (the threshold value for determining whether the test result is abnormal) is confirmed by the Youden index and the Area under curve (AUC) at the cut-off value is used as the diagnostic value. . Correlation was analyzed by Pearson correlation coefficients. A statistically significant difference is indicated when $P<0.05$ and a highly significant difference is indicated when $P<0.001$.

RESULTS

Comparison of clinical data

The age, sex, body mass index (BMI), family disease history, eating habits, and other clinical data of the research and control groups were compared, and no statistically significant differences were found ($P>0.05$, table 1), confirming comparability.

Comparison of VD

The inter-group comparison of VD revealed lower VD levels in the research group compared to the control group ($P<0.001$). According to ROC curve analysis, when VD<14.48 ng/mL, the sensitivity and specificity for diagnosing T2DM were 81.25% and 75.00%, respectively ($P<0.001$), with an AUC of 0.814, indicating a good diagnostic effect (fig. 1).

Comparison of glucose-lipid metabolism

The research group showed elevated FBG, HbA1c, TC, and TG ($P<0.001$) but similar HLD-C and LDL-C levels than the control group ($P>0.05$, fig. 2).

Relationship between VD and glucose-lipid metabolism

Pearson correlation coefficient analysis showed that VD was negatively correlated with FBG, HbA1c, TC and TG in the research group ($P<0.001$), that is, the lower the VD, the higher the FBG, HbA1c, TC and TG (fig. 3).

Table 1: Comparison of clinical data

Groups	Age	Male	Female	BMI (kg/m²)	Cigarette smoking	Non-smoking	Family history of disease	No family history of disease	Normal eating habits (3 meals/d)	Abnormal eating habits (2-3 meals/d)	Poor eating habits (1-2 meals/d)	With exercise habits	Without exercise habits
Control group (n=52)	62.69± 6.67	30 (57.69)	22 (42.31)	22.88 ±1.55	22 (42.31)	30 (57.69)	12 (23.08)	40 (76.92)	43 (76.92)	11 (21.15)	1 (1.92)	19 (36.54)	63 (63.46)
Research group (n=64)	62.98± 6.36	41 (64.06)	23 (35.94)	23.12 ±1.15	30 (46.88)	34 (53.13)	20 (31.25)	44 (68.75)	50 (78.13)	13 (20.31)	1 (1.56)	20 (31.25)	44 (68.75)
t (χ^2)	0.241	0.490		0.956	0.242		0.959			0.037		0.360	
P	0.810	0.484		0.341	0.623		0.327			0.982		0.549	

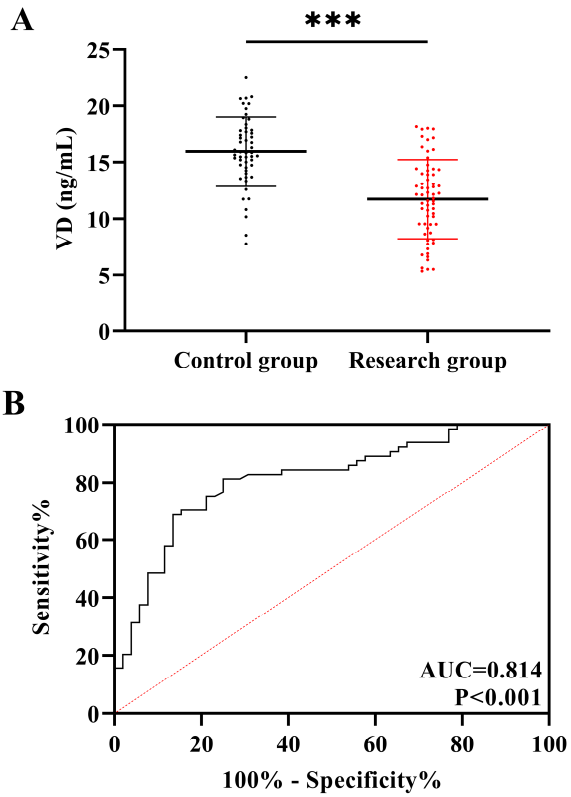

Fig. 1: VD was reduced in the research group and demonstrated excellent diagnostic results for T2DM. A: Comparison of VD between research and control groups. B: ROC of VD for the diagnosis of T2DM. ***P<0.001. Type 2 diabetes mellitus, T2DM; Vitamin D, VD; Receiver operating characteristic, ROC.

Comparison of nutritional proteins

After testing, ALB, TRF, PA and TP were found to be lower in the research group than in the control group (P<0.001, fig. 4), indicating significant malnutrition in the research group.

Comparison of VD and nutritional proteins

Pearson correlation coefficient analysis showed a positive correlation between VD and ALB, TRF, PA and TP in the research group (P<0.001, fig. 5), that is, lower VD indicates lower ALB, TRF, PA and TP levels.

Correlation between VD and prognostic progression

During the prognostic follow-up, we tracked all the patients in the research group, of whom 20 had disease progression. By comparison, the VD of patients with progressive disease was statistically reduced compared with patients without progressive disease (P<0.001). The ROC curve showed that when VD<12.22 ng/mL, the sensitivity for diagnosing prognostic disease progression was 85.00%, the specificity was 59.09% (P=0.007) and the AUC was 0.642, suggesting good diagnostic efficiency (fig. 6).

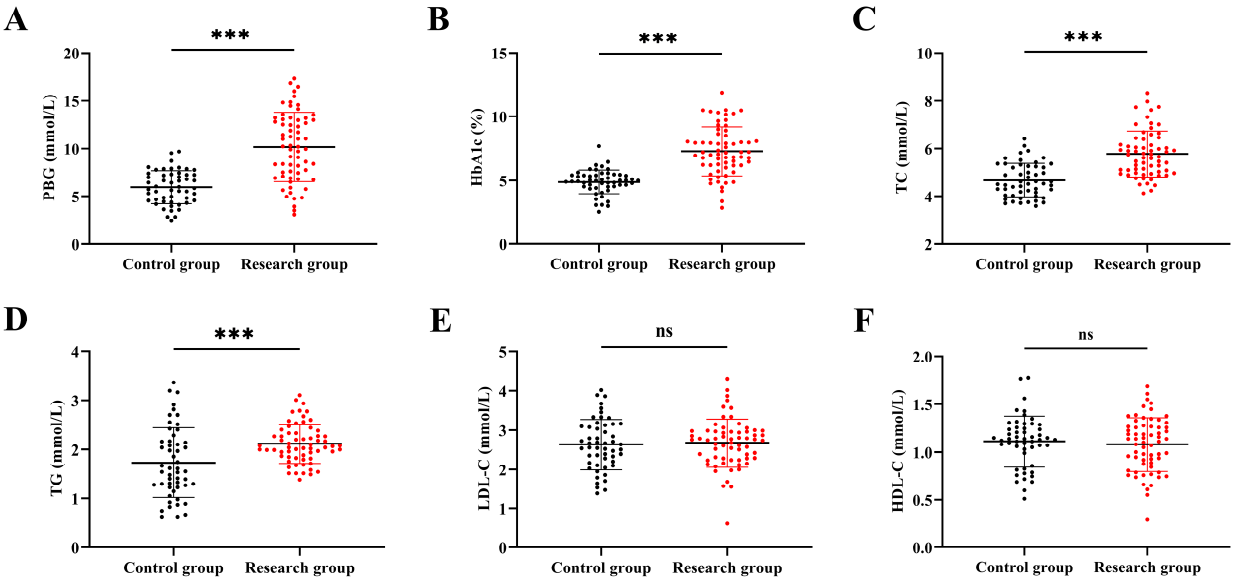

Fig. 2: Blood glucose and blood lipids were higher in the research group than in the control group. A: Comparison of FBG between research and control groups. B: Comparison of HbA1c between research and control groups. C: Comparison of TC between research and control groups. D: Comparison of TG between research and control groups. E: Comparison of LDL-C between research and control groups. F: Comparison of HDL-C between research and control groups. ***P<0.001, ^{ns}P>0.05. Fasting blood glucose, FBG; Glycosylated hemoglobin, HbA1c; Triglyceride, TG; Total cholesterol, TC; High/low-density lipoprotein cholesterol, HDL-C/LDL-C.

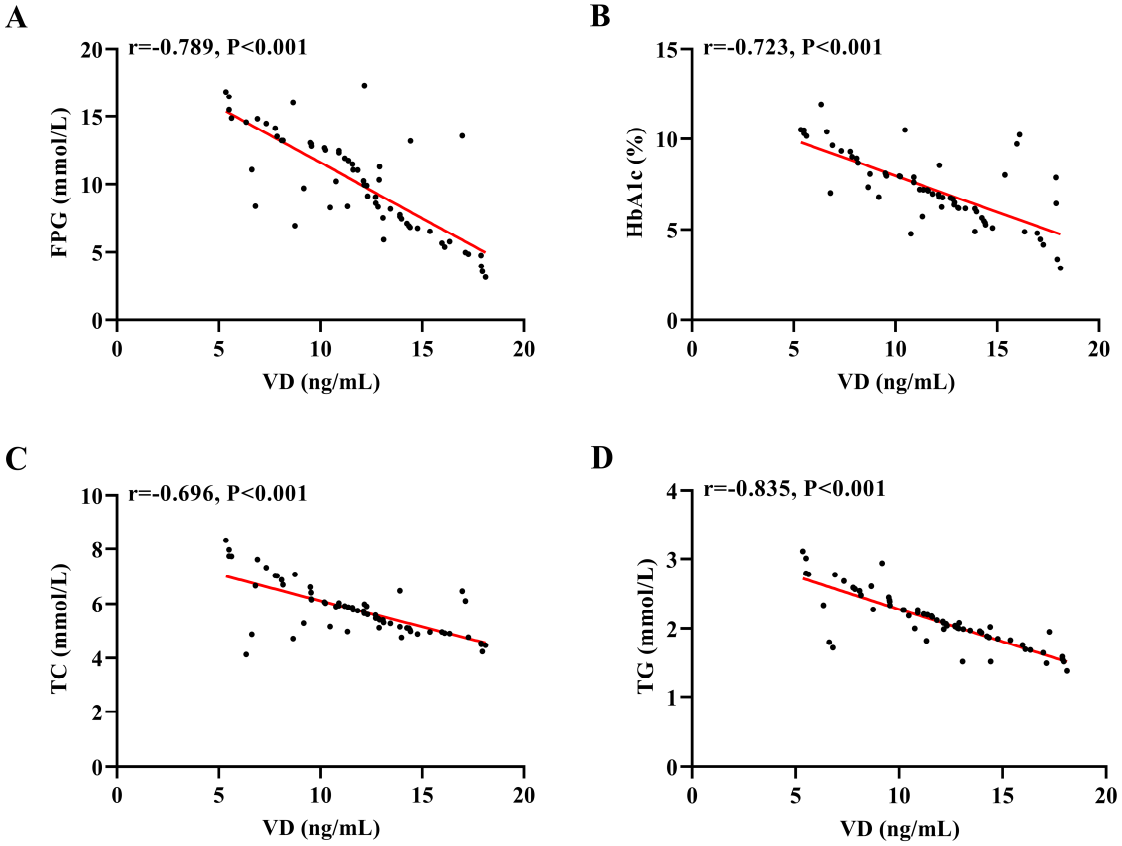

Fig. 3: VD and glucose-lipid metabolism were negatively correlated in the research group. A: Correlation between FBG and VD. B: Correlation between HbA1c and VD. C Correlation between TC and VD. D Correlation between TG and VD.

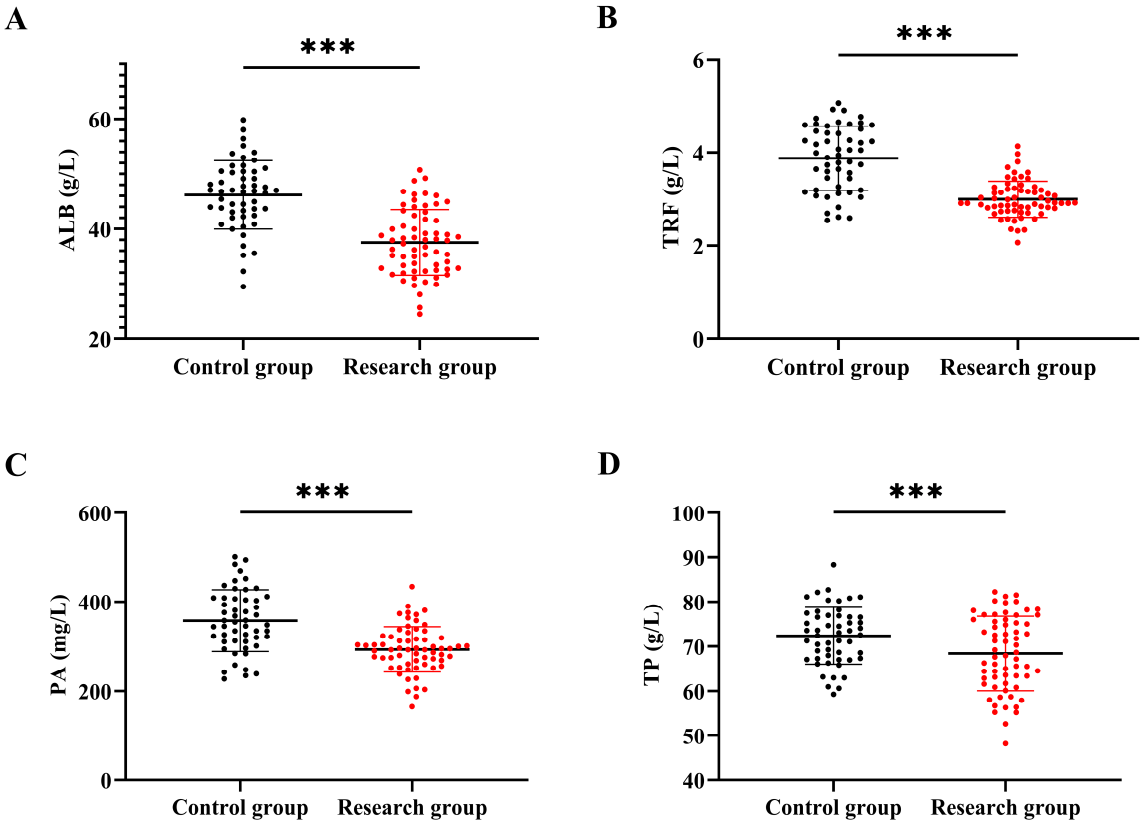

Fig. 4: Nutritional proteins were lower in the research group than in the control group. A: Comparison of ALB between research and control groups. B: Comparison of TRF between research and control groups. C: Comparison of PA between research and control groups. D: Comparison of TP between research and control groups. ***P<0.001. Albumin, ALB; Transferrin, TRF; Prealbumin, PA; Total protein, TP.

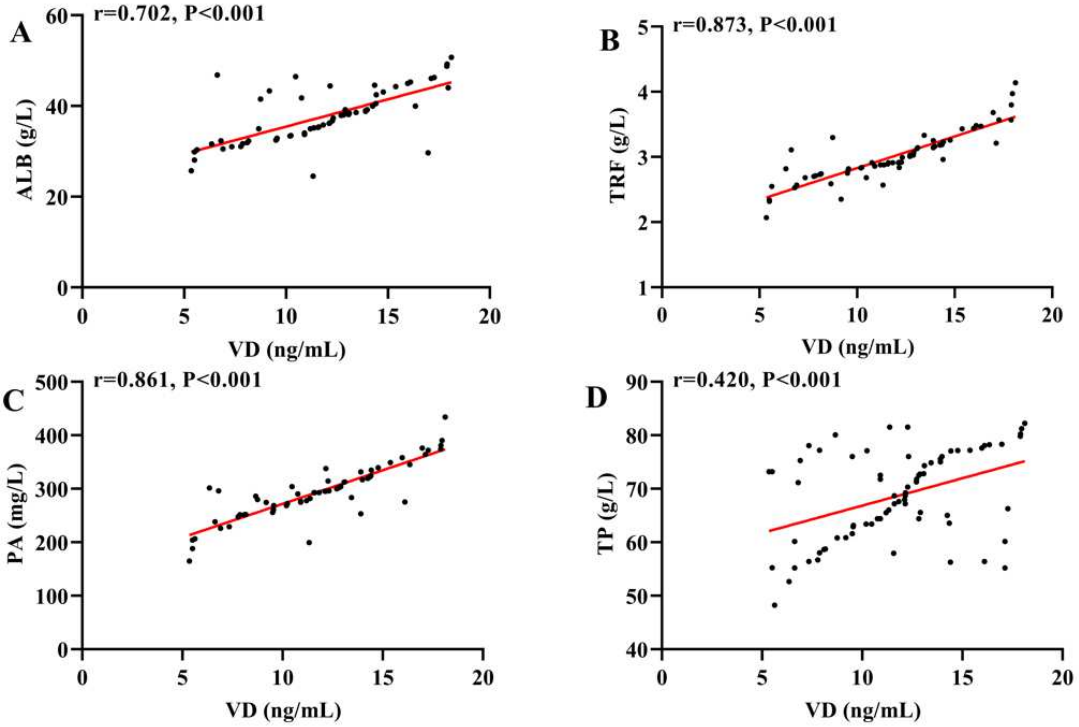

Fig. 5: VD and nutrient proteins were positively correlated in the research group. A: Correlation between ALB and VD. B: Correlation between TRF and VD. C Correlation between PA and VD. D Correlation between TP and VD.

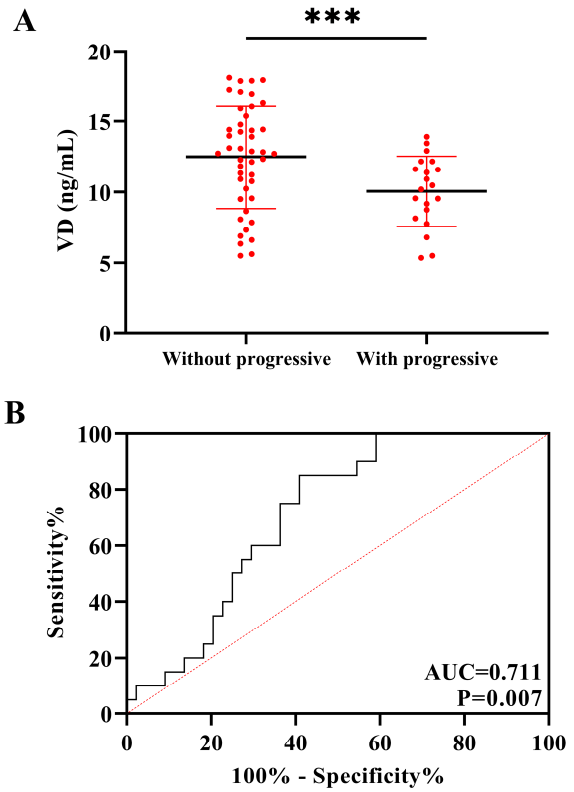

Fig. 6: VD demonstrated excellent assessment of prognostic progression in T2DM. A: Comparison of VD in patients with prognostic progression and those without progression. B: ROC curves of VD predicting prognostic progression in T2DM. ***P<0.001.

DISCUSSION

VD is generated by ultraviolet irradiation and is an essential nutrient for the human body, which binds to VD-binding proteins in the blood to be transported to the liver and catalyzed by 25-hydroxylase to synthesize 25-hydroxy vitamin D [25(OH)D] *in vivo* (Silva & Lazaretti-Castro, 2022). 25(OH)D is the main storage form of VD in the human body, which can reflect human VD levels. Under normal physiological conditions, VD is an essential substance for glucose to stimulate islet β cells to secrete insulin and maintain normal serum glucose levels (Saengsiwaritt *et al.*, 2023). Clinical studies have found that VD receptors (VDRs) are present on pancreatic β cells, and the binding of active VD to VDRs promotes the phosphorylation of tyrosine, an insulin receptor substrate, thereby stimulating islet β cells to secrete insulin and participate in the process of glucose metabolism *in vivo* (Chattranukulchai Shantavasinkul & Nimitphong, 2022). That is to say, VD deficiency can inhibit insulin secretion by islet β cells, leading to T2DM, which reveals a major link between the two.

In this study, the research group showed markedly reduced VD, ALB, TRF, PA, and TP than the control group, as well as elevated FBG, HbA1c, TC and TG, consistent with the results of previous studies (Polat *et al.*, 2022; Chen *et al.*, 2023; Zhang *et al.*, 2020). As is well known, T2DM has two important pathological mechanisms, namely insulin resistance and inadequate insulin secretion (Ojo, 2019). The deficiency of VD can induce insulin synthesis and secretion obstruction by affecting insulin signal transduction pathways. Studies have shown that VD deficiency can lead to impaired islet secretion stimulated by glucose during hyperglycemic clamp, decreased β cell proliferation, and reduced insulin sensitivity, which eventually leads to glucose metabolism imbalances in GK rats (Akhter *et al.*, 2024). It can be seen that VD deficiencies can affect the insulin signal transduction pathway, which leads to the obstruction of insulin synthesis and secretion. Through correlation analysis, we found a negative correlation between VD and FBG, HbA1c, TC and TG in T2DM patients. This is because adipose tissue can participate in the synthesis and decomposition of part of VD by expressing VDRs and VD metabolizing enzymes, with the function of storing and releasing VD (Cojic *et al.*, 2021). Obese individuals have more adipose tissue than those with a normal BMI, so the volume of distribution of VD increases accordingly. Being a fat-soluble vitamin, VD is easy to retain in adipose tissue, resulting in a decrease in the release of VD into the blood and a corresponding decline in the bioavailability of VD. A cross-sectional study showed a negative correlation between serum 25(OH)D and TG levels (Melguizo-Rodriguez *et al.*, 2021), similar to our findings. Conversely, VD can increase the expression of the lipoprotein lipase (LPL) gene in adipose tissue and muscle tissue. By activating LPL, the clearance rate of lipoprotein particles in blood circulation is accelerated, and the lipid structure is changed, thus reducing serum triglyceride levels (Argano *et al.*, 2023).

ALB, TRF, PA and TP are recognized as nutrient proteins in the clinic and they represent the normal functioning state of important organs of the body, such as the liver, kidney, and blood (Hui *et al.*, 2023). In the subsequent analysis of nutritional status, VD in T2DM patients was positively correlated with ALB, TRF, PA, and TP, which shows that VD level is directly correlated with nutritional status in T2DM patients. Clinically, it is believed that VD affects the human body mainly in the following ways: (1) promoting the absorption and transport of calcium and phosphorus in the small intestine; (2) promoting the reabsorption of calcium and phosphorus by renal tubules; (3) maintaining the normal concentration of calcium and phosphorus in the blood and promoting the normal growth of bones and teeth (Contreras-Bolivar *et al.*, 2021). Therefore, an increase in VD levels usually indicates an improvement in the patient's nutritional status. In studies related to T2DM, it is clinically recognized metabolic disorders of carbohydrates, proteins and fats will affect the absorption and utilization of vitamins and minerals by

the body, and adjusting the disturbances of the above-mentioned nutrients will help T2DM patients to correct metabolic disorders and prevent complications (Muszynski *et al.*, 2022). Therefore, we believe that VD may participate in the progression of T2DM by regulating the balance of human nutritional proteins.

Prognostic follow-up further validated our view, that is, patients with prognostic disease progression had statistically lower VD than those without progression. Moreover, VD showed excellent diagnostic effects on the occurrence and prognosis of T2DM, suggesting that the progression of T2DM can be judged by monitoring the levels of VD in patients in the future, so as to adjust the intervention strategy in time and ensure the health of patients.

CONCLUSION

VD in T2DM patients is obviously related to glucose-lipid metabolism and nutritional proteins and its decrease indicates glucose-lipid metabolism abnormalities and nutritional imbalance, which will eventually lead to related complications. In future clinical practice, the pathological progression of T2DM patients can be evaluated by monitoring their VD levels to allow for timely intervention to ensure their health. However, given the single-center retrospective design, a small number of cases, and short follow-up time, the statistical results may be contingent. In the follow-up, we need to increase the number of cases to improve the representativeness of the research results. In addition, the relationship between other vitamins and T2DM should be further explored to provide a more comprehensive clinical reference.

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REFERENCES

Akhter A, Alouffi S, Shahab U, Akasha R, Fazal-Ur-Rehman M, Ghoniem ME, Ahmad N, Kaur K, Pandey RP, Alshammari A, Akhter F and Ahmad S (2024). Vitamin D supplementation modulates glycated hemoglobin (HBA1c) in diabetes mellitus. *Arch. Biochem. Biophys.*, **753**: 109911.

American Diabetes A (2011). Diagnosis and classification of diabetes mellitus. *Diabetes Care.*, **34**(Suppl 1): S62-69.

Argano C, Mirarchi L, Amodeo S, Orlando V, Torres A and Corrao S (2023). The Role of Vitamin D and Its Molecular Bases in Insulin Resistance, Diabetes, Metabolic Syndrome and Cardiovascular Disease: State of the Art. *Int. J. Mol. Sci.*, **24**(20): 15485

Bopape PG, Wagenaar C, Poka M and Bronkhorst E (2023). Vitamin D supplementation in a post-pandemic era: A narrative review. *S. Afr. Fam. Pract* (2004). **65**(1): e1-e6.

Bouillon R, Manousaki D, Rosen C, Trajanoska K, Rivadeneira F and Richards JB (2022). The health effects of vitamin D supplementation: Evidence from human studies. *Nat. Rev. Endocrinol.*, **18**(2): 96-110.

Chattranukulchai Shantavasinkul P and Nimitphong H (2022). Vitamin D and visceral obesity in humans: What should clinicians know? *Nutrients.*, **14**(15): 3075.

Chen B, Bai Y, Tong F, Yan J, Zhang R, Zhong Y, Tan H and Ma X (2023). Glycoursodeoxycholic acid regulates bile acids level and alters gut microbiota and glycolipid metabolism to attenuate diabetes. *Gut. Microbes.*, **15**(1): 2192155.

Cojic M, Kocic R, Klisic A and Kocic G (2021). The effects of vitamin d supplementation on metabolic and oxidative stress markers in patients with type 2 diabetes: A 6-month follow up randomized controlled study. *Front. Endocrinol (Lausanne)*, **12**: 610893.

Contreras-Bolivar V, Garcia-Fontana B, Garcia-Fontana C and Munoz-Torres M (2021). Mechanisms involved in the relationship between vitamin D and insulin resistance: Impact on clinical practice. *Nutrients.*, **13**(10): 3491.

Harreiter J and Roden M (2023). Diabetes mellitus: definition, classification, diagnosis, screening and prevention (Update 2023). *Wien. Klin. Wochenschr.*, **135**(Suppl 1): 7-17.

Hui L, Zhang YY and Hu XD (2023). Multidisciplinary diagnosis and treatment nutritional support intervention for gastrointestinal tumor radiotherapy: Impact on nutrition and quality of life. *World J. Gastrointest Surg.*, **15**(12): 2719-2726.

Lovic D, Piperidou A, Zografou I, Grassos H, Pittaras A and Manolis A (2020). The growing epidemic of diabetes mellitus. *Curr. Vasc. Pharmacol.*, **18**(2): 104-109.

Manousaki D, Harroud A, Mitchell RE, Ross S, Forgetta V, Timpson NJ, Smith GD, Polychronakos C and Richards JB (2021). Vitamin D levels and risk of type 1 diabetes: A mendelian randomization study. *PLoS Med.*, **18**(2): e1003536.

Melguizo-Rodriguez L, Costela-Ruiz VJ, Garcia-Recio E, De Luna-Bertos E, Ruiz C and Illescas-Montes R (2021). Role of Vitamin D in the Metabolic Syndrome. *Nutrients.*, **13**(3): 830

Muszynski T, Polak K, Fratczak A, Miziolek B, Bergler-Czop B and Szczepanik A (2022). Vitamin D-The nutritional status of post-gastrectomy gastric cancer patients-systematic review. *Nutrients.*, **14**(13).

Naik M, Kamath US, Uppangala S, Adiga SK and Patil A (2023). Vitamin D metabolites and analytical challenges. *Anal. Methods.*, **15**(4): 399-410.

Ojo O (2019). Dietary intake and type 2 diabetes.

Nutrients., **11**(9): 2177.

Pittas AG, Kawahara T, Jorde R, Dawson-Hughes B, Vickery EM, Angellotti E, Nelson J, Trikalinos TA and Balk EM (2023). Vitamin D and risk for type 2 diabetes in people with prediabetes: A systematic review and meta-analysis of individual participant data from 3 randomized clinical trials. *Ann. Intern. Med.*, **176**(3): 355-363.

Polat I, Can Yilmaz G and Dedeoglu O (2022). Vitamin D and nerve conduction in pediatric type-1 diabetes mellitus. *Brain. Dev.*, **44**(5): 336-342.

Saengsiwaritt W, Ngamtipakon P and Udomsinprasert W (2023). Vitamin D and autophagy in knee osteoarthritis: A review. *Int. Immunopharmacol.*, **123**: 110712.

Silva ICJ and Lazaretti-Castro M (2022). Vitamin D metabolism and extraskeletal outcomes: An update. *Arch. Endocrinol Metab.*, **66**(5): 748-755.

Tinajero MG and Malik VS (2021). An update on the epidemiology of type 2 diabetes: A global perspective. *Endocrinol Metab. Clin. North Am.*, **50**(3): 337-355.

Yan Y, Wu T, Zhang M, Li C, Liu Q and Li F (2022). Prevalence, awareness and control of type 2 diabetes mellitus and risk factors in Chinese elderly population. *BMC Public. Health*, **22**(1): 1382.

Zhang H, Zhang W, Yun D, Li L, Zhao W, Li Y, Liu X and Liu Z (2020). Alternate-day fasting alleviates diabetes-induced glycolipid metabolism disorders: Roles of FGF21 and bile acids. *J. Nutr. Biochem.*, **83**: 108403.