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Research Article

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Effect of Vitamin D Deficiency on Ace2 And Inflammatory Factors in Patients with Type 2 Diabetes

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Abstract

Objective: *To analyze the levels and correlation of vitamin D, ACE2, ACE and inflammatory factors in patients with type 2 diabetes,To explore the effect of vitamin D deficiency on ACE2 and inflammatory factors and the mechanism of action on the occurrence and development of diabetes.*

Methods: *Non-diabetic control 87 cases and type 2 diabetes 96 cases,According to the level of serum 25-hydroxyvitamin D, 47 cases of non-diabetic vitamin D normal group and 40 cases of vitamin D deficiency group were divided into two groups.52 patients in the normal vitamin D group and 44 patients in the vitamin D deficient group were tested for ACE, ACE2, IL-6, TNF-A and other inflammatory indexes.The correlation and influencing factors of vitamin D and each index were analyzed.*

Results: *The levels of HOMA-IR, ACE, AngII, IL-6 and TNF-a in vitamin D deficient group were significantly higher than those in vitamin D normal group.ACE2 and IL-10 were significantly decreased ($P < 0.05$);Compared with non-diabetic vitamin D deficiency group, BMI, waist circumference, blood pressure, blood lipids, blood glucose, INS, HOMA-IR, ACE, AngII, IL-6 and TNF-A were significantly increased with the severity of vitamin D deficiency.Insulin resistance was more severe, ACE2 and IL-10 decreased significantly($P < 0.05$);Pearson correlation analysis showed that vitamin D in non-diabetic group was negatively correlated with AngII and IL-6, but positively correlated with IL-10 ($P < 0.05$ or $P < 0.01$).Vitamin D in diabetic group was positively correlated with ACE2 and IL-10, and negatively correlated with ACE, AngII, IL-6, TNF-A, HOMA-IR and HbA1c (all $P < 0.01$).Multiple linear regression analysis showed that IL-10 and AngII were the main influencing factors of vitamin D*

Foundation *Item: 2020 Government Funded Clinical Medical Talents Training Program (NO: 2020, 124) deficiency in the Non-Diabetic Group ($P < 0.05$).33.6% of the total variation of regression equation was explained.In diabetic group, ACE2, IL-6, TNF-A, IL-10 and HOMA-IR were the main influencing factors of vitamin D deficiency ($P < 0.05$), explaining 55.8% of the total variation of regression equation.*

Conclusion: *Vitamin D deficiency may change the improper regulation of ACE2 and ACE/AngII and the release of inflammatory factors, destroy the autoimmune state of the body, and participate in the occurrence and development of diabetes mellitus. The degree of vitamin D deficiency can aggravate insulin resistance by mediating RAS system and inflammatory factors, and increase the potential pathogenic effect of diabetes.ACE2, ACE/AngII and inflammatory factors can be used as markers of diabetes vitamin D deficiency.*

Keywords: Vitamin D; Diabetes; Angiotensin converting enzyme 2; Interleukin 6; Insulin resistance

Vitamin D (Vitamin D) is not only a Vitamin, but also an endocrine hormone, which is necessary for blood sugar to stimulate insulin secretion and maintain normal glucose tolerance under physiological conditions [1]. It has the functions of regulating immunity, inhibiting inflammatory response, protecting pancreatic β cell function and maintaining tissue sensitivity to insulin, etc., which is closely related to the incidence of diabetes [2]. ACE2 and ACE play a coordinated role in RAS system to maintain homeostasis.In pathological conditions, ACE/ Ang II can induce oxidative stress, protein glycoylation, inflammatory response, vasoconstriction and increased insulin resistance in diabetes mellitus.ACE2 antagonizes traditional RAS mainly through the ACE2/ ANG1-7 /Mas receptor axis to exert anti-inflammatory, anti-fibrosis and anti-proliferation effects [3].

Vitamin D is a negative endocrine RAS regulator that inhibits renin expression and production.It can induce ACE2 / ANG1-7 / MasR axis activity and inhibit renin and ACE/Ang II/AT1R axis, thus increasing the expression and concentration of ACE2, MasR and ANG1-7 with potential effects [4].Vitamin D deficiency is associated with impaired glucose tolerance, increased RAS expression, and reduced transcription of islet function-related genes [5]. There is considerable uncertainty about the underlying mechanism of diabetes caused by long-term hyperglycemia and other metabolic characteristics, and in-depth research on the etiology of diabetes has made inflammation a key pathophysiological mechanism [6]. Studies on the changes of vitamin D, ACE2 and inflammatory factors have positive significance for the regulatory mechanism of diabetes development, and there are few reports at home and abroad. This study compared the effects of different vitamin D levels on ACE2/ACE and inflammatory factors in diabetic and non-diabetic populations, and explored their interaction and correlation, providing new ideas for the diagnosis and treatment of diabetes.

Data and methods

Subjects According to the diagnostic criteria of Type 2 diabetes in China Guidelines for The Prevention and Treatment of Type 2 Diabetes (2020 Edition), fasting blood glucose ≥7.0mmol/L and postprandial blood glucose ≥11.1mmol/L.A total of 96 patients with type 2 diabetes mellitus (T2DM) who were hospitalized and outpatients in Hebei Provincial People's Hospital from July 2021 to November 2021 were divided into two groups according to serum 25-hydroxyvitamin D deficiency (n = 52 in the normal vitamin D group and n = 44 in the vitamin D deficiency group) [7]. And 87 cases of non-diabetic healthy control group (47 cases of normal vitamin D group, 40 cases of vitamin D deficiency group).The exclusion criteria for patients in type 2 diabetes group were neurological diseases, severe respiratory diseases, tumor radiotherapy and chemotherapy, pregnancy or lactation, severe mental diseases and infectious diseases, etc.Approved by the Ethics Committee of Hebei Provincial People's Hospital, informed consent and voluntary participation.

Research methods the general information of each group was recorded, including gender, age, height, weight, body mass index, waist circumference, blood pressure, blood glucose, blood lipid and other indicators. ACE2, ACE, IL-6, TNF-A and IL-10 were detected by ELISA, and Ang II was detected by chemiluminescence. Cholesterol (TC) and triglyceride (TG) levels were determined by GPO-POD method, blood glucose was determined by hexokinase method, insulin was detected by electrochemiluminescence method, homeostasis model assessment - insulin resistance index (HOMA-IR) reaction insulin resistance level, HOMA-IR= fasting blood glucose ×FINS/22.5, When the value is greater than 2.8, insulin resistance is determined.

Statistical method SPSS 21.0 software was used for statistical analysis.The measurement data were expressed by mean ± standard deviation (X ± S), and the normal distribution of variables in each group was tested. One-way anOVA was used for comparison between groups.Pearson correlation analysis was used for correlation analysis between variables, and multiple linear regression was used to analyze the relationship between dependent variables and independent variables. $P < 0.05$ was considered as statistically significant difference.

The results

Comparison of General Clinical Data in Each Group

Without diabetes or diabetes, vitamin D deficiency group more vitamin D normal waist circumference, blood fat, glycosylated hemoglobin, HOMA - a significant rise in IR, the difference was statistically significant ($P < 0.05$ or $P < 0.01$);With the decrease of vitamin D content, BMI, waist circumference, systolic blood pressure, blood lipid, hba1c and HOMA-IR were significantly different between diabetic vitamin D deficiency group and non-diabetic vitamin D deficiency group ($P < 0.05$ or $P < 0.01$). See table 1.

Table 1: Comparison of general clinical data in each group (X ± S)

	Without diabetes (Vitamin D normal group, n=47)	Without diabetes (Vitamin D deficiency group, n=40)	diabetes (N =52 in the normal vitamin D group)	diabetes (Vitamin D deficiency group, n=44)
Age (years)	60.6±9.52	60.45±9.2	61.88±11.08	63.93±9.53
BMI(kg/m2)	22.49±4.57	24.78±4.97	25.29±5.02	27.37±5.18 ^{aC}
Waist circumference (cm)	85.35±9.69	87.25±11.93 ^{a}	89.28±10.99	97.22±11.76 ^{bC}
Systolic blood pressure (mmHg)	127.61±14.37	129.08±13.35	131.78±13.73	143.04±14.56 ^{bC}
Diastolic blood pressure (mmHg)	78.92±8.89	79.05±10.28	80.29±10.94	81.03±10.37
TC(mmol/L)	4.71±0.77	5.39±0.92 ^{a}	5.42±0.98	5.99±1.15 ^{bC}
TG(mmol/L)	1.45±0.84	1.86±0.94 ^{a}	2.01±1.17	2.49±1.85 ^{bC}
LDL-C(mmol/L)	2.81±0.92	3.14±0.89 ^{a}	3.43±1.03	3.82±0.98 ^{bC}
HDL-C(mmol/L)	1.43±0.38	1.28±0.59 ^{a}	1.14±0.46	1.09±0.57 ^{bC}
HbA1c (%)	4.79±0.71	5.27±0.57^{a}	10.04±2.77	13.09±4.37 ^{bC}
FBG(mmol/L)	4.18±0.42	4.25±0.67	7.52±1.85	9.77±2.93 ^{bC}
FINS(uU/mL)	12.76±4.21	12.88±4.19	25.73±5.94	22.46±5.77^{bC}
HOMA-IR	2.35±0.69	2.73±0.73^{a}	7.15±1.52	9.81±3.19 ^{bC}
Vitamin D	51.11±12.29	25.91±5.96^{a}	41.05±9.81	18.69±5.95 ^{bC}

Note: Non-diabetic vitamin D deficiency was compared with normal, aP < 0.05; Diabetic vitamin D deficiency was compared with normal vitamin D deficiency, bP < 0.05; Compared with non-diabetic vitamin D deficiency, CP < 0.05;

Table 2: Comparison of ACE2, IL-6 and other indicators in each group (X ± S)

	Without diabetes (Vitamin D normal group, n=47)	Without diabetes (Vitamin D deficiency group, n=40)	diabetes (N =52 in the normal vitamin D group□	diabetes (Vitamin D deficiency group, n=44)
ACE2(ng/mL)	4.35±1.96	3.99±1.23	3.20±1.17	2.58±0.62^{bC}
ACE(ng/mL)	26.79±4.42	26.10±5.41	30.77±5.82	34.05 ±4.92^{bC}
AngII(pg/mL)	56.39 ±9.03	61.01 ±11.67^{a}	75.88± 14.66	85.67± 12.82^{bC}
IL-6(pg/mL)	7.67±1.66	8.86±1.83^{a}	10.68±2.8	12.82±4.37^{bC}
TNF-a(pg/mL)	943.12±194.44	1123.98±340.8^{a}	1372.96±450.76	1696.16±602.74^{bC}
IL-10(pg/mL)	367.68±113.81	340.23±82.52	256.16±109.3	202.64±58.43 ^{bC}

Note: Non-diabetic vitamin D deficiency was compared with normal, ^{a}P < 0.05; Diabetic vitamin D deficiency was compared with normal vitamin D deficiency, ^{b}P < 0.05; Compared with non-diabetic vitamin D deficiency, ^{C}P < 0.05;

Correlation analysis

Pearson correlation analysis showed that vitamin D was negatively correlated with AngII and IL-6 (R =-0.316, -0.222, P < 0.05 or P < 0.01), and positively correlated with IL-10 (R =0.461, P < 0.01). Vitamin D was positively correlated with ACE2 and IL-10 in diabetic group (r=0.532, 0.404, P < 0.01). They were negatively correlated with ACE, AngII, IL-6, TNF-A, HOMA-IR and HbA1c (R =-0.365, -0.385, -0.512, -318, -0.27, -0.48, all P < 0.01).

Project	ACE2	ACE	AngII	IL-6	TNF-a	IL-10	HOMA-IR	HbA1c
Non-diabetic group								
r	0.036	0.07	-0.316	-0.222	-0.206	0.461	-0.205	-0.176
p	0.740	0.518	0.003	0.038	0.056	0.000	0.057	0.103
Diabetes group								
r	0.532	-0.365	-0.385	-0.512	-0.318	0.404	-0.27	-0.48
p	0.000	0.000	0.000	0.000	0.002	0.000	0.008	0.000

Multiple linear regression analysis of influencing factors of vitamin D in non-diabetic and diabetic patients

Multiple linear regression analysis was performed with vitamin D as the dependent variable and related clinical indicators as independent variables. The results showed that IL-10 and AngII were the main influencing factors of vitamin D deficiency in the non-diabetic group ($P < 0.05$), explaining 33.6% of the total variation of the regression equation. In diabetic group, ACE2, IL-6, TNF-A, IL-10 and HOMA-IR were the main influencing factors of vitamin D deficiency ($P < 0.05$), explaining 55.8% of the total variation of regression equation. See table 4.

Table 4: Multiple linear regression analysis of factors affecting vitamin D in non-diabetic and diabetic groups

	B	SE	β	t	P	VIF	R	R2	Adjusted R2
Non-diabetic group	38.575	4.405		8.756	0.000		0.631	0.398	0.336
IL-10	.068	.016	.389	4.212	.000	1.105			
AngII	-.529	.157	-.314	-3.376	.001	1.123			
Diabetes group	55.895	9.671		5.779	.000		0.771	0.595	0.558
ACE2	4.505	1.042	.330	4.323	.000	1.253			
IL-6	-.885	.417	-.240	-2.125	.036	2.744			
TNF-a	-.005	.002	-.197	-2.749	.007	1.099			
IL-10	.032	.011	.214	2.965	.004	1.119			
HOMA-IR	-.805	.370	-.155	-2.177	.032	1.095			

Discussion

Abundant evidence supports a close association between vitamin D deficiency and T2DM [2,8], which is mediated by direct and indirect effects of vitamin D on insulin secretion, insulin sensitivity, insulin resistance and systemic inflammation [8].

In pancreatic β cells, vitamin D regulates calcium ion flow and intracellular calcium ion level, stimulating pancreatic β cells to promote insulin secretion through non-selective voltage channels [9].Calcium-dependent endopeptidase is produced, and the activation of calcium-dependent endopeptidase promotes the conversion of proinsulin to insulin, so vitamin D and calcium ions are essential for insulin exocytosis [10].Cell experiments showed that 1,25(OH)2 vitamin D combined with high glucose increased the insulin secretion of INS1E cells, and showed a difference with the increase of glucose concentration, and glucose stimulation of insulin secretion in INS1E β cells was associated with the type of vitamin D metabolite treatment [11].

In addition, vitamin D is an immune modulator that may affect inflammation, which can lead to diabetes. Vitamin D can improve the absolute T-regulated cell number and phenotype in diabetic patients, and vitamin D supplementation is beneficial to reduce hS-CRP and IL-6 in type 2 diabetic subjects [15]. Vitamin D can also regulate the insulin resistance pathway associated with diabetes and reduce the pathological conditions associated with insulin resistance, such as oxidative stress and inflammation [16]. Diabetes is a process of chronic inflammation accumulation, and inflammation is a bridge connecting obesity and insulin resistance [17]. Inflammatory factors and adipocytokines produced by adipose tissue can affect the insulin action process by regulating inflammatory response.

This experiment showed that the level of vitamin D in the diabetic group was much lower than that in the non-diabetic group. Both the non-diabetic and diabetic patients with vitamin D deficiency had severe insulin resistance and increased inflammation level, especially in the diabetic vitamin D deficiency group.In the non-diabetic stage, vitamin D deficiency triggers the body to turn on the RAS system, producing more hormones that narrow blood vessels and raise blood pressure, such as AngII.Ang II induces pancreatic β cell apoptosis and inhibits insulin signal transduction by regulating adipokines, and also inhibits GLUT4 expression and AMP kinase activity, leading to emerging diabetes and various diabetic complications [18]. The overactivated two functional axes of RAS system, ACE/ AngII and ACE2/A1-7, produce corresponding body effects.

In conclusion, vitamin D deficiency may change the improper regulation of ACE2 and ACE/AngII and the release of inflammatory factors, destroy the immune homeostasis of the body and participate in the occurrence and development of diabetes. ACE2 is expressed in different organs of human body, mainly in pancreatic islets and preferentially in insulin-producing β cells, and participates in activating RAS circulation in local tissues [19]. ACE2 can improve pancreatic microvascular endothelial function, regulate glucose homeostasis by regulating GAD67/GABA signal transduction in β cells, improve β cell function, and delay the development of diabetes [20].

Studies have shown that ACE2 deficiency in adipocytes increases the systolic blood pressure of obese female C57BL/6 mice [21], and TG regulates ACE2 expression by affecting the methylation level of ACE2 gene through Mthfd1 [22]. This experiment also showed that the blood pressure and blood lipid of diabetic patients were higher than that of normal group, and ACE2 expression was lower.

Study found that vitamin D can increase the angiotensin-converting enzyme 2 (ACE2) and the ratio of the ACE, thereby increasing

the hydrolysis angiotensin II and reduced subsequent inflammatory cytokine response to pathogens and lung injury [23]. For DN patients, calcitriol combined with valsartan treatment can effectively inhibit renal ACE expression, reduce Ang ii and renin levels, improve proteinuria symptoms, and improve renal function. Correlation analysis in this study showed that vitamin D in the non-diabetic group was negatively correlated with AngII and IL-6, and positively correlated with IL-10, indicating that vitamin D deficiency in the non-diabetic stage can cause stress response and release pro-inflammatory factors and inhibitory anti-inflammatory factors.Therefore, vitamin D supplementation in non-diabetic stage can delay the occurrence and development of diabetes.In the diabetic group, vitamin D was positively correlated with ACE2 and IL-10, and negatively correlated with ACE, AngII, IL-6, TNF-A, HOMA-IR and HbA1c, indicating that with the increase of vitamin D deficiency, the progressive decrease of ACE2 expression was caused. ACE2 reduces β cell apoptosis, which is the main mechanism leading to pancreatic β cell failure in type 2 diabetes patients [24, 25].

In conclusion, vitamin D deficiency can aggravate insulin resistance by mediating RAS system and inflammatory factors, and increase the potential pathogenic effect of diabetes.

Multiple linear regression analysis showed that IL-10 and AngII were the main influencing factors of vitamin D deficiency in the non-diabetic group, explaining 33.6% of the total variation of the regression equation, suggesting that the active function of pancreatic RAS and the reduction of anti-inflammatory factors affected the level of vitamin D in the non-diabetic group, which served as a warning.Vitamin D supplementation, especially at medium and high doses, can significantly reduce the risk of T2DM and improve other metabolic parameters related to blood glucose control, such as glycated hemoglobin and insulin resistance [26, 27]. In the diabetes group, ACE2, IL-6, TNF-A, IL-10 and HOMA-IR were the main influencing factors of vitamin D deficiency, explaining 55.8% of the total variation of the regression equation. It suggests that with the aggravation of vitamin D deficiency and the loss of ACE2, the potential infection accelerates, and the body is in the stress state of high expression of inflammation, which is not enough to fight the invasion of inflammatory factors and the stress response of ACE/ Ang ii to the organs of the whole body, and may cause the “inflammatory factor storm”.

In conclusion, ACE2, ACE/AngII and inflammatory factors can be used as biomarkers of diabetes vitamin D deficiency.

There are Shortcomings in this Study: there are new patients and patients taking medicine in the diabetic population, which may cause the influence bias of drugs.

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