Association Between Serum Vitamin A Levels and Long-term Outcome in Patients with T2DM

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Abstract: Previous studies suggest that vitamin A (VA) may exert potential regulatory effects on insulin sensitivity and glucose metabolism. However, whether serum vitamin A levels influence the long-term prognosis of patients with type 2 diabetes mellitus (T2DM) remains inconclusive. This study enrolled T2DM patients with available serum VA measurements between 1999 and 2018. The all-cause mortality rate serves as the primary outcome metric. When assessing the association between mortality risk and serum vitamin A (VA) levels, the Cox proportional hazards model can be employed. Subgroups are defined according to VA levels using Kaplan-Meier (KM) analysis, followed by estimation of survival outcomes. Restricted cubic spline (RCS) regression was employed to depict the nonlinear associations between serum VA levels and mortality risk. A total, 3,681 T2DM subjects were enrolled in the final analysis, with a mean serum VA concentration of 2.12 ± 0.76 μmol/L. During the follow-up period of patients, the overall all-cause mortality rate hit 36.70%. In unadjusted Cox regression, Elevated serum vitamin A levels were notably linked to an elevated risk of death, with an HR of 1.43 and a 95% CI of 1.33–1.53. After accounting for potential confounding variables, independent association between serum VA and mortality persisted (HR = 1.12, 95% CI: 1.03–1.22). Subjects with serum VA concentrations above 2.09 μmol/L exhibited significantly poorer survival than those below this threshold ($P < 0.01$). Moreover, RCS modeling revealed a U-shaped pattern linking serum VA levels to mortality risk. Blood vitamin A levels are notably associated with long-term mortality in individuals with type 2 diabetes, and our research findings necessitate further validation in other population groups.

***Keywords*:** vitamin A, NHANES, diabetes mellitus, mortality

1. Introduction

Diabetes prevalence across the globe keeps increasing steadily. As one of the chronic metabolic diseases, persistent hyperglycemia is its hallmark feature, significantly affecting 536.6 million adults worldwide [1]. This widespread phenomenon not only threatens individual health but also challenges the global public health system as the disease often progresses insidiously and leads to a series of irreversible complications. Projections indicate that by 2045, worldwide, the number of people suffering from diabetes exceeds 783.2 million, of which over 90% are type 2 diabetes cases.[1,2]. This significant increase is closely associated with the global obesity epidemic, sedentary lifestyles, and unhealthy dietary patterns. Each of these represents a key intervenable risk factor for type 2 diabetes mellitus (T2DM) development. Annual economic costs attributed to diabetes and its related complications, including cardiovascular disease, neuropathy, retinopathy, and nephropathy, have reached 830 billion, imposing a considerable socioeconomic burden on individuals, families, and healthcare systems worldwide [3]. Due to its high prevalence, poor long-term survival outcomes, and considerable medical expenses, T2DM has become a research priority in clinical and epidemiological fields, with increasing efforts focused on identifying modifiable factors that can improve patient prognosis.

For patients with T2DM, their long-term prognosis is closely associated with nutritional status and metabolic balance, and abnormal levels of micronutrients have been recognized as a potential risk factor that is often overlooked. Vitamin A

(VA), A vital micro fat-soluble nutrient, it participates widely in various physiological processes, such as vision maintenance, immune function regulation, cell differentiation and proliferation, and anti-oxidative stress responses [3, 4]. Recent studies conducted by researchers have demonstrated that vitamin A (VA) can mitigate oxidative stress responses by specifically neutralizing reactive oxygen species (ROS), thereby exhibiting antioxidant properties. Notably, Type 2 diabetes mellitus is closely associated with oxidative stress, which acts as a major contributing factor. Moreover, VA appears to modulate glucose homeostasis and insulin responsiveness by affecting the transcription of genes implicated in insulin signaling pathways [5–8]. Together, the aforementioned research findings have drawn increasing attention from scholars to the pivotal role of angiotensin-converting enzyme (ACE) in the pathogenesis and progression of diabetes mellitus.

Throughout the past 20 years, investigations into the relationship between vitamin A (VA) and diabetes have drawn much attention, but the findings need further refinement, most notably for those with type 2 diabetes mellitus (T2DM). This may be related to impaired nutrient absorption and metabolic disturbances due to autoimmune - mediated pancreatic injury [9]. In contrast, findings in T2DM populations remain controversial and inconsistent across different studies and regions. Numerous studies have demonstrated that serum vitamin A (VA) levels are notably raised in adult individuals with type 2 diabetes mellitus (T2DM), suggesting that VA accumulation may be influenced by metabolic disorders and insulin resistance [9,11,12]. As an antioxidant nutrient, VA intake has been inversely associated with the incidence of T2DM in some epidemiological investigations and may contribute to a lower risk of developing diabetes [13–15]. However, other studies have failed to replicate these findings, and some even suggest that excessive VA intake may have adverse effects on glucose metabolism.

Notably, most prior studies have focused on VA metabolism deficiency and its association with diabetic complications, whereas the effect of elevated VA concentrations on long-term mortality remains inadequately clarified. Furthermore, few large-scale population-based studies have adjusted for comprehensive confounders and this research mainly explored the association between serum vitamin A levels and all-cause mortality among individuals suffering from type 2 diabetes, and further conducted an in-depth investigation into their dose-response relationship.

It follows that the link between circulating VA levels and mortality in patients with T2DM remains unclarified and requires additional confirmatory research. The research subjects in this work were sourced based on data from the United States' NHANES database, the present study further examined the link between serum vitamin A levels and long-term all-cause mortality risk in patients with type 2 diabetes.

2. Material and methods

As a population-based cross-sectional investigation, NHANES is mainly established to gather and sort out health and nutritional relevant data of American residents. Data acquisition includes physical inspections carried out in mobile examination facilities, household interviews and laboratory assays. Ethical approval has been granted for the protocol utilized in the National Health and Nutrition Examination Survey (NHANES) approval from the National Center for Health Statistics (NCHS) Ethics Review Board. All study data were fully anonymized and are publicly accessible as detailed on the CDC website at https://www.cdc.gov/nchs/nhanes. In addition, written informed consent was obtained from every participant prior to enrollment.

The subjects selected for this study were all with a diagnosis of type 2 diabetes mellitus and aged over 18 years, and had valid serum VA measurements in NHANES cycles from 1999 to 2018. The criteria used for the diagnosis of T2DM were as follows: (1) self-reported physician diagnosis of T2DM; (2) glycated hemoglobin ≥6.5%; (3) The main aim of this analysis was to assess all-cause mortality among individuals with type 2 diabetes mellitus (T2DM), with diagnostic criteria including fasting plasma glucose > 7.1 mmol/L and 2-hour postprandial plasma glucose > 11.1 mmol/L following a standard oral glucose tolerance test (OGTT), which was defined as the primary outcome.with follow-up data obtained from NCHS records through December 31, 2019. Participants with missing key covariates, invalid VA measurements, or incomplete follow-up records were excluded from the final analytical cohort.

The following variables were extracted for statistical adjustment. Demographic indicators, such as basic information including gender, ethnicity, race, and age; socioeconomic indicators, such as the poverty line ratio and education level; lifestyle indicators, anthropometric measurements, including body mass index (BMI), as well as personal physical activity levels and smoking status, are all taken into account; clinical comorbidities including hypertension; and biochemical indicators including total cholesterol and HbA1c. Dietary VA intake and serum VA concentrations were also collected as core exposure variables.

The statistical methods employed by the institute are as follows. Data with a normal Mean ± standard deviation (SD) was used to express variables with a normal distribution, whereas median and interquartile range were applied to those with

a non-normal distribution. Categorical variables were described by means of frequencies and the corresponding percentages. When comparing different groups, the chi-square test was used for categorical variables, while continuous variables were analyzed with either the Student's t-test or Kruskal–Wallis test, depending on their distributional characteristics. To assess the association between serum vitamin A (VA) levels and all-cause mortality in patients with type 2 diabetes mellitus (T2DM), a regression analysis was conducted, specifically adopting a three-model Cox proportional hazards regression approach. Model 1 was a crude, unadjusted model without any covariate adjustments; Model 2, on the other hand, included adjustments for baseline participant characteristics such as gender, ethnicity, and age. Model 3 additionally controlled for educational attainment, hypertension, BMI, physical activity, total cholesterol, smoking status, as well as the ratio of family income to poverty. The inclusion of restricted cubic splines (RCS) in the Cox regression model enables an in-depth analysis of the underlying dose-response relationship.with four knots chosen to balance model adaptability and the risk of overfitting. Kaplan–Meier curves were plotted to estimate survival across categories of serum VA concentrations. All the collected data were processed and the analysis was conducted using R software (Version 4.3.1), where a P-value ≤ 0.05 was regarded as statistically significant, which served as the key criterion for judging the statistical validity of the research results.

3. Results

Ultimately, 3,681 participants were enrolled in the present study. diagnosed with diabetes mellitus. The baseline demographic characteristics and clinical profiles of all enrolled subjects are systematically summarized in Table 1. The study participants Participants had a median age of 63.0 years, and the interquartile range was between 53.0 and 72.0 years. When the pre-planned follow-up period came to an end, a total of 1,351 participants in the study had passed away.yielding an overall allcause mortality rate of 36.70%. The mean concentration of serum VA in the total cohort was 2.12 ± 0.76 μmol/L. Among all participants, 1,687 (45.83%) individuals with diabetes had serum VA concentrations above the threshold of 2.09 μmol/L, as visually displayed in Figure 1A. Notably, individuals with a higher level of VA demonstrated higher mortality rates (Figure 1B).

Table 1. Baseline clinical characteristics of the 3681 diabetic participants

	All N = 3681	Survival 2330 (63.30%)	Non-survival 1351 (36.70%)	P
Age, years	63.0 (53.0, 72.0)	60.0 (48.0, 67.0)	70.0 (63.0, 78.0)	0.00*
Male, n (%)	1913 (51.97%)	1159 (49.74%)	754 (55.81%)	0.00
Race, n (%)				
Mexican American	834 (22.66%)	554 (23.78%)	280 (20.73%)	
Other Hispanic	208 (5.65%)	170 (7.30%)	38 (2.81%)	0.00
Non-Hispanic White	1391 (37.79%)	726 (31.16%)	665 (49.22%)	
Non-Hispanic Black	904 (24.56%)	580 (24.89%)	324 (23.98%)	
Other Race	344 (9.35%)	300 (12.88%)	44 (3.26%)	
RFIP	1.89 (1.10, 3.48)	2.03 (1.13, 3.90)	1.70 (1.07, 2.86)	0.00
Education, n (%)				
Less than 9th grade	775 (21.26%)	394 (17.12%)	381 (28.35%)	
9-11th grade	645 (17.69%)	352 (15.30%)	293 (21.80%)	
High school graduate/GED or equivalent	814 (22.33%)	510 (22.16%)	304 (22.62%)	0.00
Some college or AA degree	883 (24.23%)	643 (27.94%)	240 (17.86%)	
College graduate or above	528 (14.49%)	402 (17.47%)	126 (9.38%)	
BMI, kg/m^2	31.79 ± 7.36	32.41 ± 7.67	30.67 ± 6.62	0.00
Hypertension, n (%)	2263 (61.53%)	1352 (58.08%)	911 (67.48%)	0.00
Physical activity, days/week	2.0 (0.0, 7.0)	2.0 (0.0, 7.0)	1.0 (0.0, 7.0)	0.00
Smoking, n (%)				
Never smokers	1824 (49.55%)	1256 (53.91%)	568 (42.04%)	0.00
Former smokers	1272 (34.56%)	712 (30.56%)	560 (41.45%)	
Current smokers	585 (15.89%)	362 (15.54%)	223 (16.51%)	
Total cholesterol, mmol/L	5.05 ± 1.24	4.97 ± 1.23	5.17 ± 1.26	0.00
Glycohemoglobin, %	7.26 ± 1.78	7.25 ± 1.78	7.29 ± 1.78	0.51
Dietary intake of VA, mcg	468.0 (258.4, 770.8)	454.0 (255.0,755.0)	487.0(266.0, 796)	0.02
Serum VA, μmol/L	2.12 ± 0.72	2.01 ± 0.63	2.29 ± 0.82	0.00

Note: VA: Vitamin A; RFIP: Ratio of family income to poverty; * P < 0.01

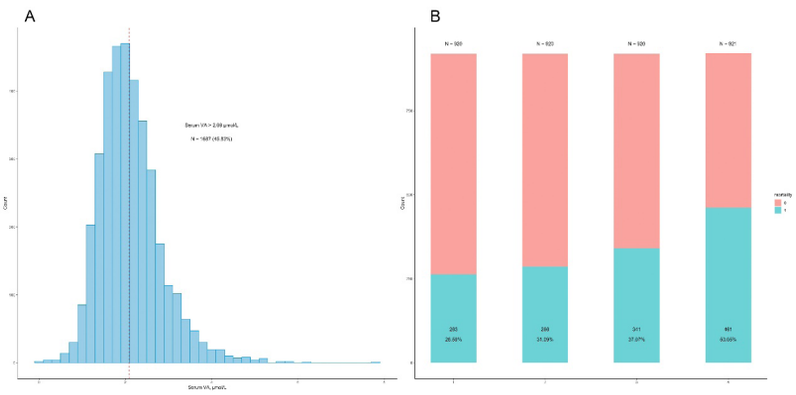

Figure 1. Distribution of serum vitamin A (VA) levels in T2DM patients and mortality across subgroups with different VA concentrations

A: Distribution of serum VA levels among T2DM patients (1687 patients exhibited VA levels > 2.09 μmol/L); B, After stratification by VA quartiles, elevated VA concentrations were associated with higher mortality risk.

It was demonstrated that the surviving group had a median age of 60.0 (48.0, 67.0) years, with the non-surviving group exhibiting a median age of 70.0 (63.0, 78.0) years, indicating a significantly higher age in the non-surviving group ($P < 0.01$). Furthermore, notable disparities were found with respect to the baseline characteristics among the two groups, including education level, household income poverty ratio, ethnicity, and gender. The BMI was markedly higher in survivors relative to nonsurvivors (32.41 ± 7.67 vs. 30.67 ± 6.62 kg/m², $P < 0.01$). Additionally, compared to survivors, non-survivors exhibited lower glycated hemoglobin levels and higher serum vitamin A concentrations, with both parameters statistically significant discrepancies were observed among the groups ($P<0.01$).and daily VA intake was also greater in non-survivors (487.0 (266.0, 796.0) vs. 454.0 (255.0, 755.0) mcg, $P = 0.02$).

The outcomes of the univariate Cox proportional hazards regression analysis are shown in Table 2. The findings suggest that with the continuous elevation of the all-cause mortality rate of patients increases markedly as their serum vitamin A levels drop, with a hazard ratio of 1.43 (95% confidence interval: 1.33–1.53; $P < 0.01$). This result indicates a significant positive how serum vitamin A levels correlate with the risk of all-cause mortality in patients among the risk factors for mortality, dietary vitamin A intake was not an independent associated factor; other factors contributing to increased mortality risk included hypertension, smoking, and Caucasian ethnicity. Factors associated with reduced mortality risk included physical activity level, body mass index (BMI), education level, poverty status, and household income level.

Table 2. Cox regression models exploring associations between variables and all-cause mortality.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.08 (1.07-1.09)	0.00	1.08 (1.07-1.09)	0.00
Male a	1.28 (1.15-1.43)	0.00*	1.36 (1.20-1.54)	0.00
Race b	1.20 (1.15-1.24)	0.00	1.11 (1.07-1.16)	0.00
RFIP	0.90 (0.87-0.94)	0.00	0.91 (0.87-0.95)	0.00
BMI	0.97 (0.96-0.98)	0.00	1.01 (1.01-1.02)	0.03
Education c	0.87 (0.84-0.91)	0.00	0.97 (0.92-1.02)	0.20
Hypertension	1.52 (1.36-1.70)	0.00	0.89 (0.79-1.02)	0.09
Physical activity	0.93 (0.91-0.94)	0.00	0.95 (0.94-0.97)	0.00
Smoking	1.15 (1.08-1.24)	0.00	1.30 (1.19-1.42)	0.00
Total cholesterol	0.96 (0.92-1.01)	0.09	1.02 (0.97-1.08)	0.38
Dietary intake of VA	1.0 (1.0-1.0)	0.73		
Serum VA	1.43 (1.33-1.53)	0.00	1.12 (1.03-1.22)	0.00

Note: In the table, HR (Risk Ratio) indicates the ratio of household income to the poverty line; RFIP denotes the ratio of household income to the poverty line; CI represents the confidence interval; and VA stands for vitamin A. The reference groups are: women (a), non-white individuals (b), and those who did not complete ninth grade education (c). *P<0.01.

Table 3 presents the multivariate Cox regression results. Upon adjusting for key covariates including race, gender, and age, the analysis revealed that vitamin A levels were significantly and independently associated with the risk of mortality,

with an HR of 1.08 (95% CI: 1.01–1.17; P = 0.03). Further adjustments were then implemented to account for other supplementary factors — including body weight, smoking status, gender, and education level — confirmed that serum vitamin A levels independently predicted there was a statistically significant increase in death risk, with a hazard ratio of 1.12 (95% confidence interval: 1.03–1.22; P < 0.01).

Table 3. Regression results of three Cox models for VA and all-cause mortality in T2DM patients

	Coefficient	HR	95%CI	P
Model 1 a	0.35	1.43	1.33 - 1.56	0.00
Model 2 b	0.08	1.04	1.01 - 1.17	0.03
Model 3 c	0.12	1.12	1.03 - 1.22	0.00

Note: HR: hazard ratio; CI: confidence interval

aModel 1: Unadjusted; bModel 2: Adjusted for indicators such as gender, race, and age; cModel 3: Adjusted for indicators such as hypertension, smoking, education level, and race.

The Kaplan-Meier survival curves, stratified by the serum vitamin A levels of patients diagnosed with type 2 diabetes, are presented in Figure 2, with the serum vitamin A cutoff value of 2.09 μmol/L. The trend depicted in the figure indicates that when patients exceed this cutoff value, they exhibited significantly poorer survival outcomes compared with those with VA levels at or below this threshold (log-rank P < 0.01) (Figure 2A). When the cohort was stratified into quartiles according to serum VA concentrations, individuals in higher VA quartiles showed progressively lower survival probabilities (Figure 2B).

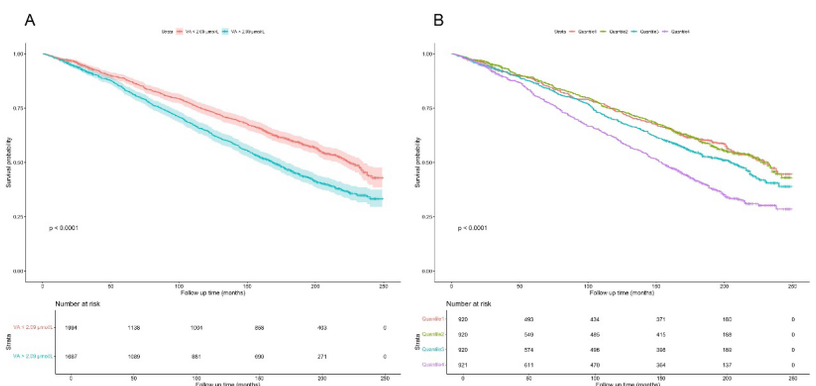

Figure 2. Distribution of VA levels in T2DM patients; Mortality rates by different VA concentration subgroups

A. Serum VA levels in T2DM patients, with>2.09 μmol/L: 1,687 patients; B. After quartile stratification of VA levels, higher VA concentrations were associated with higher mortality rates.

The detailed association between VA concentrations and mortality risk is illustrated in Figure 3. In the unadjusted crude model, mortality risk increased significantly when VA exceeded 2.04 μmol/LThe hazard ratio was 1.009 (95% CI: 1.005–1.013) (Figure 3A). After fully adjusting for potential confounding factors, the correlation between serum VA and mortality risk presented a U-shaped pattern (Figure 3B). Mortality risk declined with rising VA concentrations below 1.55 μmol/L (HR = 1.079, 95% CI: 1.000–1.163) and increased with increasing VA levels above 2.65 μmol/L (HR = 1.117, 95% CI: 1.002–1.247).

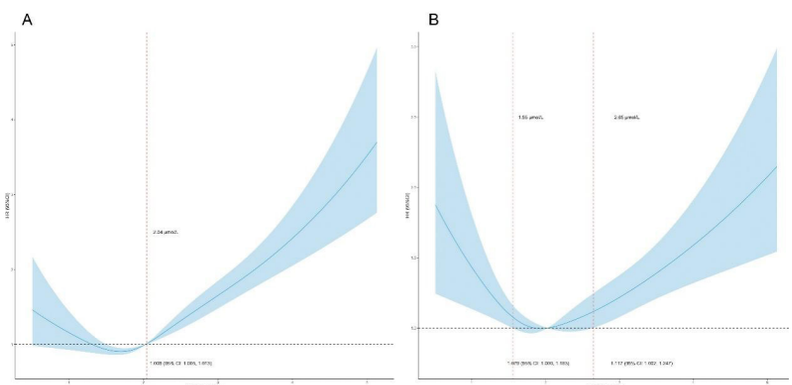

Figure 3. The all-cause mortality risk ratio obtained from the constrained cubic spline Cox regression model

Figure A represents the unadjusted model; Figure B illustrates the adjusted association between vitamin A (VA) concentration and all-cause mortality after adjusting for confounding factors including education level and age.

4. Discussion

The survey data from this study indicated that more than half of diabetic patients had serum vitamin A (VA) concentrations exceeding 2.09 μmol/L, suggesting that an increase in VA levels was linked to a lower survival probability. Multivariate Cox regression analysis showed that serum VA levels served as an independent predictor for mortality, the restricted cubic spline (RCS) analysis explicitly demonstrated a U-shaped correlation between VA concentrations as well as the mortality risk among patients suffering from type 2 diabetes mellitus (T2DM). Our findings suggested that diabetic patients whose serum vitamin A (VA) concentrations were lower than 1.55 μmol/L faced an increased risk of mortality. Previous studies have demonstrated that VA supplementation may reduce mortality associated with diabetes-related complications, such as nephropathy [16], retinopathy [17], and neuropathy [18]. Compared with elevated VA status (>2.09 μmol/L), low VA levels are more prevalent in diabetic populations, especially in developing countries [19], which may lead to impaired quality of life and higher mortality risk [20]. Plasma VA homeostasis is mainly maintained through dietary intake and exogenous supplementation. Inadequate VA consumption and malnutrition may contribute to reduced plasma VA levels as diabetes progresses.

The vitamin A deficiency and the factors contributing to increased mortality rates, as well as the association between them, may be influenced by different types of biological pathways. VA possesses antioxidant capacity that helps alleviate oxidative stress injury [20], and insufficient VA may lead to aggravated oxidative damage and further deterioration of diabetic complications. VA also plays a role in maintaining normal immune function [21]. Diabetic patients are more susceptible to infection [22], and VA deficiency may further impair immune responses, thereby increasing morbidity and mortality. These mechanisms are consistent with our observation that decreased serum VA levels were related to higher mortality risk.

Notably, the U-shaped relationship identified in this study carries important clinical implications. Both low VA status (<1.55 μmol/L) and high VA status (>2.65 μmol/L) were associated with elevated mortality risk, suggesting that VA levels in T2DM patients should be maintained within an appropriate range rather than simply supplemented.

The findings of this study are consistent with multiple conclusions from existing cross-sectional studies, yielding a common conclusion: persistently elevated serum vitamin levels among subjects with type 2 diabetes mellitus (T2DM) increase in long-term mortality, thereby expanding the evidence base from previous research.

The mechanisms linking high VA levels to poor prognosis in diabetic patients have not been fully elucidated. Current evidence suggests that VA may promote insulin resistance through retinol-mediated signaling pathways. Retinoic acid, Microorganism A contains a relatively abundant array of active metabolites, which effectively regulate the expression levels of phosphoenolpyruvate carboxykinase (PEPCK) in the liver [23]. PEPCK is a key enzyme involved in gluconeogenesis; its upregulation can enhance glucose production in hepatocytes and attenuate the inhibitory effect of insulin on gluconeogenesis [24].

In the serum, VA circulates as retinol and forms a 1:1 complex with retinol-binding protein 4 (RBP4) [25]. Therefore, elevated retinol levels imply increased serum RBP4 concentrations. High serum RBP4 levels are regarded as a marker of metabolic syndrome [26]. Numerous previous studies have confirmed that diabetic patients with insulin resistance exhibit more pronounced elevations in serum RBP4 levels [26]. Significant correlations exist between these changes and impaired glucose tolerance, obesity levels, among other factors [27]. Animal experiments demonstrate that as insulin resistance worsens, serum RBP levels continue to rise, specifically inhibiting insulin receptor substrate (IRS) 1 and modulating insulin sensitivity [23]. Recent research further indicates that RBP4 accelerates the activation of NLRP3 inflammasomes, via the TLR4/MD2 complex pathway, which enhances glucose-dependent signaling mediated by TLR2.thereby stimulating the secretion of interleukin1β (IL1β). This, in turn, inhibits cellular insulin signaling and induces insulin resistance [28]. Collectively, these pathways may partially explain the adverse prognostic effects of excess VA in T2DM patients.

From a clinical perspective, our study suggests that routine monitoring of serum VA levels may be reasonable for T2DM patients. Blind high-dose VA supplementation should be avoided. For patients with VA deficiency, appropriate supplementation is recommended, while those with elevated levels should adjust dietary patterns to maintain optimal nutritional status.

This study still has certain limitations.To begin with, all enrolled subjects were derived from the US-based NHANES database, hence further investigations are required to validate the generalizability of our results to other geographic areas, especially developing nations. Second, only a single baseline measurement of serum VA was available for each subject, and longitudinal changes in VA levels were not assessed. Third, given the observational design of this research, We have

not yet been able to definitively establish the causal relationship between VA status and the risk of death. In addition, this study did not consider the influences of VA-related gene polymorphisms, dietary sources, or liver function on circulating VA concentrations. In the future, intervention-based and prospective studies could be conducted to further validate our conclusions and conduct in-depth investigations into the underlying mechanisms involved.

5. Conclusions

In conclusion, we found that diabetes patients whose serum VA levels were evaluated had lower survival probabilities. Serum VA concentration was identified as an independent factor associated with longterm allcause mortality. Further verification of our results in other populations is warranted.

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Authorship

All authors participated in data collection, statistical analysis, and result interpretation. Xuepeng Zhang designed the research protocol and drafted the initial manuscript. Yan Deng revised the manuscript. Yan Deng and Xuepeng Zhang together obtained financial support for this study. All authors have consented to the final manuscript prior to submission.

All authors assume full responsibility for the reliability, objectivity, and unbiased interpretation of all data and analyses presented in this article.

Declaration of interests

The authors declare no potential conflicts of interest.

Data statement

The present study data were obtained from the following publicly accessible resource: National Health and Nutrition Examination Survey (NHANES) database, available at https://www.cdc.gov/nchs/nhanes/index.htm.

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