Original Communication

Vitamin D3 supplementation improves serum SFRP5 and Wnt5a levels in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial

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Abstract: *Objective:* To explore the effect of vitamin D3 on novel serum adipokines, secreted frizzled-related protein 5 (SFRP5) and Wingless-Type MMTV Integration Site Family Member 5a (Wnt5a) levels in Type 2 Diabetes Mellitus (T2DM) patients. *Methods:* Forty patients (16 women and 24 men) with type 2 diabetes participated in this double-blind, randomized, placebo-controlled clinical trial study. Participants were randomly assigned to receive 4000 IU vitamin D_3 (n = 20) or placebo (n = 20) daily for 2 months. Anthropometric indices, fasting blood glucose (FBS), hemoglobin A1c (HbA1c), insulin, serum tumor necrosis factor (TNF)-α, Wnt5a, SFRP5, physical activity, lipid profile, dietary intake, and serum calcidiol were assessed at the baseline and after 8 weeks. *Results:* In the group receiving Vitamin D, a significant increase in Calicidiol (15.03 ± 10.44 vs. 27.33 ± 11.2 ng/dl; P = < 0.001), SFRP5 (3.6 ± 0.46 vs. 3.98 ± 0.59 ng/ml; P = 0.01), and Wnt5a (0.33 ± 0.129 vs. 0.29 ± 0.047; P = 0.03) was observed. After two months supplementation, there were significant between-group differences in Calicidiol (27.33 ± 11.2 vs. 17.9 ± 12.95 ng/dl; P = 0.01), TNF-α (89.22 ± 34.28 vs. 164.93 ± 120.45 ng/ml; P = 0.006), Wnt5a (0.29 ± 0.047 vs. 0.33 ± 0.09; P = 0.04), and HbA1c (6.6 ± 0.96 % vs. 7.64 ± 1.15 %; *p* = 0.002). Moreover, the net changes (end − baseline) of Calicidiol (P = < 0.001), SFRP5 (P = 0.04), Wnt5a (P = 0.005), TNF-α (P = 0.01), insulin (P = 0.03), and QUICKI (P = 0.01) was significant between the groups. There were no significant effects on FBS and homeostasis model of assessment-estimated insulin resistance (HOMA-IR). *Conclusion:* 8 weeks of vitamin D3 supplementation for patients with type 2 diabetes may increase serum anti-inflammatory adipokine SFRP5 but decrease serum pro-inflammatory Wnt5a and TNF-α.

Keywords: Type 2 diabetes, Vitamin D, SFRP5, Wnt5a, TNF-α

Introduction

Diabetes mellitus is considered as a common chronic metabolic disorder worldwide. The type 2 diabetes is estimated to consist 90 % of all diabetic cases, and its prevalence is dramatically increasing because of altered lifestyles, consisting of low levels of physical activity, unhealthy diet, and high rate of obesity [1]. International Diabetes Federation has estimated a growth in the number of diabetic adults from 415 million in 2015 to 642 million in 2040 through the world. In Iran, 4.6 million adults have Type 2 Diabetes Mellitus (T2DM) [2].

Adipose tissue releases approximately 600 adipokines such as interleukin (IL)-6, IL-8, IL18, tumor necrosis factor (TNF)-α, secreted frizzled-related protein 5 (SFRP5) and Wingless-Type MMTV Integration Site Family Member 5a

(Wnt5a) [3]. High level of adiposity is the main risk factor for insulin resistance (IR) and T2DM [4, 5]. Dietary modification is a strategy to prevent and improve these disorders [6, 7]. SFRP5, a recently identified protein released by adipocytes, is a family member of SFRP which is considered as an anti-inflammatory adipokine that inhibits wnt5a. Wnt5a is considered as a pro-inflammatory adipokine because of its potential role in reducing the differentiation of pre-adipocytes into mature fat [8].

Recent studies have reported that TNF-α is able to downregulate gene expression and protein secretion of SFRP5 in 3t3-L1 adipocytes. Moreover, it can stimulate Wnt signaling resulting in inflammation and blocking adiposity differentiation [9, 10]. Some studies have reported that vitamin D may regulate inflammatory cytokines and consequently influence on insulin sensitivity and beta cell survival [11]. In this regard, it has been identified that 1,25-dihdroxyvitamin D_3 has a significant decreasing effect on pro-inflammatory mediators expression including TNF-α, IL-6, IL-1 and IL-8, which are expressed at higher amounts in type 2 and 1 diabetic patients compared to controls, supporting its immunomodulatory roles [12]. Due to the lack of efficient evidence supporting the association of Vitamin D with serum Wnt5a and SFRP5 levels, this study aimed to explore the effect of vitamin D supplementation on serum SFRP5, wnt5a, and TNF-α levels in type 2 diabetic patients.

Material and methods

Study participants

This double blind placebo-controlled clinical trial study was performed in the diabetes medical center of Iran, Tehran. Out of the total of 65 diabetic patients, 40 persons met the inclusion criteria and completed the study. 40 participants with type 2 diabetes enrolled and were randomly (1 : 1 ratio) allocated to drug or placebo groups by permuted block randomization in strata (body mass index) method. Participants in the vitamin D group, received 100 micrograms or 4000 IU (one tablet per day) and placebo group took 1 placebo tablet per day for 2 months. Literate volunteers with 30–65 years old, body mass index (BMI) of 20–35 kg/m^2, and with stable weight and physical activity were included. The diagnosis of T2DM was according to the World Health Organization (WHO) criteria [13]. The exclusion criteria were as follows: Those with liver, gastrointestinal, respiratory, and blood disorders, chronic kidney disease, cancer, hypothyroidism, hyperthyroidism, orlistat or sibutramine treatment for weight loss, pregnancy and lactation, insulin or thiazolidinedione therapy, the use of dietary supplements including vitamins, and herbal products for at least 3 months prior to the intervention, smoking, being on weight management diets over the past year or menopause. This study was approved by the International Campus of Tehran University of Medical Sciences (TUMS-IC) ethical committee, and written informed consent was obtained from all participants. The trial has been registered at www.clinicaltrial.org as NCT 01876563.

Clinical and biochemical evaluation

before and after intervention, anthropometric measurements (weight, height, hip, and waist circumference) were taken by a measuring scale and BMI was calculated using the following formula: weight/(height*height) . Fasting serum glucose level was examined by glucose-oxidase method with a ZistShimi Kit (ZistShimi Co., Iran). Moreover, diet information was collected by a 3-day dietary record, and analyzed by Nutrition IV software (First Databank, San Bruno, CA), which converted the data into daily energy and macro-and micro-nutrient intakes. Physical activity level was evaluated by International Physical Activity Questionnaire (IPAQ). Duration of sun exposure was estimated using sunlight exposure measurement questionnaire (SEMQ). The serum samples were isolated and kept frozen at –80°c until performing enzyme-linked immunosorbent assay (ELISA) and laboratory tests. SFRP-5 (ZellBbio GmbH, Germany, Cat NO: ZB-12186-H9648) and Wnt-5a (ZellBbio GmbH, Germany, Cat NO: ZB-12352-H9648) concentrations were determined using ELISA kit, respectively. Furthermore, a specific kit (Crystal day Biotech Co., Ltd, china, Cat NO: E0082Hu) was used to measure the serum concentration of TNF-α. To determine the Serum calcidiol, chemiluminescence method with ELECSYS system 2010 by Roche kit (code number: 05894973) was used. Serum insulin was assessed by using human insulin ELISA kit (Diametra, Italy) with the sensitivity of 0.25 mcIU/ml and an intra-assay and interassay of ≤5 % and ≤10 %, respectively. Homeostasis model of assessment-estimated insulin resistance (HOMA-IR) [14] and quantitative insulin sensitivity check index (Quicki) [15] were calculated by the following formula: HOMA-IR = glucose(mmol/L)*insulin(μU/mL)/22.5 and Quicki = 1/log insulin (mg/dl) + log glucose (μIU/ml), respectively.

Statistical analysis

All data analyses were done by the statistical package for social sciences, version 21 (SPSS, Inc.). Data were reported as mean ± SD, frequencies and percentages. Kolmogrovsmirnov was performed to examine the normality distribution of all quantitative variables. For data with normal

distribution, T-Test was used to compare mean levels between the two groups and paired t-test was performed within each group. The analysis of covariance (ANCOVA) was done to remove the effects of confounding factors. χ^2 test was used to determine differences between categorical variables. To have an 80 % power to detect 3 ng/ml of SFRP5 difference between the two groups when the standard deviation of the SFRP5 was assumed to be 3.3 in both groups and type I error was assumed to be 0.05, a sample of 19 was required. We admitted 20 samples in each group. P ≤ 0.05 was considered as statistical significant.

Results

In the current study, we randomly divided 40 diabetic patients into 2 groups based on receiving 100 µg vitamin D_3 (n = 20) or placebo (n = 20) for 2 months and all of the subjects completed the trial (Figure 1). The mean age of participants was 49.31 ± 4.58 years. The sun exposure duration did not show significant difference between the two groups (P = 0.6). Demographic characteristics are provided in Table 1. It can be seen from the data that anthropometric indices were not significantly different between the two groups before and after the trial. After two months supplementation, there were significant between-group differences in Calicidiol (27.33 ± 11.2 vs. 17.9 ± 12.95 ng/dl; P = 0.01), TNF-α (89.22 ± 34.28 vs. 164.93 ± 120.45 ng/ml; P = 0.006), Wnt5a (0.29 ± 0.047 vs. 0.33 ± 0.09; P = 0.04), and HbA1c (6.6 ± 0.96 % vs. 7.64 ± 1.15; p = 0.002) (Table 2). According to the 3-day dietary records, the mean intake of macro and micronutrients did not show significant difference within- or between-groups (Table 3).

In addition, receiving vitamin D_3 supplement in the vitamin D group for 8 weeks resulted in a significant increment in serum SFRP5 (0.39 ± 0.68 vs. –0.001 ± 0.55 mg/dL, p = 0.041) and calcidiol (12.3 ± 8.33 vs. 2.16 ± 5.08 mg/dL, p <0.001), while significant decrease in HbA1c (p = 0.003), serum Wnt5a (–0.04 ± 0.09 vs. 0.03 ± 0.08 mg/dL, p = 0.036), and TNF-α (–35.76 ± 87.82 vs. 16.84 ± 65.72 mg/dL, p = 0.07) was observed in comparison to the placebo group. The distribution of insulin was not normal, so was converted to insulin logarithms. The insulin logarithms revealed significant difference between vitamin D and placebo groups (p = 0.041). Statistical difference in insulin was remained significant after removing confounder variables (p = 0.032). After using ANCOVA to control baseline effects for HbA1c, wnt5a, TNF-α and SFRP5, the differences in these variables were still significant. Moreo-

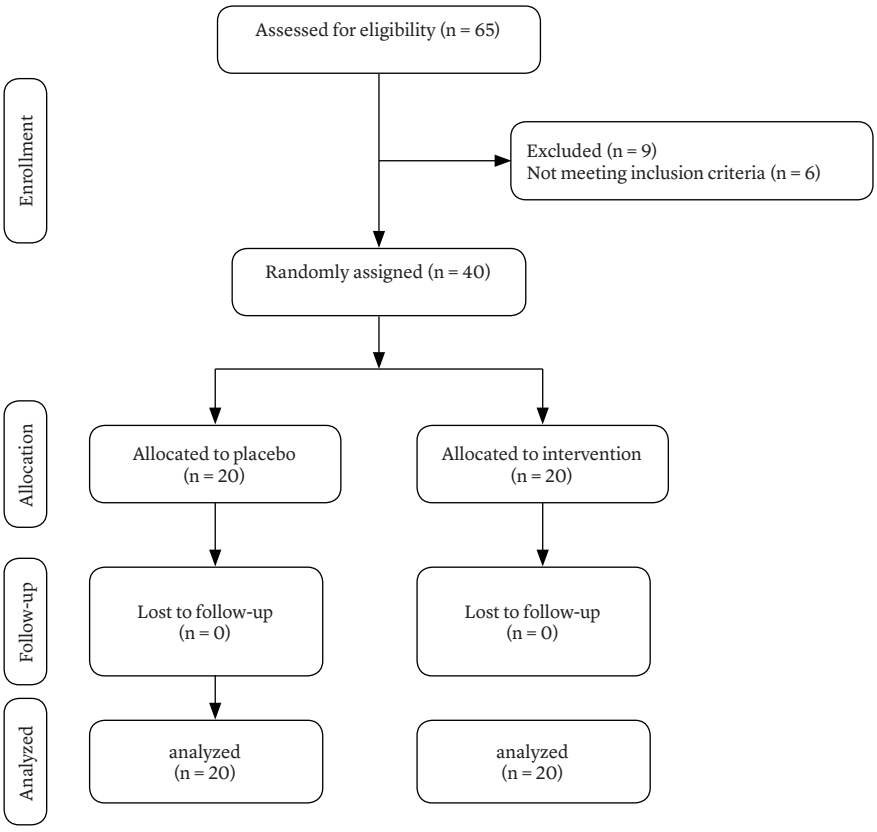

Figure 1. Summary of patient flow diagram.

ver, mean difference for Quicki was significant (p = 0.01), but HOMA-IR did not show any significant difference between or within the groups (Table 4).

Discussion

To our knowledge, this is the first research that explored the effect of vitamin D_3 supplementation on serum SFRP5 and Wnt5a in patients with type 2 diabetes. The study revealed that vitamin D3 supplementation significantly decreases serum levels of Wnt5a and TNF-α, in comparison to placebo. Moreover, compared to the placebo group, the net changes of SFRP5 was significantly higher in the group receiving vitamin D supplementation, whereas, changes in Wnt5a and TNF-α was lower, indicating that vitamin D might have a beneficial effect on controlling inflammation in patients with diabetes. Also, we did not observe any significant difference in terms of weight, BMI, waist circumference, hip circumference and waist hip ratio between the baseline and endline measurements.

In line with our results, several studies reported the beneficial effects of vitamin D on the glycemic status in type 2 diabetic patients [16–18]. However, some other investigations failed to find such a finding [19, 20]. These discrepancies might be due to the differences in follow-up period and inclusion criteria in the previously conducted studies.

In line with our findings, the majority of the previous studies have reported that vitamin D3 supplementation decreases inflammatory cytokines, in particular TNF-α. TNF-α may play a leading role in developing insulin resistance [21]. Heidari *et al.* [22] demonstrated an inverse significant relationship between serum 25(OH)D and TNF-α levels, while did not find any significant association with other inflammatory markers. In addition, the results of experimental studies indicate the ability of vitamin D to suppress TNF-α production [23].

Previous studies revealed a link between SFRP5 and the development of type 2 diabetes, but the results are inconsistent [24–27]. There are evidences demonstrating that SFRP5 concentration in type 2 diabetic patients is enhanced compared with non-diabetic subjects [25, 28]. In

Table 1. Baseline demographic characteristics of study participants.*

	Vitamin D group (n = 20)	Placebo group (n = 20)	*p-value*[i]
Age, year	49.13 ± 4.94	49.50 ± 4.86	0.80
Height, cm	164.2 ± 9.01	168.08 ± 8.56	0.15
Weight, kg	75.08 ± 17.59	79.15 ± 13.88	0.39
BMI, kg/m^2	27.66 ± 5.07	28.08 ± 5.31	0.78
WC, cm	91.31 ± 13.12	93.93 ± 11.43	0.32
HC, cm	104.25 ± 10.76	105.15 ± 8.14	0.75
WHR	0.87 ± 0.073	0.89 ± 0.063	0.41
Dibetes duration, year	6.18 ± 4.91	6 ± 4.15	0.89
Sun exposure, minutes/day	25.7 ± 12.0	24 ± 11.0	0.60

* Data are presented as mean ± SD. [i] *P*-value Resulted from the independent sample *t*-test between 2 groups (intervention and placebo). BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: waist/hip ratio

Table 2. Comparison of the baseline and final various parameters within and between groups.*

Group	Vitamin D group (n = 20)			Placebo group (n = 20)				
Variable	**Before**	**After**	**P[i]**	**Before**	**After**	**P[i]**	**P[ii]**	**P[iii]**
FBS, mg/dl	142.95 ± 51.54	142.41 ± 51.58	0.963	155.18 ± 43.93	166.32 ± 44.93	0.081	0.40	0.11
SFRP5, ng/ml	3.6 ± 0.46	3.98 ± 0.59	0.013	3.81 ± 0.55	3.81 ± 0.46	0.991	0.16	0.28
Wnt5a, ng/ml	0.33 ± 0.129	0.29 ± 0.047	0.036	0.3 ± 0.05	0.33 ± 0.09	0.062	0.31	0.04
TNF-α, ng/ml	124.98 ± 100.65	89.22 ± 34.28	0.07	148.44 ± 95.29	164.93 ± 120.45	0.252	0.27	0.006
Calicidiol, ng/dl	15.03 ± 10.44	27.33 ± 11.2	< 0.001	16.5 ± 13.08	17.9 ± 12.95	0.065	0.68	0.01
HbA1C, %	7.17 ± 1.27	6.6 ± 0.96	< 0.001	7.74 ± 1.39	7.64 ± 1.15	0.3	0.16	0.002
Insulin, μIU/ml	8.29 ± 5.53	6.29 ± 1.27	0.023	7.37 ± 3.49	7.85 ± 5.92	0.703	0.6	0.19
HOMA-IR	3.27 ± 4.26	2.2 ± 0.88	0.2	2.86 ± 1.83	3.42 ± 3.62	0.19	0.67	0.13
Quicki	0.33 ± 0.026	0.34 ± 0.01	0.093	0.33 ± 0.02	0.32 ± 0.023	0.225	0.7	0.03

* Data are presented as mean ± SD. *P*[i]: within group difference; p[ii]: between-group before intervention; p[iii]: between group after the intervention. FBS: Fasting blood sugar; SFRP5: Secreted frizzled-related protein 5; Wnt5a: Wingless-Type MMTV Integration Site Family, Member 5A; TNF-α: Tumor necrosis factor α; HOMA-IR: Homeostatic model assessment-insulin resistance; Quicki: Quantitative insulin sensitivity check index

Table 3. Dietary intakes of patients with type 2 diabetes.*

Variable	vitamin D group (n = 20)	placebo group (n = 20)	P[i]
Energy, Mcal/d	21 ± 0.9	21 ± 0.2	0. 41
Carobohydrate, g/d	269 ± 56	284 ± 60	0.40
Protein, g/d	70 ± 15	72 ± 20	0.63
Fat, g/d	93 ± 26	100 ± 20	0.34
SFAs, g/d	22 ± 7	25 ± 13	0.29
PUFAs, g/d	26 ± 9	27 ± 9	0.76
MUFAs, g/d	35 ± 9	35 ± 8	0.28
TDF, g/d	17 ± 4	16 ± 4	0.72
Vitamin D, µg/d	2.8 ± 0.6	2.7 ± 0.5	0.57
Calcium, g/d	1.2 ± 0.2	1.1 ± 0.2	0.53
Magnesium, mg/d	271 ± 66	288 ± 72	0.43
Zinc, mg/d	9 ± 3.7	9 ± 2.3	0.86

*Data are presented as mean ± SD. SFA: Saturated fatty acid; PUFA: Polyunsaturated fatty acid; MUFA: Monounsaturated fatty acid; TDF: Total dietary fiber. *p*[i]: *p*-value was resulted from independent samples Student's t test.

Table 4. Comparison of changes in outcome measures between groups.*

Variable	change in vitamin D group (n = 20)	Change in placebo group (n = 20)	P[i]
FBS, mg/dl	−0.54 ± 54.65	11.13 ± 28.46	0.38
SFRP5, ng/ml	0.39 ± 0.68	−0.001 ± 0.55	0.041
Wnt5a, ng/ml	−0.04 ± 0.09	0.03 ± 0.08	0.005
TNF-α, ng/ml	−35.76 ± 87.82	16.84 ± 65.72	0.01
Calicidiol, ng/dl	12.3 ± 8.33	2.16 ± 5.08	< 0.001
HbA1C, %	7.29 ± 0.22	6.76 ± 0.18	< 0.001
Insulin, µlU/ml	−2 ± 4.72	0.47 ± 2.82	0.03
HOMA-IR	−1.07 ± 3.87	0.55 ± 1.97	0.08
Quicki	0.002 ± 0.007	−0.01 ± 0.006	0.01

*Data are presented as mean ± SD. *P*[i]: *P*-values for differences were assessed by independent *t*-test. FBS: Fasting blood sugar; SFRP5: Secreted frizzled-related protein 5; Wnt5a: Wingless-Type MMTV Integration Site Family, Member 5A; TNF-α: Tumor necrosis factor α; HOMA-IR: Homeostatic model assessment-insulin resistance; Quicki: Quantitative insulin sensitivity check index

contrast, some studies reported reduced SFRP5 levels in type 2 diabetic patients [24, 27]. Therefore, data regarding changes in SFRP5 levels in diabetic patients is inconclusive and needs further investigations.

A previous study has demonstrated a 22% and 32% reduction in SFRP5 mRNA expression in 3T3-L1 adipocytes which were treated by insulin and TNF-α, respectively. Correspondingly, 17% and 30% reduction was reported for SFRP5 protein secretion [10]. There are several reported mechanisms for this finding. One underlying mechanism is that vitamin D_3 is able to improve insulin secretion through calcium reflux in pancreatic ß cells; therefore, vitamin D deficiency may be related to systematic inflammation [29]. In another mechanism reported by Guilietti *et al.* [30], the expression of inflammatory profile of type 2 diabetic patients including TNF-α, IL-6, IL-8, IL-1, cyclooxygenase (COX)-2 and intercellular adhesion molecule (ICAM)-1 was shown to be significantly higher than healthy controls and type 1 diabetic subjects. They also illustrated that 1, 25 Dihydroxyvitamin D_3 was capable to decrease the expression of TNF-α, IL-6, IL-1, and pro-inflammatory profile, which supports its immunomodulatory effects [30]. In the present study, we also showed an inverse association between vitamin D_3 supplementation and circulating TNF-α value.

Based on the study executed by Schulte *et al.* [31], caloric restriction significantly increased the serum anti-inflammatory SFRP5 level while decreased HOMA-IR in obese individuals. Therefore, they proposed a new regulatory system of low-grade inflammation in obesity, which can be affected by nutritional treatment. This is in agreement with the findings of Hu *et al.* [32], who observed that plasma SFRP5 concentration was diminished in Chinese obese and type 2 diabetic patients and also introduced the SFRP5 as an independent factor influencing glucolipid metabolism, inflammation and Insulin resistance. They concluded that SFRP5 may play a substantial role in the development of obesity and T2DM [32]. Lu *et al.* found a mechanism that SFRP5 increases differentiation of adipocytes through blocking canonical wnt signaling [33]. In one study, high fat calorie diet in mice without SFRP5 resulted in further adipose tissue inflammation and insulin resistance compared to mice having uninhibited wnt5a function [8]. Moreover, high levels of SFRP5 expression in the mice adipocytes obstructed Wn5a function and inhibited inflammation and insulin resistance condition [8].

There were some limitations to our study. Small number of participants and short intervention period may limit the ascertainment of the association between vitamin D and anthropometric measurements, glycemic indices, and anti-inflammatory and pro-inflammatory markers. In addition, we measured only serum SFRP5 and wnt5a but measuring the extractive genes is still needed.

In summary, for the first time, we found that vitamin D_3 supplementation for 8 weeks could increase SFRP5 and decrease Wnt5a. These findings might indicate the benefi-

cial effects of vitamin D on improving type 2 diabetes complications by reducing the inflammatory factors such as TNF-α. Additional clinical studies are required to reveal the underlying mechanism.

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Conflict of Interest

The authors declare that they have no conflict of interests.

References

1. Shaw, J.E., R.A. Sicree, and P.Z. Zimmet, Global estimates of the prevalence of diabetes for 2010 Shaw, J.E., Sicree, R.A. and Zimmet, P.Z. (2010) Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 87, 4–14.
2. Guariguata, L., Whiting, D., Hambleton, I., Beagley, J., Linnenkamp, U. and Shaw, J. (2014) Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract. 103, 137–149.
3. Lehr, S., Hartwig, S. and Sell, H. (2012) Adipokines: a treasure trove for the discovery of biomarkers for metabolic disorders. Proteomics Clin Appl. 6, 91.
4. Wang, C.P., Chung, F.M., Shin, S.J. and Lee, Y.J. (2007) Congenital and environmental factors associated with adipocyte dysregulation as defects of insulin resistance. Rev Diabet Stud. 4, 77–84.
5. Bloomgarden, Z.T. (2002) Adiposity and diabetes. Diabetes Care. 25, 2342–2349.
6. Lean, M., Powrie, J., Anderson, A. and Garthwaite P. (1990) Obesity, weight loss and prognosis in type 2 diabetes. Diabet Med. 7, 228–233.
7. Williamson, D.F., Thompson, T.J., Thun, M., Flanders, D., Pamuk, E. and Byers, T. (2000) Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care. 23, 1499–1504.
8. Ouchi, N., Higuchi, A., Ohashi, K., Oshima, Y., Gokce, N., Shibata, R., Akasaki, Y., Shimono, A. and Walsh, K. (2010) SFRP5 is an anti-inflammatory adipokine that modulates metabolic dysfunction in obesity. Science. 329, 454–457.
9. Gustafson, B. and Smith, U. (2006) Cytokines promote Wnt signaling and inflammation and impair the normal differentiation and lipid accumulation in 3T3-L1 preadipocytes. J Biol Chem. 281, 9507–9516.
10. Lv, C., Jiang, Y., Wang, H. and Chen, B. (2012) SFRP5 expression and secretion in adipocytes are up-regulated during differentiation and are negatively correlated with insulin resistance. Cell Biol Int. 36, 851–855.
11. Wolden-Kirk, H., Overbergh, L., Christesen, H.T., Brusgaard, K., & Mathieu, C. (2011) Vitamin D and diabetes: its importance for beta cell and immune function. Mol Cell Endocrinol. 347, 106–120.
12. Giulietti, A., van Etten, E., Overbergh, L., Stoffels, K., Bouillon, R. and Mathieu, C. (2007) Monocytes from type 2 diabetic patients have a pro-inflammatory profile: 1, 25-Dihydroxyvitamin D3 works as anti-inflammatory. Diabetes Res Clin Pract. 77, 47–57.
13. World Health Organization. (2006). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. *World Hearth Org*.
14. Matthews, D., Hosker, J., Rudenski, A., Naylor, B., Treacher, D. and Turner, R. (1985) Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 28, 412–419.
15. Hrebicek, J., Janout, V., Malinčíkovä, J., Horäkovä, D. and Čížek, L.k. (2002) Detection of insulin resistance by simple quantitative insulin sensitivity check index QUICKI for epidemiological assessment and prevention. J Clin Endocrinol MeTab. 87, 144.
16. Shab-Bidar, S., Neyestani, T.R., Djazayery, A., Eshraghian, M.R., Houshiarrad, A., Gharavi, A.A., Kalayi, A., Shariatzadeh, N., Zahedirad, M., Khalaji, N. and Haidari, H. (2011) Regular consumption of vitamin D-fortified yogurt drink (Doogh) improved endothelial biomarkers in subjects with type 2 diabetes: a randomized double-blind clinical trial. BMC Med. 9, 125.
17. Nikooyeh, B., Neyestani, T.R., Tayebinejad, N., Alavi-Majd, H., Shariatzadeh, N., Kalayi, A., Zahedirad, M., Heravifard, S. and Salekzamani, S. (2014) Daily intake of vitamin D- or calcium-vitamin D-fortified Persian yogurt drink (doogh) attenuates diabetes-induced oxidative stress: evidence for antioxidative properties of vitamin D. J Hum Nutr. 27, 276–283.
18. Nasri, H., Behradmanesh S., Maghsoudi, AR., Ahmadi, A, Nasri, P., Rafieian-Kopaei, M. (2014) Efficacy of supplementary vitamin D on improvement of glycemic parameters in patients with type 2 diabetes mellitus; a randomized double blind clinical trial. J Renal Inj Prev. 3, 31–34.
19. George, P.S., Pearson, E.R. and Witham, M.D. (2012). Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. Diabet Med. 29.
20. Ryu, O.H., Lee, S., Yu, J., Choi, M.G., Yoo, H.J. and Mantero, F. (2014). A prospective randomized controlled trial of the effects of vitamin D supplementation on long-term glycemic control in type 2 diabetes mellitus of Korea. Endocr J. 61, 167–176.
21. Nikooyeh, B., Neyestani, T.R., Tayebinejad, N., Alavi-Majd, H., Shariatzadeh, N., Kalayi, A., Zahedirad, M., Heravifard, S. and Salekzamani, S. (2014) Daily intake of vitamin D-or calcium-vitamin D-fortified Persian yogurt drink (doogh) attenuates diabetes-induced oxidative stress: evidence for antioxidative properties of vitamin D. J Hum Nutr Diet. 27, 276–283.
22. Haidari, F., Zakerkish, M., Karandish, M., Saki, A. and Pooraziz, S. (2016) Association between serum vitamin D level and glycemic and inflammatory markers in non-obese patients with type 2 diabetes. Iran J Med Sci. 41, 367–373.
23. Peterson, C.A. and Heffernan, M.E. (2008) Serum tumor necrosis factor-alpha concentrations are negatively correlated with serum 25(OH)D concentrations in healthy women. J Inflamm. 5, 10.
24. Hu, Z., Deng, H., Qu, H. (2013) Plasma SFRP5 levels are decreased in Chinese subjects with obesity and type 2 diabetes and negatively correlated with parameters of insulin resistance. Diabetes Res Clin Pract. 99, 391–395.

25. Lu, Y.C., Wang, C.P., Hsu, C.C., Chiu, C.A., Yu, T.H., Hung, W.C., Lu, L.F., Chung, F.M., Tsai, I.T., Lin, H.C. and Lee, Y.J. (2013) Circulating secreted frizzled-related protein 5 (Sfrp5) and wingless-type MMTV integration site family member 5a (Wnt5a) levels in patients with type 2 diabetes mellitus. Diabetes Metab Res Rev. 29, 551–556.
26. Carstensen, M., Herder, C., Kempf, K., Erlund, I., Martin, S., Koenig, W., Sundvall, J., Bidel, S., Kuha, S., Roden, M. and Tuomilehto, J. (2013) Sfrp5 correlates with insulin resistance and oxidative stress. Eur J Clin Invest. 43, 350–357.
27. Hu, W., Li, L., Yang, M., Luo, X., Ran, W., Liu, D., Xiong, Z., Liu, H. and Yang, G. (2013) Circulating Sfrp5 is a signature of obesity-related metabolic disorders and is regulated by glucose and liraglutide in humans. J Clin Endocrinol MeTab. 98, 290–298.
28. Canivell, S., Rebuffat, S., G Ruano, E., Kostov, B., Sisó-Almirall, A., Novials, A., Ceriello, A. and Gomis, R. (2015) Circulating SFRP5 levels are elevated in drug-naïve recently diagnosed type 2 diabetic patients as compared with prediabetic subjects and controls. Diabetes Metab Res Rev. 31, 212–219.
29. Krishnan, A.V. and Feldman, D. (2011) Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. Annu Rev Pharmacol Toxicol. 51, 311–336.
30. Giulietti, A., vanEtten, E., Overbergh, L., Stoffels, K., Bouillon, R. and Mathieu, C. (2007) Monocytes from type 2 diabetic patients have a pro-inflammatory profile. 1,25-Dihydroxyvitamin D(3) works as anti-inflammatory. Diabetes Res Clin Pract. 77, 47–57.
31. Schulte, D.M., Muller, N., Neumann, K., Oberhauser, F., Faust, M., Gudelhofer, H., Brandt, B., Krone, W. and Laudes, M. (2012) Pro-inflammatory wnt5a and anti-inflammatory sFRP5 are differentially regulated by nutritional factors in obese human subjects. PLoS ONE. 7, e32437.
32. Hu, Z., Deng, H. and Qu, H. (2013) Plasma SFRP5 levels are decreased in Chinese subjects with obesity and type 2 diabetes and negatively correlated with parameters of insulin resistance. Diabetes Res Clin Pract. 99, 391–395.
33. Lu, Y.C., Wang, C.P., Hsu, C.C., Chiu, C.A., Yu, T.H., Hung, W.C., Lu, L.F., Chung, F.M., Tsai, I.T., Lin, H.C. and et al. (2013) Circulating secreted frizzled-related protein 5 (Sfrp5) and wingless-type MMTV integration site family member 5a (Wnt5a) levels in patients with type 2 diabetes mellitus. Diabetes Metab Res Rev. 29, 551–556.

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