Association between Serum Vitamin D Level and Glycemic and Inflammatory Markers in Non-obese Patients with Type 2 Diabetes

Fatemeh Haidari1, PhD; Mehrnoosh Zakerkish2, DMD; Majid Karandish3, PhD; Azadeh Saki3, PhD; Sakineh Pooraziz4, MS

1Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; 2Health Research Institute, Diabetes Research Center, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; 3Department of Biostatistics, Faculty of Medical Science, Ahvaz Jundishapur University of Medical sciences, Ahvaz, Iran

Correspondence: Sakineh Pooraziz, MS: Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
Tel: +98 912 7588606
Fax: +98 61 33738253
Email: s.pooraziz@yahoo.com
Received: 11 January 2015
Revised: 25 April 2015
Accepted: 14 June 2015

Abstract

Background: Low serum 25-hydroxy vitamin D (25(OH)D) has been shown to correlate with an increased risk of type 2 diabetes mellitus (T2DM). The objective of this study was to investigate the association between serum 25(OH)D and glycemic and inflammatory markers in non-obese patients with T2DM.

Methods: Eighty-four non-obese patients with T2DM were recruited in this cross-sectional study. Demographic, anthropometric, and dietary information was obtained from all the participants. The serum concentrations of glucose, HbA1C, insulin, 25(OH)D, and inflammatory markers including tumor necrosis factor-alpha (TNF-α) and high sensitive C-reactive protein (hs-CRP) were measured. A homeostatic model of insulin resistance (HOMA-IR) was also evaluated.

Results: The mean serum concentration of 25(OH)D was 11.01±5.55 ng/mL. Severe deficiency, deficiency, and insufficiency of vitamin D were detected in 60.71%, 35.72%, and 3.57% of the participants, respectively. The results showed that those in the lowest group of serum 25(OH)D had significantly higher TNF-α than did those in the highest group (P=0.026). Although the association between serum 25(OH)D and fasting blood sugar and TNF-α was statistically significant (P=0.049 and P=0.044, respectively), the other glycemic markers and hs-CRP did not have any significant relationships with 25(OH)D.

Conclusion: According to the high prevalence of vitamin D deficiency in the diabetic patients and the inverse relationship between serum 25(OH)D and fasting blood sugar and TNF-α in this study, vitamin D status may be a determining factor of systemic inflammation in patients with T2DM. Further studies with larger sample sizes are suggested in this regard.

Please cite this article as: Haidari F, Zakerkish M, Karandish M, Saki A, Pooraziz S. Association between Serum Vitamin D Level and Glycemic and Inflammatory Markers in Non-Obese Patients with Type 2 Diabetes. Iran J Med Sci 2016;41(5):367-373.

Keywords • Diabetes mellitus • Type 2 • Inflammatory factors • Obesity • Vitamin D

Introduction

Type 2 diabetes mellitus (T2DM) is a major metabolic disorder that has become increasingly prevalent.1,2 The number of people suffering from diabetes is expected to become more than double by 2030 from 171 million to an astonishing 366 million people worldwide, with 90% of them suffering from T2DM.3 The pathogenesis of T2DM remains unknown since there are many malfunctioning mechanisms that occur simultaneously and
can lead to the development of the disease. Besides the genetic factors that predispose people to developing T2DM, there are also many environmental factors contributing significantly to its development. These factors include physical inactivity, poor nutrition (habits), and obesity. Nevertheless, growing evidence indicates that vitamin D deficiency (as measured by serum 25-hydroxy vitamin-D3 concentration) may also result in the pathogenesis of T2DM. Vitamin D deficiency occurs when individuals do not have a proper dietary intake or are exposed to ultraviolet B (UVB, 290–320 nm). Vitamin D and its metabolites may be important in preventing T2DM by increasing insulin production and secretion and improving overall β-cell function. Moreover, one of the hallmarks of T2DM is low-grade inflammation, which can result from a rise in circulating cytokines. High amounts of circulating inflammatory cytokines such as tumor necrosis factor-alpha (TNF–α) and interleukin 6 (IL-6) contribute significantly to insulin resistance in muscle and adipose tissues. It has been suggested that vitamin D3 metabolites such as 1,25 (OH)2D3 cause an increase in insulin sensitivity by increasing insulin receptor gene expression and reducing inflammatory cytokines. Furthermore, 1,25 (OH)2D3 is believed to be vital for insulin exocytosis by increasing the expression of calbindin-D28K in β-cells. Moreover, calbindin-D28K plays a protective role by decreasing inflammatory cytokine-induced β-cell apoptosis.

The rapid growth of obesity in recent years has been responsible for the rise in T2DM prevalence. Also, obesity is related to vitamin D deficiency through different mechanisms, including less exposure to sunlight due to lower exercise and mobility and trapping in adipose tissue because of its lipophilic structure. However, as obesity itself is a low-grade inflammation condition and may affect the circulating levels of inflammatory factors, in the present study only non-obese patients with T2DM were studied to control this confounding factor. Additionally, it was hypothesized that vitamin D status per se, independent of obesity, is a contributing factor in T2DM development.

To examine this hypothesis, we conducted this study on non-obese patients with clinically diagnosed T2DM in Ahvaz, Iran, to determine vitamin D status in subjects and to determine the relationship between circulating 25(OH)D and inflammatory and glycemic biomarkers.

Patients and Methods

Participants
This cross-sectional study was performed during winter 2013 on 84 non-obese (body mass index [BMI]=18.5–29.9)(patients with T2DM randomly selected from patients attending the Diabetes Clinic of Golestan Hospital in Ahvaz, Iran. All the participants completed a face-to-face administered questionnaire encompassing personal and family medical history, sociodemographic data, history of medications, history of chronic illnesses including diabetes and heart disease, exercise habits, duration of direct sun exposure in their outdoor activities, and history of sun protection use. Additionally, an 80-question, self-administered, semiquantitative food frequency questionnaire was utilized as a validated tool to assess the participants’ habitual dietary intake. Patients with acute or chronic diseases other than T2DM or supplementation of oral calcium plus vitamin D were excluded from this study. All the participants provided written informed consent. Ethics approval for this study was obtained from Ahvaz Jundishapur University of Medical Sciences, Iran (ETH-640).

Anthropometry Assessment
Weight was measured with light clothes and without shoes to the nearest 0.1 kg using a digital scale (Seca GmbH, Hamburg, Germany), and height was measured without shoes using a digital stadiometer (Heightronic 235; Measurement Concepts, Snoqualmie, WA). BMI was calculated using the equation BMI=weight (kg)/height (m)2. Hip circumference and waist circumference were both measured using a measuring tape to the nearest 0.1 cm. Waist circumference was determined at the midpoint between the lowest rib and iliac crest while the subject was in a standing position and after expiration. The percentage of body fat was evaluated using a bioelectrical impedance analysis (BIA) system (Quad Scan 4000, U.K.).

Laboratory Assessment
Blood samples were obtained from the participants, who were fasting. Vitamin D3 levels were analyzed using a 25-OH-vitamin D ELISA Kit (Diagnostika, GmbH, Hamburg, Germany). The intra-assay and inter-assay coefficients of variation for 25(OH)D were 4.9% and 7.8%, respectively. TNF–α and high sensitive C-reactive protein (hs-CRP) were measured using an enzyme-linked immunosorbent assay method and with commercial reagents (Orgenium Laboratories, Finland for TNF–α and Labor
Diagnostika Nord for hs-CRP) according to the manufacturer’s specifications. Glycosylated hemoglobin (HbA1C %) was measured in whole blood with NycoCard READER II using a NycoCard kit (Norway). Serum insulin levels were also determined according to the ELISA method using a commercial kit (DiaPlus, U.S.A.). The assay sensitivity was found to be 0.5 µU/mL. Insulin resistance was evaluated by homeostasis model assessment of insulin resistance (HOMA-IR) using the following equation:¹⁵

\[ \text{HOMA-IR} = \frac{\text{Fasting plasma glucose} (\text{mmol/L}) \times \text{Serum insulin} (\mu\text{U/mL})}{22.5}. \]

### Statistical Analysis

The descriptive characteristics of the participants are expressed as means±SD for the continuous variables with a normal distribution and as percentages for the categorical variables. Comparison of groups with different vitamin D statuses was made using the one-way ANOVA analysis (for the continuous variables with a normal distribution) or rank transformation test (for the categorical and continuous variables with a skewed distribution). Multiple linear regression was performed in the total sample to examine the association between 25(OH)D (dependent variable) and the following clinical, anthropometric, and metabolic variables (independent variables): age, sex, BMI, waist circumference, fasting blood glucose, fasting blood insulin, HOMA-IR, HbA1C, body fat, TNF-α, and hs-CRP. All the statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) (version 18; SPSS Inc., Chicago, IL). P<0.05 were considered statistically significant.

### Results

In total, 84 patients at 51.79±9.01 years of age were included in the study. The study population comprised 45 females and 39 males with T2DM. The anthropometric and biochemical characteristics of the participants are summarized in table 1. The mean serum concentration of 25(OH)D was 11.01±5.55 ng/mL. According to the results, the levels of HbA1C and hs-CRP were significantly higher in the female patients than in the male patients (P=0.032 and P=0.027, respectively). The serum concentration of 25(OH)D in the female group was also significantly lower than that in the male group (9.72±4.88 vs. 11.65±3.34; P=0.040). This may be attributed to the higher body fat percentage in the females than that in the males (35.44% vs. 24.36%; P<0.001).

In the present study, the participants were categorized using the vitamin D nutritional status into 3 groups: severe vitamin D deficiency (5–10 ng/mL), deficiency (10–20 ng/mL), and insufficiency (20–30 ng/mL) (table 2). The results showed that vitamin D suboptimal insufficiency, deficiency, and severe deficiency were present in 3.57%, 35.72%, and 60.71% of the participants, respectively. The results also demonstrated that those in the lowest tertile of serum 25(OH)D had significantly higher TNF-α levels than did those in the highest tertile of it (P=0.026). However, the comparison of other inflammatory and glycemic markers between groups of 25(OH)D did not show any significant differences.

The associations between 25(OH)D levels and the anthropometric and biochemical (glycemic and inflammatory) traits are shown in table 3. In the present study, the serum 25(OH)D concentration was inversely correlated with fasting blood sugar (FBS) (r=-0.224; P=0.049) and TNF-α (r=-0.229; P=0.044) in the whole study population.

Some factors estimated as those affecting the development of vitamin D deficiency are shown in table 4. In the current study, there was no significant association between vitamin D deficiency and some affecting factors.

### Discussion

The objective of this study was to examine the relationships between vitamin D status and FBS, HbA1C, insulin resistance, and inflammatory markers in non-obese patients with T2DM. To our knowledge, this is the first study to investigate the association between vitamin D status and inflammatory markers in non-obese individuals with T2DM. Based on the hypotheses that obesity (as defined by body fat mass) is associated with inflammation and that extra body fat contributes to a poor vitamin D status by sequestrating vitamin D, we first excluded obese patients with T2DM from the study. Garcia et al.¹⁶ demonstrated that adipose tissue was an endocrine organ that secreted adipokines and cytokines, thus the inflammatory process with an expanded fat mass might be involved in the development of insulin resistance and T2DM.¹⁶

However, in the current study, serum 25(OH)D was not associated with waist circumference, fat mass, and BMI. Unlike this finding, an association between vitamin D status and anthropometric indices was reported by Nikooyeh et al.¹⁷ In this study, controlling for BMI was done, which can explain the insignificant association between vitamin D status and anthropometric indices.
In the present study, the serum 25(OH)D values were lower than the ideal level of 32 ng/mL (80 nmol/L). However, the range of the serum 25(OH)D concentration in the participants was in accordance with that in a number of other studies establishing the prevalence of vitamin D deficiency in T2DM. The high occurrence of vitamin D deficiency in this study may be explained by many reasons, including blood sampling during the cold season, when the dermal synthesis of vitamin D is negligible; very inefficient direct sun exposure; and the absence of vitamin D fortification. In the present study, it was obvious that the subjects had less sunlight exposure (<60 min), despite the fact that they lived in a tropical region rich with sunlight almost throughout the year. Moreover, dietary vitamin D typically comprises only about 10–30% of the vitamin D calculated. An inadequate vitamin D intake is prevalent around the world, regardless of age or health status. In the present study, the mean intake of vitamin D according to our food frequency questionnaire was 1.35±0.17 µg/d; accordingly, the vitamin D intake in this study was lower than the recommended daily allowance (RDA). There is evidence that a higher intake of vitamin D and calcium is associated with a lower risk of T2DM. In the current study, despite such

### Table 1: Anthropometric and biochemical characteristics of the participants by sex

|                     | Mean (n=84) | Female (n=45) | Male (n=39) | P value |
|---------------------|-------------|---------------|-------------|---------|
| Age (year)          | 51.79±9.01  | 51.16±7.96    | 52.51±10.13 | 0.491   |
| Weight (kg)         | 69.79±9.74  | 64.93±7.96    | 75.39±8.58  | <0.001  |
| Height (cm)         | 163±9.10    | 157.57±5.11   | 170.53±7.63 | <0.001  |
| BMI (kg/m²)         | 26.06±2.54  | 26.16±2.69    | 25.95±2.38  | 0.702   |
| WC (cm)             | 93.71±7.90  | 93.42±8.78    | 94.05±6.84  | 0.721   |
| HC (cm)             | 98.96±5.40  | 98.77±5.83    | 99.17±4.93  | 0.748   |
| WHR                 | 0.94±0.06   | 0.94±0.08     | 0.94±0.051  | 0.950   |
| Body fat (%)        | 30.30±7.80  | 35.44±6.43    | 24.36±4.22  | <0.001  |
| FBS (mg/dL)         | 159.80±63.01| 171.47±69.58  | 146.33±52.14| 0.075   |
| HbA1C (%)           | 8.03±1.69   | 8.39±1.81     | 7.61±1.46   | 0.032   |
| Dietary vitamin D intake (µg/d) | 13.50±1.77 | 13.80±2.00 | 13.20±2.73 | 0.851   |

Data are expressed as mean±SD. P values were resulted from the independent sample t-test between 2 groups (male and female). BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist-to-hip ratio; FBS: Fasting blood sugar; HbA1C: Glycosylated hemoglobin; HOME-IR: Homeostatic model of insulin resistance; TNF-α: Tumor necrosis factor-alpha; hs-CRP: High sensitive C-reactive protein

### Table 2: Anthropometric and biochemical characteristics of the participants according to vitamin D nutritional status

|                     | Severe Deficiency (5–10 ng/mL) (n=51) | Deficiency (10–20 ng/mL) (n=30) | Suboptimal Insufficient (20–30 ng/mL) (n=3) | P value |
|---------------------|--------------------------------------|---------------------------------|---------------------------------------------|---------|
| Number (%)          | 51 (60.71)                           | 30 (35.72)                      | 3 (3.57)                                    | -       |
| BMI (kg/m²)         | 26.05±2.58                           | 26.07±2.58                     | 26.16±2.13                                 | 0.930   |
| WC (cm)             | 93.41±9.00                           | 94.03±5.99                     | 95.67±6.11                                 | 0.95    |
| HC (cm)             | 99.88±5.78                           | 97.43±4.07                     | 98.67±8.96                                 | 0.145   |
| WHR                 | 0.93±0.07                            | 0.96±0.06                      | 0.97±0.06                                  | 0.102   |
| Body fat (%)        | 31.21±8.21                           | 28.48±6.73                     | 32.90±10.13                                | 0.131   |
| FBS                 | 160.14±64.60                         | 158.17±60.66                   | 156.33±82.80                               | 0.351   |
| HbA1C (%)           | 7.97±1.71                            | 8.08±1.71                      | 8.46±1.81                                  | 0.780   |
| Insulin             | 16.18±13.099                         | 16.79±15.93                    | 14.53±12.03                                | 0.825   |
| HOME-IR             | 6.41±6.22                            | 6.13±5.10                      | 5.28±4.63                                  | 0.835   |
| TNF-α               | 5.05±9.62                            | 0.93±3.68                      | 0.31±0.54                                  | 0.026   |
| hs-CRP              | 4.08±3.63                            | 4.18±3.21                      | 5.07±3.088                                 | 0.890   |

Data are expressed as mean±SD. P values were resulted from the one-way ANOVA. BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist-to-hip ratio; FBS: Fasting blood sugar; HbA1C: Glycosylated hemoglobin; HOME-IR: Homeostatic model of insulin resistance; TNF-α: Tumor necrosis factor-alpha; hs-CRP: High sensitive C-reactive protein

In the present study, the serum 25(OH)D values were lower than the ideal level of 32 ng/mL (80 nmol/L). However, the range of the serum 25(OH)D concentration in the participants was in accordance with that in a number of other studies establishing the prevalence of vitamin D deficiency in T2DM. The high occurrence of vitamin D deficiency in this study may be explained by many reasons, including blood sampling during the cold season, when the dermal synthesis of vitamin D is negligible; very inefficient direct sun exposure; and the absence of vitamin D fortification. In the present study, it was obvious that the subjects had less sunlight exposure (<60 min), despite the fact that they lived in a tropical region rich with sunlight almost throughout the year. Moreover, dietary vitamin D typically comprises only about 10–30% of the vitamin D calculated. An inadequate vitamin D intake is prevalent around the world, regardless of age or health status. In the present study, the mean intake of vitamin D according to our food frequency questionnaire was 1.35±0.17 µg/d; accordingly, the vitamin D intake in this study was lower than the recommended daily allowance (RDA). There is evidence that a higher intake of vitamin D and calcium is associated with a lower risk of T2DM. In the current study, despite such
an association between 25(OH)D status and BMI, there was no correlation between 25(OH)D status and HbA1C. In contrast, Salehpour et al. showed a significant correlation between HbA1C and 25(OH)D concentrations.

Inflammation both predicts and precedes diabetes, and studies have shown that inflammatory processes occurring in adipocytes contribute to systemic low-grade inflammation, resulting in insulin resistance and diabetes. In support of this notion, we found that TNF-α was significantly elevated among our patients with T2DM and that low levels of circulating 25(OH)D after adjusting for multiple factors (age, sex, waist circumference, and smoking status) were inversely correlated with pro-inflammatory markers like TNF-α. These results agree with experimental studies showing that vitamin D is capable of suppressing TNF-α production. Vitamin D3 supplementation has been shown to reduce inflammatory cytokines such as TNF-α, playing a significant role in inducing insulin resistance. This supports the notion that the active form of vitamin D can boost insulin secretion by enhancing calcium flux in pancreatic β cells, so that vitamin D deficiency may contribute to systemic inflammation.

A sensitive marker of low-grade inflammation, CRP is the most commonly measured marker of inflammation. Research in subjects with diabetes or clinical vitamin D deficiency has demonstrated negative associations between hs-CRP concentrations and vitamin D status. Nonetheless, in the current study, there was no significant correlation between CRP and vitamin D status. This may be partially explained by the fact that whereas the observation was

### Table 3: Association between the 25(OH) D level and anthropometric indices and biochemical markers

| Variables          | β coefficients | r    | P value |
|--------------------|----------------|------|---------|
| Weight (kg)        | 0.191          | 0.082| 0.482   |
| Height (cm)        | −0.150         | −0.102| 0.377   |
| BMI (kg/m²)        | −0.495         | −0.056| 0.634   |
| WC (cm)            | −3.321         | −0.203| 0.074   |
| HC (cm)            | 2.032          | 0.196| 0.085   |
| WHR                | 3.078          | 0.228| 0.044   |
| Body fat (%)       | −0.179         | −0.199| 0.080   |
| FBS                | −0.210         | −0.224| 0.049   |
| HbA1C (%)          | 0.039          | 0.012| 0.849   |
| Insulin            | 0.051          | 0.055| 0.643   |
| HOMA-IR            | −0.155         | −0.041| 0.730   |
| TNF-α              | −0.216         | −0.229| 0.044   |
| hs-CRP             | 0.047          | 0.050| 0.675   |

1. Multiple linear regression was used. BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist-to-hip ratio; FBS: Fasting blood sugar; HbA1C: Glycosylated hemoglobin; HOMA-IR: Homeostatic model of insulin resistance; TNF-α: Tumor necrosis factor-alpha; hs-CRP: High sensitive C-reactive protein

### Table 4: Factors affecting the development of vitamin D deficiency

| Variables          | Severe Deficiency (n=51) | Deficiency (n=30) | Insufficiency (n=3) | OR     | CI      | P value |
|--------------------|--------------------------|-------------------|---------------------|--------|---------|---------|
| Sex                |                          |                   |                     |        |         |         |
| Female             | 31                       | 11                | 3                   | 1.8    | (0.7 4.3)| 0.18    |
| Male               | 20                       | 19                | 0                   | Ref    |         |         |
| Duration of sun exposure |                    |                   |                     |        |         |         |
| No                 | 3                        | 3                 | 0                   |        |         |         |
| 10-60 minutes      | 44                       | 23                | 3                   | 1.5    | (0.2 7.8)| 0.6     |
| 60-120 minutes     | 2                        | 4                 | 0                   | 0.5    | (0.06 5.2)| 0.6     |
| ≥120 minutes       | 2                        | 0                 | 0                   | .      | (0 *)   | 0.9     |
| Sun protection applied |                    |                   |                     |        |         |         |
| Yes                | 8                        | 6                 | 1                   | 1.5    | (0.5 4.5)| 0.4     |
| No                 | 43                       | 24                | 2                   |        |         |         |
| Body exposure       |                          |                   |                     |        |         |         |
| Face               | 18                       | 8                 | 2                   | -      | -       | -       |
| Hand               | 5                        | 3                 | 0                   | 1.04   | (0.2 5.2)| 0.9     |
| Face & hand        | 27                       | 18                | 0                   | 0.94   | (0.3 2.4)| 0.9     |
| Arm                | .                        | .                 | .                   | .      | .       | .       |
| Leg                | 1                        | 1                 | 1                   | 0.14   | (0.01 1.5)| 0.1     |
| Education          |                          |                   |                     |        |         |         |
| Under diploma      | 32                       | 21                | 3                   | Ref    |         |         |
| Diploma            | 15                       | 8                 | 0                   | 1.5    | (0.5 4.1)| 0.4     |
| BSc & MSC          | 4                        | 1                 | 0                   | 3.1    | (0.3 29.9)| 0.9     |

*Ordinal logistic regression was used
made in T2DM, we report our observations in non-obese subjects; consequently, the association was attenuated.

There are limitations to the present study. Our small sample size may have led to weaker associations between vitamin D status and anthropometric, glycemic, and inflammatory markers. Another drawback of note is that we performed blood sampling in winter, when insufficient cutaneous synthesis due to limited sunlight exposure is common. That we did not use a skin-typing questionnaire, a reliable method of determining skin pigmentation and response to UVB exposure, is another limitation, which may have affected our findings vis-à-vis vitamin D status.

**Conclusion**

In the present study, all the subjects had a low vitamin D status. The vitamin D levels were negatively correlated with FBS and serum TNF-α levels in our non-obese subjects with T2DM. However, there was no significant association between vitamin D status and the other inflammatory and glycemic biomarkers in this study. That the present study was designed as a cross-sectional study with a relatively small sample size may explain the lack of statistical significance for some correlation results. Given the high prevalence of diabetes and vitamin D deficiency in communities and the possible contribution of poor vitamin D status to systemic inflammation often seen in T2DM, further studies with larger sample sizes are needed to re-examine the anti-inflammatory function of vitamin D.

**Acknowledgment**

This paper is part of a Master of Science thesis by S. Pouraziz. This work was financially supported by the Nutrition and Metabolic Diseases Research Center of Ahvaz Jundishapur University of Medical Sciences (Grant # NRC-9107). The authors thank Shahram Arsang-Jang for assisting us in the analysis and interpretation of data. We also thank Mrs. Dehghan and Mrs. Hardani for their sincere cooperation in laboratory work.

**Conflict of Interest:** None declared.

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