

Correlation Between Serum Vitamin E and HOMA-IR in Patients with T2DM

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Background: Peroxidation is one of the important causes of insulin resistance (IR), and vitamin E is a natural antioxidant, and there may be some correlation between serum vitamin E levels and insulin resistance.

Purpose: The correlation between serum vitamin E and insulin resistance in type 2 diabetes mellitus (T2DM) population.

Methods: Two hundred and forty-two people (119 with T2DM) were included. One hundred and nineteen patients with T2DM were selected as the case group, and 123 people with non-T2DM were selected as the control group. People insulin resistance was detected by the homeostasis model assessment method (HOMA-IR) greater than 2.69 were included in the diabetic insulin resistance group, and those with HOMA-IR less than 2.69 were included in the diabetic non-insulin resistance group. Record the general body indicators, biochemical indicators, hepatic function indicators, vitamin E, and other indicators. Correlation analysis, logistic regression, trend analysis, and restricted cubic spline (RCS) were performed using SPSS 25.0 and R 4.1.1 software. Correlation analysis, logistic regression, trend analysis, restricted cubic spline (RCS) analysis were conducted on general body indicators, biochemical indicators, hepatic function indicators, vitamin E, and other indicators.

Results: The logistic regression results showed that after adjusting for confounding factors, vitamin E was an independent influencing factor for insulin resistance in T2DM patients ($P < 0.001$). The trend analysis results show that with the decrease of serum vitamin E levels, the risk of insulin resistance in T2DM patients gradually increases. The RCS results showed that the risk of insulin resistance was significantly increased when the serum vitamin E level was lower than 10,575.23 ng/mL.

Conclusion: Serum vitamin E levels are lower in T2DM patients than in healthy populations; Vitamin E is an independent influencing factor for HOMA-IR in T2DM patients. The risk of insulin resistance gradually increases in T2DM patients as serum vitamin E levels decrease. Vitamin E is a risk factor for insulin resistance at serum vitamin E levels below 10,575.23 ng/mL. At higher serum vitamin E levels than 10,575.23 ng/mL, vitamin E is a protective factor for insulin resistance.

Keywords: Vitamin E, type 2 diabetes mellitus, insulin resistance, oxidative stress

Introduction

At present, the number of people with diabetes in the world is about 468 million.¹ By 2030, there will be 643 million people suffering from diabetes in the world, and it will increase to 783 million by 2045. Diabetes has become a serious public health problem.² T2DM is the most prevalent metabolic disorder and is associated with an increased^{3–5} risk of cardiovascular disease (CVD), chronic kidney disease, retinopathy, and mortality. It is characterized by chronic hyperglycemia and an inadequate response of peripheral tissues to circulating insulin, leading to insulin resistance.^{6,7} Insulin resistance has a complex pathophysiology, and it is contributed by multiple factors, including oxidative stress. Oxidative stress refers to the imbalance between free radical production and antioxidant systems, which leads to decreased peripheral insulin sensitivity, produces insulin resistance, and promotes the development^{8–10} of T2DM through a variety of molecular mechanisms. Vitamin E is a potent antioxidant composed of two classes of compounds: tocopherols and tocotrienols, which protect cells and tissues from oxidative damage.^{11–15} Since oxidative stress is a key factor in insulin resistance, the antioxidant capacity of vitamin E improves the level of insulin resistance, which in turn affects blood glucose levels.^{16–20} This article analyzed the serum vitamin E level in patients with T2DM and explored the correlation between serum vitamin E and insulin resistance in T2DM patients.

Materials and Methods

Study Population

A total of 242 patients in the wards and physical examination center of Hebei General Hospital were selected. Among them, 119 patients with T2DM in the endocrinology ward were selected as the case group, and 123 patients without T2DM in the physical examination center were selected as the control group. The basic information and serum vitamin E levels of the included subjects were recorded.

The diagnostic criteria of type 2 diabetes mellitus, according to the Chinese Guidelines for the Prevention and Treatment of Type 2 diabetes mellitus (2020):

- ① Typical diabetic symptoms (polydipsia, polyuria, polyphagia, unexplained weight loss);
- ② random blood glucose ≥ 11.1 mmol/L; Or OGTT2h blood glucose ≥ 11.1 mmol/L;
- ③ or fasting blood glucose ≥ 7.0 mmol/L;
- ④ or HbA1c $\geq 6.5\%$;
- ⑤ Patients without typical symptoms of diabetes should be rechecked another day.

Random blood glucose refers to blood glucose at any time of the day regardless of the last meal time. It cannot be used to diagnose impaired fasting glucose or impaired glucose tolerance. A fasting state is defined as at least 8 hours without eating calories.

Inclusion Criteria

- (1) Adults aged 18–75 years with normal communication ability.
- (2) those who met the diagnostic criteria for T2DM.

Exclusion Criteria

- (1) Patients with serious cardiac, liver, kidney, and other complications or combined with other serious primary diseases or mental patients.
- (2) patients with acute complications, such as diabetic ketoacidosis, coma, and lactic acidosis in the past 1 month.
- (3) pregnant and lactating women.
- (4) type 1 or other types of diabetes.

Compliance with any of the above can be excluded.

Clinical Assessment and Biochemical Measurements

All subjects included in this experiment were fasted for 8–12 hours, and venous blood was taken in the morning. Blood samples were stored in refrigerated containers, centrifuged within 1 hour after collection, and determined by HitWChi 7600 automatic biochemical analyzer from Hitachi. The detection indicators include FBG, fasting insulin (FINS), glycosylated hemoglobin (HbA1c), glutamine transaminase (ALT), glutamate transaminase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), glomerular filtration rate (GFR), serum creatinine (Scr), serum total protein (TP), serum albumin (ALB), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and vitamin E. Human serum vitamin E level was measured by liquid chromatography tandem mass spectrometry (LC-MS/MS).

Calculation of Parameter

$$\text{HOMA-IR index} = \text{FBG} \times \text{FINS} / 22.5.$$

$$\text{Body mass index (BMI)} = \text{weight (kg)} / \text{height (m)}^2;$$

The HOMA-IR score greater than 2.69 was defined as IR group, and the HOMA-IR value less than 2.69 was defined as non-IR group. The case group was divided into IR group and non-IR group according to HOMA-IR value.

Statistical Analysis

SPSS statistical software was used to process the data. First, the data were checked to see if they were normally distributed. If the data did not conform to the normal distribution, the rank sum test was used.

The factors with $P < 0.05$ in the results of rank sum test or t -test were further correlated with vitamin E to explore the correlation between multiple indicators. Linear correlation was used if the data conformed to normal distribution. If the data did not conform to the normal distribution, rank correlation analysis was used. If Sig (two-tailed) was less than 0.05, it was considered to be related to vitamin E.

The value of Sig (two-tailed) < 0.05 in the correlation analysis of vitamin E and SIG (two-tailed) was used as the covariate, and insulin resistance (HOMA-IR > 2.69) was used as the dependent variable. Binary multivariate Logistic regression analysis was performed, and $P < 0.05$ was considered statistically significant.

Trend test was used to analyze whether insulin resistance changes with the change of vitamin E level in T2DM patients. Vitamin E levels were divided into quartiles, and the trend test was conducted between vitamin E and insulin resistance levels.

The restricted cubic spline curve of vitamin E level and insulin resistance were drawn to further evaluate whether the trend of insulin resistance changes with the change of vitamin E level in T2DM patients.

Results

Comparison of Baseline Data Between T2DM Group and Non-T2DM Group

A total of 242 patients were included in this study, with a median age of 53. A total of 112 women and 130 men were enrolled, all of whom were Chinese. The T2DM group vitamin E level was significantly lower than that in the non-T2DM group (11,659.03[9154.44,13,254.9] vs 10,575.23[8357.94,12,187.77], $P < 0.001$). Comparison of the data between the non-T2DM group and the T2DM group showed that the body weight, BMI, abdominal circumference, total protein, albumin, direct bilirubin, bilirubin, glutamate, ALT, glutamyltransferase, alkaline phosphatase, creatinine, glomerular filtration rate, triglycerides, HDL, and fasting blood glucose were less than 0.05. There were no significant differences between gender, age, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), globulin, total bilirubin, indirect bilirubin, urea, uric acid, total cholesterol, and LDL groups ($P > 0.05$), as shown in Table 1.

Table 1 Comparison of Baseline Data Between T2DM Group and Non-T2DM Group

Variables	Total (n=242)	Non-T2DM (n=123)	T2DM (n=119)	P
Gender, male, n (%)	130(53.719)	60(48.780)	70(58.824)	0.117
Gender, Female, n (%)	112(46.281)	63(51.220)	49(41.176)	0.117
Diabetes duration days	0.000 [0.000,730.000]	0.000 [0.000,0.000]	730.000 [60.000,3285.000]	$< 0.001^{**}$
Age, year	53.000 [44.000,60.000]	55.000 [49.000,61.000]	51.000 [39.000,59.000]	0.022*
Height, cm	166.000 [161.000,172.000]	166.000 [161.000, 171.000]	166.000 [160.000, 172.000]	0.972
Weight, Kg	71.000 [62.700,82.000]	68.000 [60.000,77.000]	73.000 [64.200,87.000]	0.004*
BMI, Kg/m ²	25.590 [23.380,28.230]	24.860 [22.650,27.080]	26.470 [23.930,30.020]	$< 0.001^{**}$
AC, cm	90.000 [82.000,96.000]	88.000 [80.000,94.000]	91.000 [85.000,102.000]	0.004*
SBP, mmHg	129.451±18.555	127.948±18.308	130.940±18.679	0.22
DBP, mmHg	83.657±11.855	83.302±11.697	84.009±12.000	0.651
TP, g/L	71.146±5.715	72.154±3.816	70.104±7.016	0.006*
ALB, g/L	43.600 [41.500,45.100]	43.700 [42.500,45.400]	43.400 [40.400,44.900]	0.007*
GLB, g/L	27.969±4.792	28.254±3.396	27.676±5.883	0.355
TBIL, umol/L	14.300 [11.100,18.300]	14.000 [10.800,18.100]	14.600 [11.600,19.500]	0.218
DBIL, umol/L	2.200 [1.600,3.000]	2.000 [1.600,2.500]	2.600 [1.800,3.400]	$< 0.001^{**}$
IBIL, umol/L	12.100 [9.500,15.600]	11.900 [9.400,15.300]	12.300 [9.500,15.900]	0.648
ALT, U/L	19.000 [14.600,29.600]	17.600 [13.200,25.000]	21.800 [15.300,34.200]	$< 0.001^{**}$
AST, U/L	20.900 [17.600,26.000]	20.600 [17.800,24.600]	21.400 [17.400,30.400]	0.411

(Continued)

Table 1 (Continued).

Variables	Total (n=242)	Non-T2DM (n=123)	T2DM (n=119)	P
GGT, U/L	22.900 [18.600,32.100]	20.600 [17.800,24.600]	28.500 [19.900,43.700]	<0.001**
ALP, U/L	71.000 [60.100,89.400]	68.600 [58.700,81.900]	78.700 [62.400,96.300]	0.001*
Urea, mmol/L	4.900 [4.300,5.800]	4.950 [4.380,5.760]	4.900 [4.200,5.800]	0.816
Cr, μ mol/L	61.700 [53.900,72.100]	63.300 [55.000,76.300]	59.600 [51.500,66.600]	0.004*
UA, μ mol/L	323.500 [276.400,392.600]	328.300 [284.300,384.300]	323.000 [260.900,401.900]	0.917
GFR, mL/min	102.550 [94.670,111.390]	99.280 [93.360,107.700]	104.920 [98.000,117.360]	<0.001**
TC, mmol/L	5.210 [4.540,5.950]	5.240 [4.710,5.810]	5.160 [4.230,6.220]	0.344
TG, mmol/L	1.510 [1.050,2.320]	1.380 [0.980,1.990]	1.730 [1.210,2.630]	<0.001**
HDL, mmol/L	1.250 [1.020,1.490]	1.410 [1.230,1.620]	1.060 [0.920,1.300]	<0.001**
LDL, mmol/L	3.420 \pm 0.946	3.407 \pm 0.758	3.433 \pm 1.108	0.835
FBG, mmom/L	5.560 [5.090,6.370]	5.350 [5.050,5.670]	6.230 [5.480,7.330]	<0.001**
Vitamin E, ng/mL	11,151.090 [8441.450,12,814.97]	11,659.030 [9154.440,13,254.9]	10,575.230 [8357.94,12,187.77]	0.009*

Note: *P < 0.05, **P < 0.01.

Abbreviations: BMI, body mass index; AC, abdominal circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TP, total albumin; ALB, serum albumin; GLB, serum globulin; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, glutamyltransferase; ALP, alkaline phosphatase; Cr, creatinine; Urea, Urea nitrogen; UA, uric acid; GFR, glomerular filtration rate, TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein- cholesterol; LDL, low-density lipoprotein-cholesterol; FBG, fasting blood glucose; FINS fasting insulin; VE, vitamin E; CP, Fasting C-peptide;HbA1c Glycosylated hemoglobin.

Comparison of Baseline Indicators Between IR and Non IR Group

Baseline comparison showed that age, weight, BMI, SBP, direct bilirubin, total cholesterol, triglycerides, LDL, HbA1c, fasting blood glucose, fasting insulin, fasting C-peptide, and vitamin E in IR ($P < 0.05$). Disease course, gender, height, diastolic blood pressure, total protein, albumin, globulin, total bilirubin, indirect bilirubin, glutaminase, transglutaminase, glutamyltransferase, alkaline phosphatase, urea, creatinine, uric acid, glomerular filtration rate, and high-density lipoprotein ($P > 0.05$), as shown in Table 2.

Table 2 Comparison of Baseline Indicators Between IR and Non-IR Group

Variables	Total(n=119)	Non-IR (n=62)	IR (n=57)	P	
General physical indicators	Gender, male, n (%)	70(58.824)	35(56.452)	35(61.404)	0.583
	Diabetes duration days	730.0 [60.0,3285.0]	730.0 [30.0,2920.0]	730.0 [183.0,3650.0]	0.186
	Age, year	51.0 [39.0,59.0]	46.0 [38.0,56.0]	57.0 [43.0,64.0]	0.011*
	Height, cm	166.0 [160.0,172.0]	166.0 [160.0,172.0]	166.0 [160.0,173.0]	0.519
	Weight, Kg	73.0 [64.2,87.0]	69.0 [63.6,82.5]	75.0 [65.0,95.0]	0.025*
	BMI, Kg/m ²	26.470 [23.930,30.020]	25.080 [23.530,28.210]	28.4 [25.270,31.0]	0.005*
	AC, cm	91.0 [85.0,102.0]	89.0 [83.0,96.0]	94.0 [87.0,102.0]	0.101
	SBP, mmHg	129.0 [119.0,142.0]	127.0 [114.0,138.0]	132.0 [125.0,145.0]	0.026*
	DBP, mmHg	84.009 \pm 12.0	83.377 \pm 13.210	84.696 \pm 10.481	0.553
Biochemical indexes	TP, g/L	70.104 \pm 7.016	70.158 \pm 7.547	70.046 \pm 6.389	0.931
	ALB, g/L	43.4 [40.4,44.9]	43.0 [40.0,44.2]	43.4 [40.7,45.1]	0.437
	GLB, g/L	27.676 \pm 5.883	28.037 \pm 6.358	27.282 \pm 5.290	0.489
Hepatic function indices	TBIL, μ mol/L	14.6 [11.6,19.5]	14.3 [10.9,19.4]	15.6 [12.1,20.6]	0.149
	DBIL, μ mol/L	2.6 [1.8,3.4]	2.4 [1.7,3.2]	2.8 [2.0,3.6]	0.050*
	IBIL, μ mol/L	12.3 [9.5,15.9]	11.4 [9.1,15.4]	12.7 [10.0,16.3]	0.186
	ALT, U/L	21.8 [15.3,34.2]	21.9 [15.3,32.2]	20.4 [15.3,43.0]	0.621
	AST, U/L	21.4 [17.4,30.4]	21.0 [17.5,28.8]	21.9 [17.3,32.4]	0.700
	GGT, U/L	28.5 [19.9,43.7]	25.6 [19.9,42.6]	31.5 [19.1,43.9]	0.567
	ALP, U/L	78.7 [62.4,96.3]	75.1 [62.3,98.0]	80.8 [65.2,95.9]	0.807
	BA, μ mol/L	2.94 [1.920,4.31]	2.83 [1.820,4.31]	3.13 [2.290,4.31]	0.481

(Continued)

Table 2 (Continued).

Variables		Total(n=119)	Non-IR (n=62)	IR (n=57)	P
Renal function indices	Urea, mmol/L	4.9 [4.2,5.8]	4.9 [3.9,5.8]	5.0 [4.5,5.8]	0.302
	Cr, μ mol/L	59.6 [51.5,66.6]	58.5 [49.4,65.9]	63.0 [53.1,68.7]	0.237
	UA, μ mol/L	323.0 [260.9,401.9]	323.5 [242.0,401.9]	323.0 [280.8,397.7]	0.467
	GFR, mL/min	104.92 [98.0,117.36]	109.82 [101.810,119.61]	103.72 [94.4,114.66]	0.055
Blood lipid indices	TC, mmol/L	5.16 [4.230,6.22]	5.67 [4.840,6.73]	4.76 [4.020,5.49]	<0.001**
	TG, mmol/L	1.73 [1.210,2.63]	2.04 [1.310,3.35]	1.46 [1.2,2.51]	0.037*
	HDL, mmol/L	1.06 [0.920,1.3]	1.07 [0.950,1.3]	0.99 [0.880,1.23]	0.307
	LDL, mmol/L	3.433 \pm 1.108	3.769 \pm 1.172	3.067 \pm 0.9	<0.001**
Glucose metabolism indices	HbA1c	9.3 [7.9,11.1]	10.0 [8.2,11.8]	9.0 [7.4,10.8]	0.030*
	FBG, mmol/L	6.23 [5.48,7.33]	5.66 [4.910,6.61]	6.86 [5.9,7.88]	<0.001**
	FINS, mmol/L	8.69 [5.09,14.46]	5.09 [3.56,7.12]	15.71 [10.420,20.36]	<0.001**
	C-P, ng/mL	2.397 \pm 1.164	1.666 \pm 0.742	3.192 \pm 1.009	<0.001**
	Vitamin E, ng/mL	10,575.23 [8357.94,12,187.77]	11,560.88 [10,645.09,13,513.23]	8357.94 [6641.36,9446.02]	<0.001**

Note: *P \leq 0.05, **P < 0.01.

Abbreviations: BMI, body mass index; AC, abdominal circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TP, total albumin; ALB, serum albumin; GLB, serum globulin; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, glutamyl-transferase; ALP, alkaline phosphatase; Cr, creatinine; Urea, Urea nitrogen; UA, uric acid; GFR, glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein- cholesterol; LDL, low-density lipoprotein-cholesterol; FBG, fasting blood glucose; FINS fasting insulin; VE, vitamin E; CP, Fasting C-peptide; HbA1c Glycosylated hemoglobin.

Correlation Analysis Between Vitamin E and Other Indicators

Spearman correlation coefficient was used to study the correlation between serum Vitamin E level and other indicators. The results showed that vitamin E was negatively correlated with direct bilirubin, fasting blood glucose, fasting insulin, and fasting C-peptide ($r = -0.246, -0.282, -0.504, -0.513$, P values were 0.008, 0.002, <0.001, <0.001, respectively). Vitamin E was positively correlated with total cholesterol, triglyceride, low-density lipoprotein ($r = 0.452, 0.333, 0.368$, respectively, P values were <0.001, <0.001, <0.001). There was no significant correlation between other indicators, as shown in Table 3. The heat map of vitamin E and correlation is shown in Figure 1.

Logistic Regression of HOMA-IR and Vitamin E

Multivariate logistic regression was used to evaluate the effects of vitamin E, direct bilirubin, total cholesterol, triglyceride, low-density lipoprotein, and fasting C-peptide on insulin resistance. The AUC in the model was 0.953, and the prediction effect of the model was good, as shown in Figure 2. Binary multivariate logistic regression analysis

Table 3 Correlation Analysis Between Vitamin E and Other Indicators

Variables	r	P
Age	-0.067	0.472
Weight	-0.167	0.074
BMI	-0.116	0.214
SBP	-0.129	0.169
DBIL	-0.246	0.008*
TC	0.452	<0.001**
TG	0.333	<0.001**
LDL	0.368	<0.001**
HbA1c	0.157	0.092
FBG	-0.282	0.002*
FINS	-0.504	<0.001**
C-P	-0.513	<0.001**

Note: *P < 0.05, **P < 0.01.

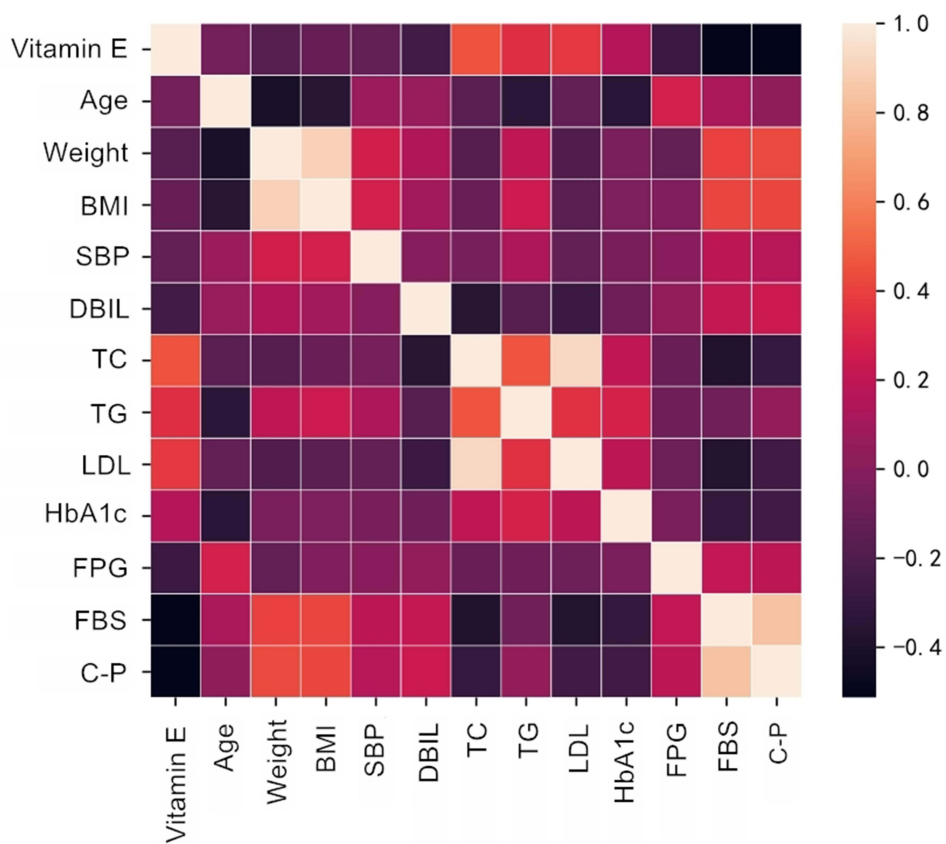


Figure 1 Correlation Analysis Heat Map.
Note: AUC=0.953 (95% CI 0.914–0.993).

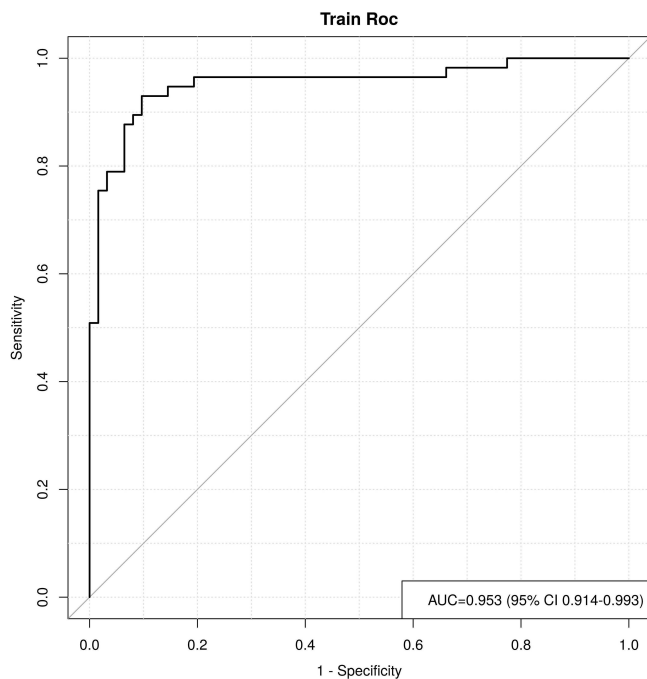


Figure 2 ROC curve.

showed that vitamin E, total cholesterol, triglyceride, low-density lipoprotein, and fasting C-peptide were independent influencing factors of insulin resistance in T2DM patients ($P < 0.05$). The other indicators were not independent influencing factors of insulin resistance in T2DM patients ($P > 0.05$), as shown in Table 4.

Trend Testing Analysis

The IR and non-IR groups were grouped by quartiles of serum vitamin E concentration, and the median of that group was assigned to each group. Then, with insulin resistance as the dependent variable and vitamin E as the independent variable, the trend analysis was carried out, $P < 0.05$, showing that there was a statistically significant difference in the trend. With the change of vitamin E concentration, the trend of insulin resistance changed.

The covariates of Model 1 adjusted model in trend test were duration of disease, age, height, weight, BMI, systolic blood pressure, diastolic blood pressure, and gender, $P < 0.001$. The covariates of Model 2 adjusted model were duration of disease, gender, age, height, weight, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein, very low-density lipoprotein, fasting C-peptide, $P = 0.001$. P values were less than 0.05, indicating that the trend was statistically significant, and insulin resistance changed with the change of vitamin E concentration. The results are shown in Table 5:

Cubic Spline Regression Analysis of the Relationship of Vitamin E and HOMA-IR

To further evaluate the trend of insulin resistance with vitamin E, ROC curves were plotted with insulin resistance as the dependent variable and serum vitamin E as the independent variable. The P -nonlinear value of the model was 0.002, indicating that there was a nonlinear relationship between vitamin E and insulin resistance in T2DM patients. The reference point ($OR = 1$) was 10,575.23 ng/mL. When serum vitamin E level was lower than 10,575.23 ng/mL, vitamin E was a risk factor for insulin resistance in T2DM patients ($OR > 1$), and when serum vitamin E level was higher than 10,575.23 ng/mL, vitamin E was a protective factor for insulin resistance in T2DM patients ($OR < 1$), as shown in Figure 3.

Table 4 Logistic Regression Result

Variables	β	P	OR	Lower	Upper
Vitamin E	-0.001	<0.001**	0.999	0.999	1
DBIL	0.001	0.998	1.001	0.566	1.792
TC	2.562	0.008*	12.965	2.161	101.855
TG	-0.494	0.008*	0.61	0.402	0.849
LDL	-3.349	0.006*	0.035	0.003	0.325
C-P	2.519	<0.001**	12.412	4.749	43.486

Note: * $P < 0.05$, ** $P < 0.01$.

Table 5 Trend Testing Analysis Result

Variables	Crude Model			Model 1			Model 2		
	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P
Q1 (4771.51, 8176.59)	I (Ref)			I (Ref)			I (Ref)		
Q2 (8244.51, 10,525.87)	0.148	[0.029,0.752]	0.021	0.038	[0.004,0.332]	0.003	0.038	[0.002,0.863]	0.040
Q3 (10,575.23, 12,187.77)	0.008	[0.001,0.053]	<0.001	<0.001	[0.000,0.010]	<0.001	<0.001	[0.000,0.059]	0.003
Q4 (12,286.44, 25,835.86)	0.023	[0.004,0.119]	<0.001	0.001	[0.000,0.026]	<0.001	<0.001	[0.000,0.049]	0.002
P for trend	0.999	[0.999,1.000]	<0.001	0.999	[0.999,1.000]	<0.001	0.999	[0.999,1.000]	0.001

Notes: Model 1: adjusted for Duration diabetes, Gender, Age, Weight, BMI, SDP, DBP; Model 2: adjusted for Duration diabetes, Gender, Age, Weight, BMI, SDP, DBP, TC, TG, LDL, C-P.

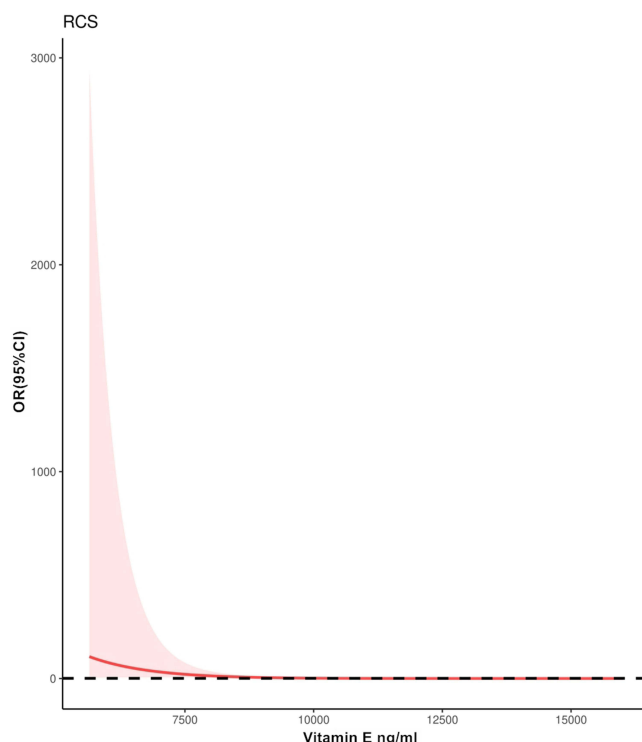


Figure 3 Cubic spline regression analysis of the relationship of VE and HOMA-IR.

Discussion

Lipid oversupply, chronic inflammation, and oxidative stress are fundamental causes^{21,22} of the development and worsening of insulin resistance.^{23,24} Oxidative stress is not only associated^{25–28} with insulin resistance, but also with a variety of complications of diabetes.^{29–35} When glucose and free fatty acids (FFA) are increased, they cause oxidative stress while activating stress-sensitive signaling pathways. Activation of these pathways in turn worsens insulin action and secretion, leading to pronounced insulin resistance. Reducing the degree of oxidative stress and activating oxidative stress signaling pathways can be used as part of the treatment regimen for patients³⁶ with T2DM.

The mechanism of vitamin E reducing oxygen free radicals is related to the structure of vitamin E itself. In the molecular structure of vitamin E, there is a phenylpropylene dihydropyran ring, and the hydrogen on the phenylpropylene dihydropyran ring combines with oxygen free radicals to form reproductive quinone and is excreted from the body. Vitamin E can also prevent the chain reactions of lipid peroxidation by reducing the production of oxygen free radicals, thereby preventing the peroxidation of polyunsaturated fatty acids in the cell membrane. Vitamin E not only reduces the damage caused by oxidative stress, but also prevents the harmful biological effects caused by lipid peroxidation products.³⁷

In this study, patients were divided into T2DM group and non-T2DM group. The vitamin E level in the T2DM group was significantly lower than that in the non-T2DM group ($P < 0.05$). To further investigate the correlation between serum vitamin E level and the mechanism of insulin resistance in T2DM patients, we divided T2DM patients into IR group and Non-IR group, and the results showed that the vitamin E level in IR group was significantly lower than that in non-IR group.

Logistic regression analysis also showed that serum vitamin E level was an independent risk factor for insulin resistance. Therefore, our data suggest that vitamin E plays an important role in the development of insulin resistance in T2DM patients and may be an independent predictor of insulin resistance risk.

We divided the subjects into four groups, Q1, Q2, Q3, and Q4, according to their serum vitamin E levels from high to low. In the test of the correlation between serum vitamin E levels and the risk of insulin resistance in patients with type 2 diabetes, we found that as vitamin E levels increased, the differences between the original model, model 1 and model 2 were statistically significant ($p < 0.05$). Compared with the Q1 group, the risk of the Q2 group reduced by 85.2% times, the Q3 group increased by 0.008 times, and the Q4 group reduced by 97.7%.

Previous studies have demonstrated a possible mechanistic link between vitamin E and insulin sensitivity. It is suggested that the up-regulation of α -tocopherol and γ -tocopherol is involved in the activation of the endogenous ligand of PPAR γ , and PPAR γ plays an important role³⁸ in the up-regulation. Studies have also shown that high doses of vitamin E (>1300 mg/day) not only have hypoglycemic effects, but also may have adverse effects^{39–42} on the body. There is evidence that relatively high doses of vitamin E supplementation do not inhibit oxidative stress processes⁴³ involved in hemoglobin glycation. Thus, low-dose vitamin E supplementation appears to be more effective than high-dose supplementation in patients with diabetes.

Overall, as no known side effects of vitamin E supplements have been reported, and vitamin E can be used as supplemental therapy in these patients. However, this recommendation should be implemented with caution for patients with T1DM and those with diabetic nephropathy and/or neuropathy, as there are few studies in this area. Further, randomized controlled trials, especially those with low risk of bias, are needed to evaluate the effects of vitamin E supplementation on biochemical parameters in patients with T1DM and diabetic nephropathy and/or neuropathy.

At present, there are more and more studies on the antioxidant effect of serum vitamin E at home and abroad, but there are relatively few domestic studies on the relationship between serum vitamin E and insulin resistance in type 2 diabetes, especially the clinical research on the relationship between serum vitamin E and HOMA-IR in type 2 diabetes. Therefore, the results of this article will provide more evidence for clinical treatment. There are also some limitations in this study, including small sample size and cross-sectional control study, which may lead to bias. It is necessary to collect large sample data to verify the results of this study. In addition, a comparison of insulin resistance levels after vitamin E supplementation was not performed in this study. Recently, TyG and Tgy-BMI are also considered as the insulin resistance parameters, and further analysis is needed to investigate the association of vitamin E levels with other insulin resistance indices is warranted.⁴⁴

In conclusion, there is a risk correlation between serum vitamin E and insulin resistance in patients with type 2 diabetes. With the decrease of serum vitamin E level, the risk of insulin resistance in patients with type 2 diabetes increases gradually. However, the mechanism of vitamin E and insulin resistance is still unclear, and relevant prospective studies are needed to further prove it in the future.

Conclusion

Serum vitamin E levels are lower in T2DM patients than in healthy populations; Vitamin E is an independent influencing factor for HOMA-IR in T2DM patients. The risk of insulin resistance gradually increases in T2DM patients as serum vitamin E levels decrease. Vitamin E is a risk factor for insulin resistance at serum vitamin E levels below 10,575.23 ng/mL. At higher serum vitamin E levels than 10,575.23 ng/mL, vitamin E is a protective factor for insulin resistance.

Declaration and Terms

This study complies with the Declaration of Helsinki and the relevant laws and regulations.

Institutional Review Board Statement

Approved by the Medical Ethics Committee of Hebei General Hospital.

Data Sharing Statement

The data that support the findings of the study are available from the first author, upon reasonable request.

Informed Consent Statement

Consent was obtained from all people. In the population of hospitalization or physical examination, select the patients who meet the protocol admission criteria according to the protocol, introduce the content, risks and benefits of the clinical trial to the patients and their families, and invite the patients to participate in the study.

Disclosure

The authors report no conflicts of interest in this work.

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