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Original Article

Vitamin D deficiency enhances insulin resistance by promoting inflammation in type 2 diabetes

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Abstract: Objective: This study was aimed to analyze the level of serum 25(OH)D in patients with type 2 diabetes (T2DM), and explore the relationship between serum 25(OH)D and insulin resistance. Methods: 60 health people and 106 patients with T2DM were measured the level of serum 25(OH)D, fasting blood glucose, insulin, TNF-α, IL-6, IL-8, and IL-1β, etc. We established a rat model of T2DM and vitamin D (VD) deficiency, and studied the effects of VD deficiency on homeostasis model assessment insulin resistance (HOMA-IR) and pancreatic inflammation. Results: The level of serum 25(OH)D in patients with T2DM was significantly lower than that in health people, and HOMA-IR decreased with the increasing of the serum 25(OH)D level. Pearson correlation analysis showed that the serum 25(OH)D level in patients with T2DM had a negative correlation with HOMA-IR (r=-0.750, P<0.001), TNF-α (r=-0.705, P<0.001), IL-1β (r=-0.661, P<0.001), IL-8 (r=-0.645, P<0.001), and IL-6 (r=-0.609, P<0.001). In animal experiment, Vitamin D deficiency enhanced HOMA-IR in rats with T2DM and reversed it by supplementing VD. Vitamin D deficiency could increase the inflammatory response by up-regulating p-p65/RelB in the pancreas tissue. Conclusion: Serum 25(OH)D was elevated and Vitamin D deficiency enhanced insulin resistance by promoting inflammation via NF-kB pathway in patients with T2DM.

Keywords: Vitamin D, Type 2 diabetes, inflammation, NF-kB pathway

Introduction

The international diabetes federation (IDF) predicted that global diabetes patients are expected to exceed 435 million in 2030, with more than 90% of patients having type 2 diabetes mellitus (T2DM) [1]. In patients with T2DM, the ability to produce insulin is not completely lost, even excessive in some patients, but the effect of insulin is poor, so insulin is a relatively lacking in these patients [2, 3]. The pathogenesis of T2DM is complex and is caused by a combination of factors. Previous studies have confirmed that the onset of type 2 diabetes is associated with insulin resistance caused by decreased insulin sensitivity [4]. Early studies pointed out [5] that inflammation affected insulin resistance. In recent years, a large number of studies have found [6] that inflammation was one of the important factors leading to IR, and inflammatory factors such as interleukins, tumor necrosis factor, MCP-1, CRP, NF-kB, etc. could affect insulin sensitivity and islet beta cell function through blood or paracrine, which in turn causes IR.

Vitamin D is a ring-opening steroidal compound that plays an important role in regulating calcium and phosphorus metabolism and maintaining bone health. In recent years, a large number of studies have shown that Vitamin D (VD) plays a more extensive role in the body, such as regulating inflammation and immune response, affecting cognitive function, and providing protection against metabolic syndrome, cardiovascular disease, etc [7]. In addition, lots of studies have confirmed that the development of T2DM is closely related to vitamin D [8, 9], and studies have found VD receptors on insulin beta cells, and confirmed that vitamins were involved in the body's glucose metabolism process, while vitamin D deficiency could increase the risk of type 2 diabetes [10, 11].

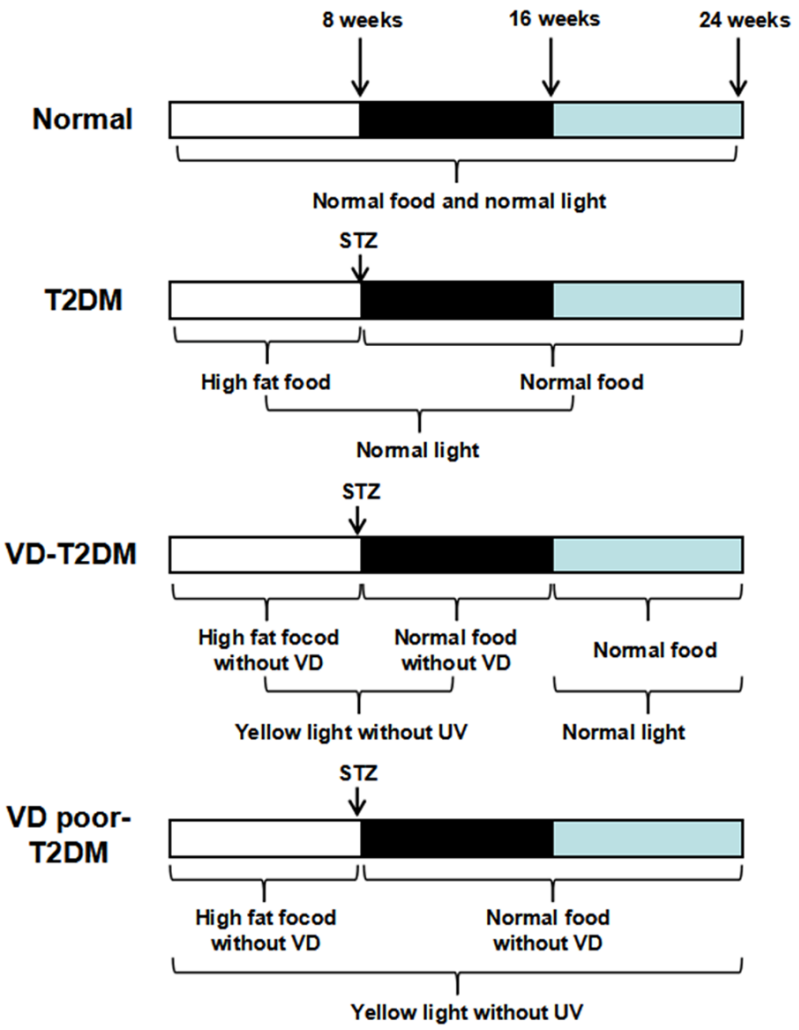

Figure 1. Grouping and processing of experimental rats.

However, the relationship between vitamin D, inflammation and insulin resistance in patients with T2DM was still unclear. In this study, we found that serum 25(OH)D was declined, and had a negative correlation with HOMA-IR, inflammatory factors, and animal experiments have shown that vitamin D deficiency enhances insulin resistance in rats with T2DM by promoting inflammation through NF-kB pathway.

Materials and methods

Patients

A total of 106 patients with T2DM in Shijiazhuang First Hospital were included in this study, 59 males and 47 females, ages from 35 years to 68 years, average age was 50.12 ± 13.05 years. Inclusion criteria: (1) the duration of type 2 diabetes is less than 10 years; (2) serum iPTH is 15.0-65.0 pg/mL, blood calcium <2.45 mmol/L; (3) normal liver function, serum creatinine, urea nitrogen, and electrolyte; (4) no use of insulin, insulin analogues, insulin sensitizers (thiazolidinediones), vitamin D preparations and active vitamin D; (5) no recent history of taking calcium, estrogen and glucocorticoids. Exclusion criteria: (1) patients without type 2 diabetes; (2) diabetic ketosis, diabetic ketoacidosis, hyperosmolar state of diabetes; (3) blood phosphorus >1.60 mmol/L, iPTH >65.00 pg/mL or <15.00 pg/mL; (4) acute or chronic infections (tuberculosis, HIV or HCV, etc), cancer, pregnancy and lactation women.

60 healthy people undergoing physical examination were included as normal control. All people in this study signed an informed consent form. The study methodologies met the standard set by the Declaration of Helsinki and were approved by Shijiazhuang First Hospital.

ELISA

For human, peripheral blood (5-10 ml) was collected with EDTA-containing tubes, then centrifuge (1000 × g) for ten minutes (5810R, Eppendorf AG, Germany) to collect serum. The following kits were used: human Vitamin D Assay ELISA Kit (AC-57F1, IDS, UK) for detection of human or rat serum VD content, IL-10 Kit (50R-E.1095H, BIOVALUE, AUS) for human IL-10; IL-8 Kit (H-EL-IL-8, ZYscience, USA) for human IL-8, IL-6 Kit (H-EL-IL-6, ZYscience, USA) for human IL-6, and TNF-α Kit (50R-E.1693H, BIOVALUE, AUS) for human TNF-α.

Animal experiment

2-3 weeks old SD rats were used in this study, and they were divided into 4 groups (10 rats per group) and treated as in **Figure 1**. Streptozotocin (STZ) (s0130, sigma, CA, USA) was adminis-

tered by intraperitoneal injection at a dose of 30 mg/kg. Rats were fasted for 14-16 hours before measuring fasting blood glucose and insulin, and Rat Insulin (INS) ELISA Kit (ZY-INS-Ra, Shanghai Zeye Biotechnology Co., Ltd., Shang Hai, China) was used to measure fasting insulin (FINS) while blood glucose meter (Sinocare, Chang Sha, China) was used to measure FBG. HOMA-IR = [FINS (mIU/L) × FBG (mmol/L)]/22.5.

Real-time fluorescence quantitative PCR

Levels of rats mRNA were measured as described previously by real-time fluorescence quantitative PCR (RT-qPCR) [12, 13]. GAPDH mRNA transcription was used for internal loading control. PCR primer: TNF-α-F: 5'-CTGAACTTCGGGGTGATCGG-3', TNF-α-R: 5'-GGCTTGTCACTCGAATTTTGAGA-3'; IL-6-F: 5'-TCTATACCACTTCACAAGTCGGA-3', IL-6-R: 5'-GAATTGCCATTGCACAACTCTTT-3'; IL-8-F: 5'-TCGAGACCATTTACTGCAACAG-3', IL-8-R: 5'-CATTGCCGGTGGAAATTCCTT-3'; IL-1β-F: 5'-GAAATGCCACCTTTTGACAGTG-3', IL-1β-R: 5'-TGGATGCTCTCATCAGGACAG-3'.

Western blot

Levels of rat proteins were measured as described previously by western blot [12, 13]. GAPDH protein transcription was used for internal loading control. Antibody: anti-NF-kB p65 (phospho S536) antibody (1:2000, ab86299, abcam, UK), anti-RelB antibody [EPR7076]-C-terminal (1:2000, ab180127, abcam, UK).

Statistical analysis

Data was presented as mean ± standard deviation and analyzed by SPSS 25.0. Student's t-test was used to compare differences between two groups, and one-way ANOVA with Duncan's post-hoc test was used for comparing multiple groups. Pearson's correlation coefficient was used to analyze the correlation between two factors. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Serum 25(OH)D was declined in patients with T2DM

Total of 60 health people and 106 T2DM patients were measured the serum 25(OH)D. As showed in **Figure 2A**, the serum of 25(OH)D in 106 T2DM patients was significantly higher than that in health people. Mover, we divided 106 patients with T2DM into three groups based on serum 25(OH)D, i.e. serum 25(OH)D ≤20 ng/mL (Vitamin D deficiency group n=50), 20-30 ng/mL and ≥30 ng/mL (n=24). And then we calculated HOMA-IR by detecting fasting blood glucose and serum insulin levels in T2DM patients, and found that HOMA-IR decreased with increasing serum 25(OH) levels (**Figure 2B**). Pearson correlation analysis showed that there was a negative correlation ($r=-0.750$, $P<0.001$) between serum 25(OH)D and HOMA-IR in T2DM patients (**Figure 2C**). These results indicated that serum 25(OH)D might be involved in insulin resistance in T2DM patients.

Correlation between serum 25(OH)D and inflammatory factor

Previous studies have shown that chronic inflammation causes insulin resistance by impairing normal lipid distribution, adipose tissue function, mitochondrial function, and endoplasmic reticulum stress [14, 15]. Therefore, we also tested the inflammatory factor in T2DM patients, and we analyzed the relationship between inflammatory factors and serum 25(OH)D, and found that (**Figure 3**) the level of serum 25(OH)D in T2DM patients had a negative correlation with serum TNF-α ($r=-0.705$, $P<0.001$), IL-1β ($r=-0.661$, $P<0.001$), IL-8 ($r=-0.645$, $P<0.001$) and IL-6 ($r=-0.609$, $P<0.001$). These results suggested that serum 25(OH)D might be involved in insulin resistance via inflammation in T2DM patients.

VD deficiency exacerbated insulin resistance in T2DM rats

We established a T2DM rat model by feeding high fat diet and injecting STZ, and establishing a VD-deficient rat model by feeding food without VD and yellow light without UV lamp. As showed in **Figure 4A**, the levels of serum 25(OH)D in normal group and T2DM group were stable during the 24 weeks of the experiment, while the levels of serum 25(OH)D in VD-T2DM group and VD poor-T2DM group had been falling during 0-16 week, However, after giving normal food and light, the level of serum 25(OH)D in VD-T2DM group had been raised. We also measured the level of FBG (**Figure 4B**) and FINS (**Figure 3C**), and calculated HOMA-IR (**Figure**

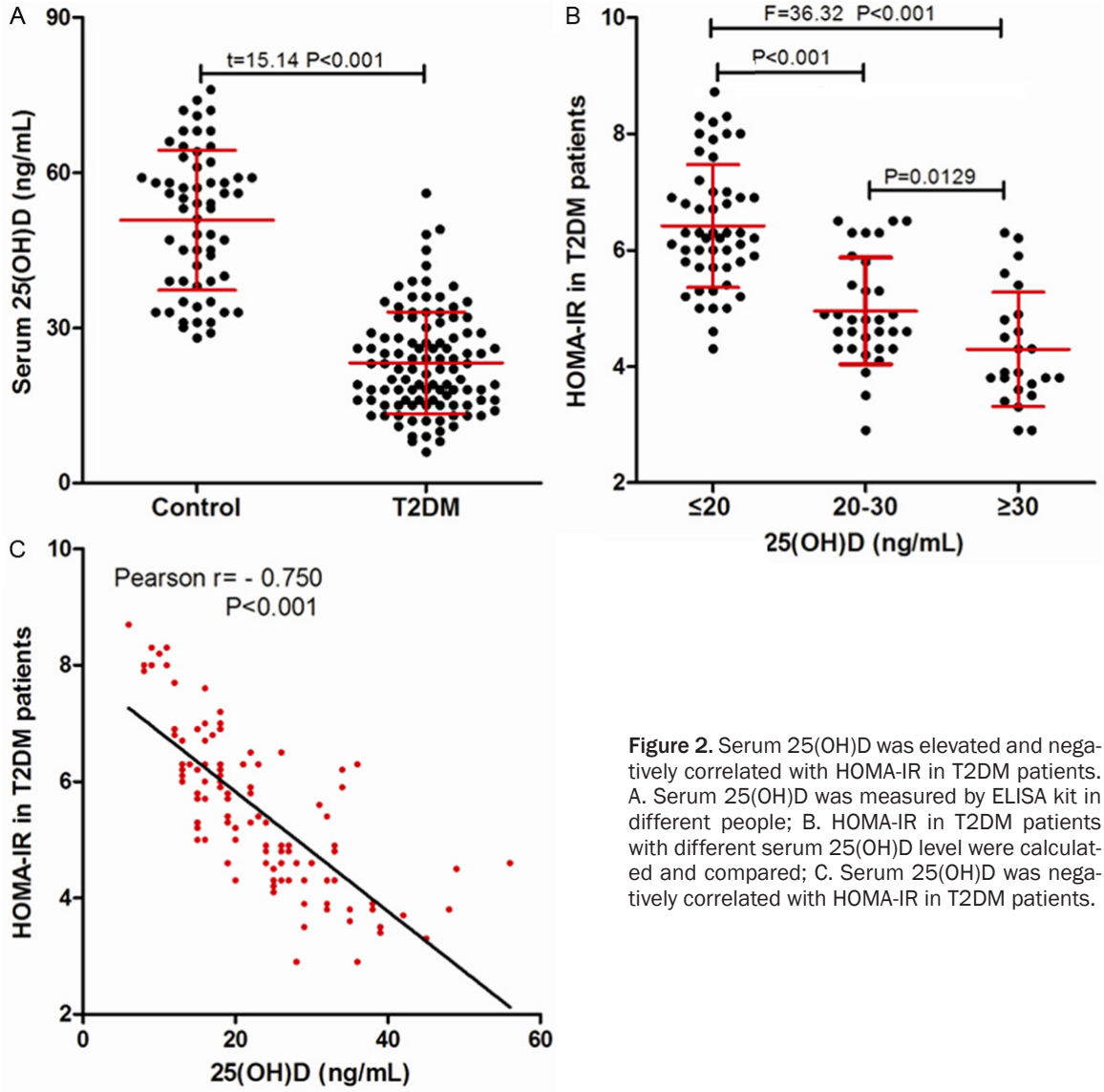

Figure 2. Serum 25(OH)D was elevated and negatively correlated with HOMA-IR in T2DM patients. A. Serum 25(OH)D was measured by ELISA kit in different people; B. HOMA-IR in T2DM patients with different serum 25(OH)D level were calculated and compared; C. Serum 25(OH)D was negatively correlated with HOMA-IR in T2DM patients.

4C). We found that the HOMA-IR of rats in T2DM group, VD-T2DM group and VD poor-T2DM group had been rising during 0-16 week, and the HOMA-IR of rats in VD-T2DM group and VD poor-T2DM group were significantly higher than that in T2DM group. However, after giving normal food and light, the HOMA-IR of rats in VD-T2DM group had been decreased. It suggested that VD deficiency exacerbated insulin resistance in T2DM rats, and VD supplementation could reverse it.

VD deficiency promoted inflammation via NF-kB pathway in pancreas of T2DM rats

We sacrificed all rats at 24 weeks and obtained their pancreatic tissue, and detected the expression of mRNA by RT-qPCR and the expression of protein by western blot. As showed in **Figure 5A**, the expression of TNF-α, IL-1β, IL-8 and IL-6 in pancreas of rats in VD poor-T2DM group were highest, and that in VD-T2DM group were significantly higher than that in T2DM group. Moreover, we also detected the expression of key protein in NF-kB pathway, and found that that VD deficiency increased/RelB (**Figure 5B**, **5C**).

Discussion

More and more evidence show that in addition to the traditional risk factors, some newly discovered factors are also closely related to T2DM, such as VD deficiency and hyperhomo-

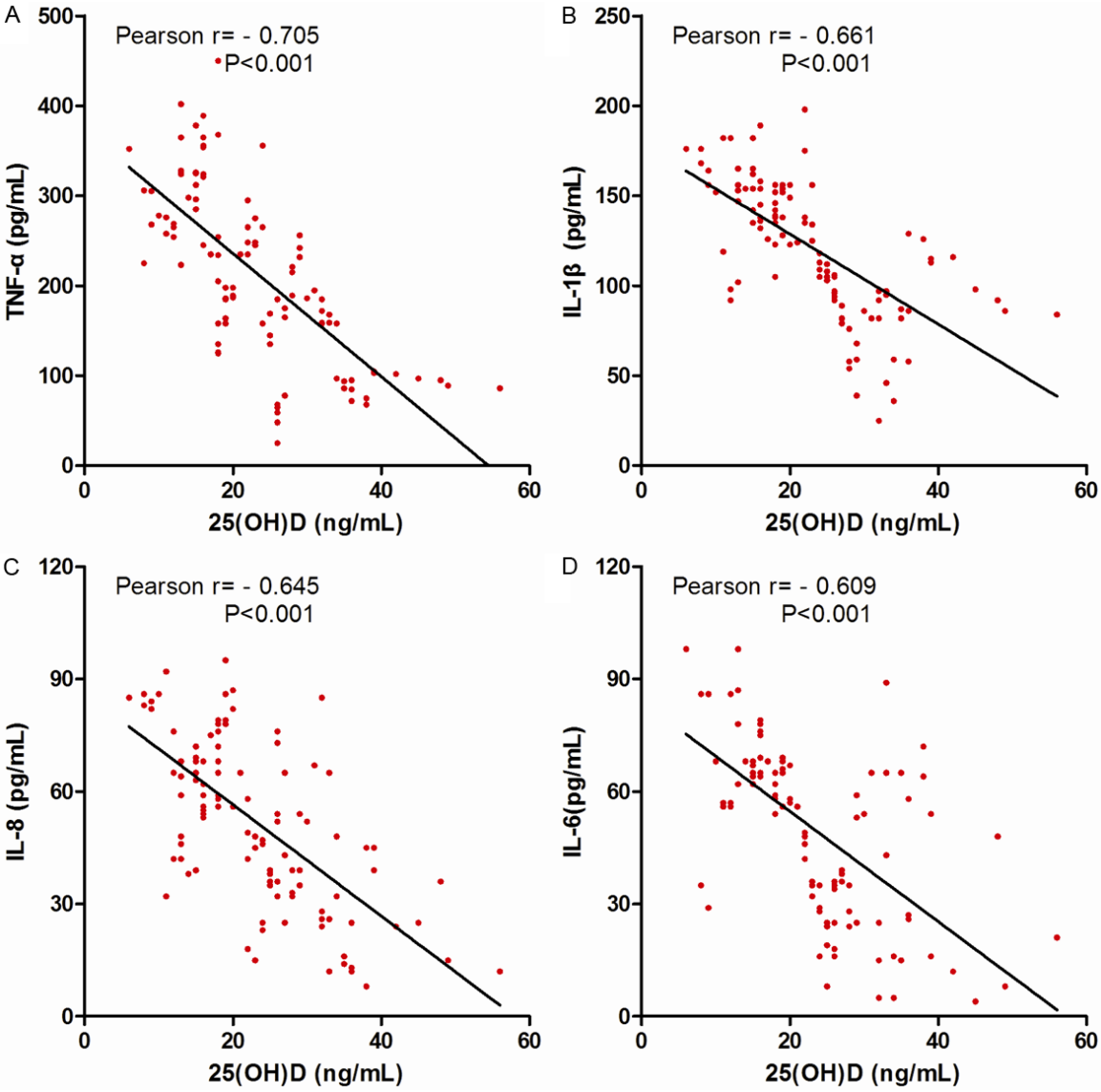

Figure 3. Serum 25(OH)D was positively associated with inflammatory factors in T2DM patients. (A-D) Serum 25(OH)D was positively associated with TNF-α (A), IL-1β (B), IL-8 (C) and IL-6 (D).

cysteinemia. The synthesis in the skin is the main source of physiological conditions [16, 17]. Recent studies have found that VD is essential for human health such as: lower the blood pressure [18, 19], increase insulin secretion [20], improve insulin resistance [21], regulate tissue cell differentiation and proliferation process, and has anti-inflammatory, anti-atherosclerosis and other effects [22].

In this study, we found that the level of serum 25(OH)D in patients with T2DM was significantly lower than that in health people, and had a negative correlation with HOMA-IR, TNF-α, IL-1β, IL-6 and IL-8. On the one hand, although we do not know which occurs first between insulin resistance and inflammatory response in patients with type 2 diabetes, it is clear that inflammation is the causative agent of insulin resistance [23]. On the other hand, studies have shown that VD deficiency can enhance vascular inflammatory responses due to the fact that VD can promote the secretion of anti-inflammatory cytokines, inhibit the secretion of inflammatory cytokines, and inhibit inflammation [24, 25].

These above researches are only the final results and we can not know the dynamic relationship between serum 25(OH)D and insulin

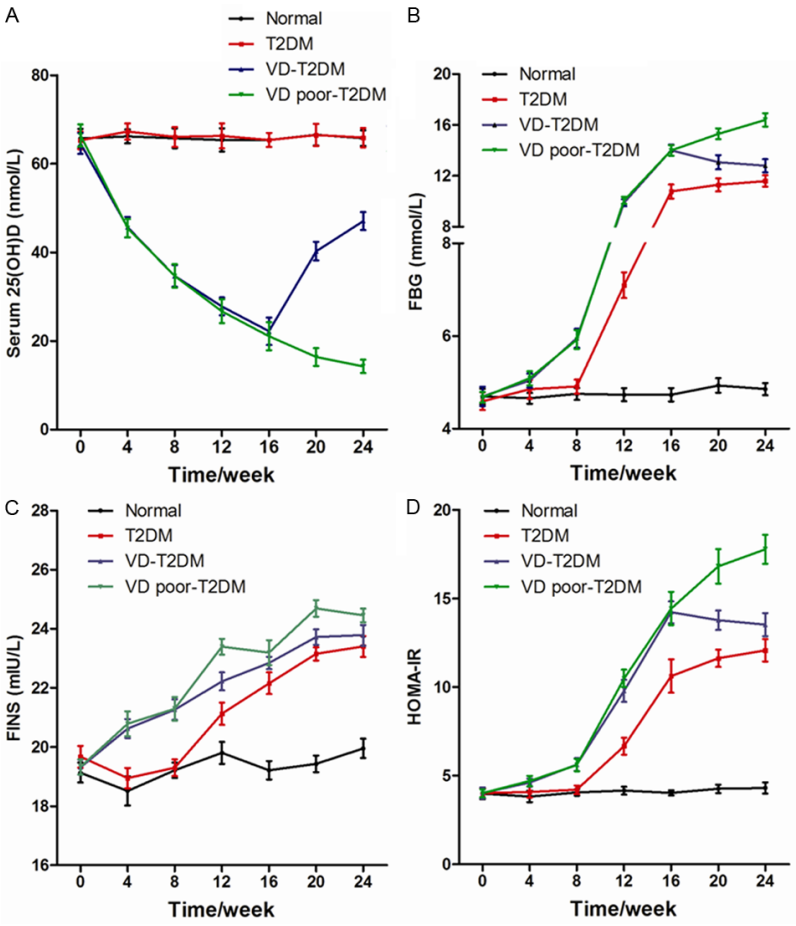

Figure 4. Dynamic changes of serum 25(OH)D and HOMA-IR in rats. (A-D) Serum 25(OH)D (A), FBG (B), FINS (C) and calculated HOMA-IR (D) in different groups at different time.

resistance, and can not confirm the relationship between serum 25(OH)D and inflammation. Therefore, we designed animal experiments. In animal experiments, we found that vitamin D deficiency enhanced insulin resistance in rats with T2DM by promoting inflammation through enhanced proportion of p-p65/RelB. p65 and RelB protein were key molecules in the NF-kB signaling pathway. The p65 protein is phosphorylated to form p-p65, which indicates that the NF-kB pathway is activated to play a pro-inflammatory role, while RelB plays a anti-inflammatory role in NF-kB pathway [26, 27]. Activation of the NF-kB signaling pathway can participate in the regulation of a large number of key physiological processes and regulate lots of downstream genes, such as TNF-α, IL-1β and IL-6. NF-kB can regulate the transcriptional expression of cellular genes in both directions, and then participate in the occurrence and development of a series of diseases by controlling the expression of related genes such as autoimmune responses, inflammatory responses, and apoptosis.

Moreover, more and more studies have confirmed that NF-kB signaling pathway plays an important role in regulating insulin resistance [28, 29]. Insulin is secreted by islet β cells, and the main role of insulin is to regulate glucose metabolism, so β cell damage can cause insulin secretion disorders leading to disorders of glucose metabolism. Studies have found that NF-kB pathway causes islet beta cell volume reduction, insulin secretion disorder, and insulin sensitivity decrease by regulating amylin secretion and islet amyloid deposition, and then regulating insulin resistance [30, 31]. In addition, the increased activity of NF-kB caused an increase in the expression of downstream cytokines and chemokines, leading to leukocytosis of islets and direct damage to β cells [32].

All in all, NF-kB signaling pathway is not only closely related to inflammation, but also affects insulin resistance in many ways. Firstly, NF-kB can cause changes in beta cell volume and function, and interfere with insulin secretion [30, 31]. Secondly, NF-kB can affect insulin signaling pathway through key molecules such as IRS, AKT, and PI3K [33, 34]. And more importantly, NF-kB not only exerts effects on peripheral insulin-sensitive organs such as liver [35, 36], skeletal muscle [37], and adipose tissue [38], but also affects the maintenance of energy and blood sugar in the central nervous system, especially the hypothalamus [39].

In this study, we found that vitamin D deficiency enhanced the expression of RelB and p-p65 protein. Increased expression of p-p65 indi-

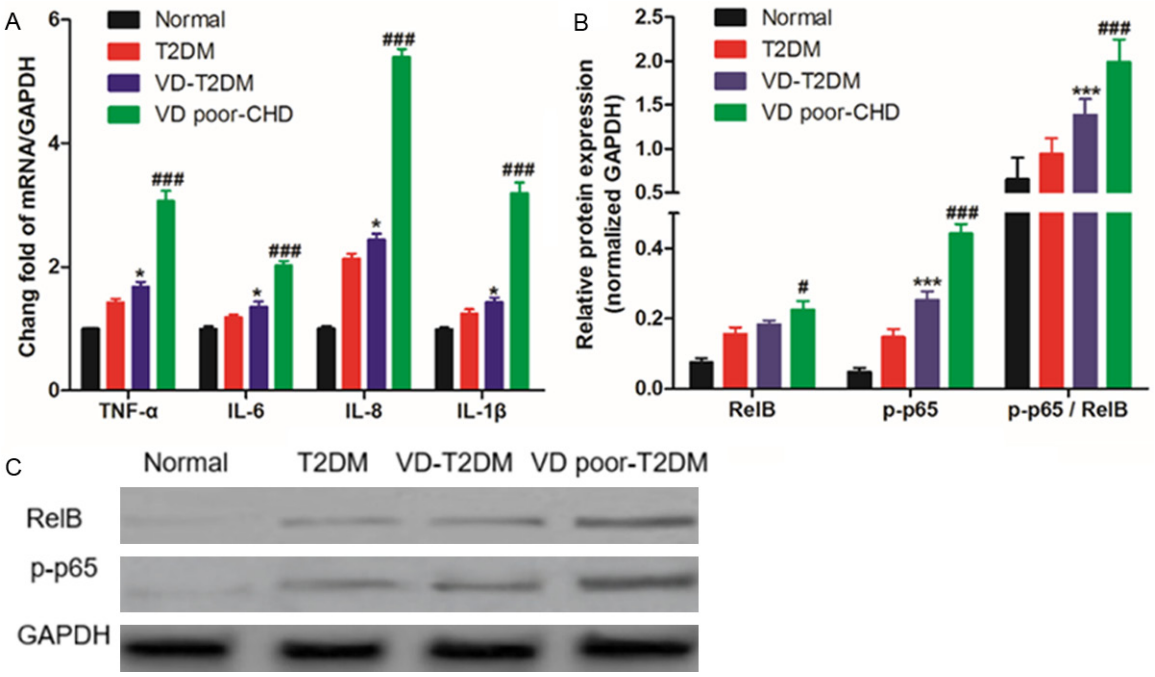

Figure 5. Expression of pancreatic inflammatory factor and NF-kB pathway. (A) The relative expression of TNF-α, IL-1β, IL-8 and IL-6 mRNA was detected by RT-qPCR in pancreatic tissues of rats; (B, C) The relative expression of RelB and p-p65 protein was detected by western blot in pancreatic tissues of rats, and typical strip display (C). *P<0.05 and ***P<0.001 vs T2DM group; #P<0.05 and ###P<0.001 vs VD-T2DM.

cates that the NF-kB signaling pathway is activated, and elevated expression of RelB is considered to be the body's self-protection effect. More importantly, we found that vitamin D deficiency caused the proportion of p-p65/RelB to increase which indicated that the NF-kB signaling pathway shifts to pro-inflammatory. Of course, the expression of TNF-α, IL-1β, IL-8 and IL-6 mRNA confirmed it. All in all, animal experiments showed that vitamin D deficiency enhances insulin resistance in rats with T2DM by promoting inflammation through NF-kB pathway.

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Disclosure of conflict of interest

None.

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