Comparative Effect of Two Different Doses of Vitamin D on Diabetic Foot Ulcer and Inflammatory Indices among the Type 2 Diabetic Patients: a Randomized Clinical Trial

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Abstract

Objective: The current study was conducted to compare the effect of 150,000 and 300,000 IU of vitamin D on the healing status of diabetic foot ulcer among the patients with diabetes.

Materials and Methods: This randomized clinical trial was carried out on 47 patients with diabetic foot ulcer and vitamin deficiency during four weeks follow-up. The patients were randomly assigned into two groups; group G150 was administered 150000 IU of vitamin D and group G300 was administered 300000 IU of vitamin D. Serum 25-hydroxyvitamin D, ulcer area, fasting blood sugar (FBS), c-reactive protein (CRP), white blood cells (WBC) and erythrocyte sedimentation rate (ESR) were measured in both groups before and after intervention.

Results: Serum vitamin D level in both groups was significantly increased compared to the baseline (P<0.01). The mean of serum vitamin D changes were 12.6±5.0 and 18.4±6.4 ng/ml (P=0.001) in G150 and in G300, respectively. The ulcer area was significantly reduced in both groups compared to the baseline (P<0.01).WBC, ESR, FBS and CRP were significantly declined compared to the baseline in both groups. However, the mean changes of serum FBS and CRP levels were found to be significantly different between groups.

Discussion: The findings showed administration of 150,000 and 300,000 IU of vitamin D improved the ulcer and vitamin D status and reduced ESR, CRP, WBC and FBS in the patients with diabetic foot ulcer. In addition, the 300,000 IU of vitamin D was significantly more effective than 150,000 IU.

Keywords: Diabetic foot ulcer, Vitamin D, Fasting blood sugar, C-reactive protein

Introduction

Diabetes mellitus is one of the most common endocrine disorders that is characterized by blood glucose increase and caused by deficient secretion or function of insulin or both. High blood glucose in diabetic patients is accompanied by the disorders and dysfunctions of different organs, especially eyes, feet, kidneys, nerves and

blood vessels in the long term. Foot ulcer is one of the major complications of diabetes that is manifested as sore or wound on the feet of the diabetic patients. Foot ulcer is caused by poor glycemic control, peripheral neuropathy, peripheral vascular disease and immunosuppression (1). This complication is an important issue, especially the costs it imposes on the health system and individuals. It is even a major cause of the ailment and death of diabetic patients. These ulcers are improved slowly and require intensive care due to their susceptibility to infection and gangrene. It's estimated that approximately 15% of patients with diabetes worldwide develop diabetic foot ulceration with recurrence rate of more than 50% after 3 years (2,3).

Vitamin D has many receptors in different body tissues. It is responsible for numerous cellular functions. Apart from its known effects in regulation of calcium and phosphorus, vitamin D is involved in the local control of the various tissues cells, including cutaneous keratinocyte cells that are supported by growth factors and cytokines (2,4). Various studies have shown the inducing effect of vitamin D in differentiation and mytogenic growth of keratinocytes. Keratinocytes can act through activation of TGF-α and inhibition of interleukin-1 (IL-1), IL-6 and IL-7 or stimulation of the production of the compounds similar to cutaneous growth factor and Platelet-derived growth factor (PDGF). PDGF improves collagen synthesis and extracellular matrix and acts as an efficient factor for fibroblasts, monocytes and neutrophils whose activities contribute to ulcer amelioration (2,5). PDGF cooperates with many growth factors and its receptors are not normally seen in keratinocytes and epidermis.

Vitamin D bonds to its hormone receptor (VDR) in the skin and causes the increased secretion of cathelicidin (hCAP18). Cathelicidin is present in white blood cells (WBC) and in epithelial cells when immune defense is initiated. Cathelicidin is slightly expressed in the skin and is highly increased during ulcer without any control (6-8). There is strong evidence that shows vitamin D plays a critical role in protection, flawless performance of epithelial cells and increased restoration of tissues (9,10). Vitamin D has recently been introduced as an inducing factor for the transcription of hCAP18/LL37 genes. The significance of vitamin D and cathelicidin in improving the ulcer has made it an efficient inducing factor for gene transcription (11).

Since there is no consensus about the effect of vitamin D on improvement of diabetic ulcer and even about the best dose and administration method in diabetic patients and patients with diabetic foot ulcer (12-15), the present study investigate this issue. Various studies have been performed on supplementation with vitamin D and its administration method, oral or intravenous and duration (16-22) and different results have been obtained. On the other hand, few studies have been conducted on the short-time effect of mega-dose vitamin D supplementation on diabetic foot. We hypothesized that single injection of two megadoses of vitamin D can improve diabetic foot. Thus, the current research was aimed to compare the effect of injection of two different doses of vitamin D on improvement of diabetic foot ulcer among the diabetic patients during four weeks follow up.

Materials and Methods

Study type and participants

A total of 47 outpatients with diabetic foot ulcer referring to the diabetic center of Hamadan University of Medical Sciences during four weeks treatment plan were selected according to the following inclusion and exclusion criteria.

The inclusion criteria included having diabetic foot ulcer and Wagner wound ≤2. The exclusion criteria were; pregnancy, autoimmune disease, taking anticonvulsants and antibiotics, osteomyelitis, renal insufficiency, hypertension, cutaneous tumors on venous ulcers or lymphedema, ulcer

infection, lower limb paresthesia and surgical debridement requirement.

Considering α=5%, SD=5 and minimum improvement of ulcer surface= 3% (3% reduction of ulcer than before vitamin D administration), i.e. the mean percentage of ulcer surface reducing from 72% to 69%, the study sample was calculated to be 44 patients (22 patients in each group) plus 15% drop out rate which finally yielded 50 samples (25 patients in each group). The demographic information checklist including; age, diabetes duration, ulcer history and ulcer duration was completed and recorded.

First, serum 25-hydroxyvitamin D, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), WBC and ulcer size were measured in the patients with diabetic foot ulcer and vitamin D deficiency (According to an Endocrine Society Guideline for evaluation of vitamin D deficiency, vitamin D deficiency was defined as a 25 (OH) D level below 20 ng/ml) (22). Then, the patients were randomly divided into two groups A and B according to the table of random numbers. Group A received 150,000 IU of vitamin D (half of 1 ml vitamin D ampule) and group B was received 300,000 IU of vitamin D through intramuscular injection. The patients were asked to refer to the diabetic center four weeks later. Weekly follow-up was done by telephone until the end of intervention. Vitamin D supplements for injection were made by the Iran Hormone Corp. (Tehran, Iran) in the form of 1-ml ampoules (each containing 300,000 IU cholecalciferol). The vials of this supplement were preserved out of light at 15-30 °C before use.

Measurements

The height, weight and ulcer size were measured by standard methods, Seca scale with accuracy of 5%cm, 1% kg and Auto CAD-18 software (Auto desk co, USA, 2010), respectively. After a minimum of eight hours fasting, 6 ml peripheral blood sample was taken from the participants at the beginning and end of the study to analyze CRP, ESR, FBS, WBC and 25-hydroxyvitamin D. FBS was measured according to Enzymatic-Colorimetric/CHOD-PAP technique and autoanalyzer machine (Echoplus co, Italy). CRP was determined by ELISA method and assay (Labor Diagnostika Nord GmbH & Co.KG) with sensitivity of 10 ng/ml.WBC was counted by measuring the proportion of neutrophil to lymphocyte using Hematology Analyzer. ESR was determined by adding blood sample to the tubes containing EDTA and adding citrate using Westergren test in the first hour. Serum 25-hydroxyvitamin D was measured by Tosoh AIA 1800 machine (made in Japan) using immunofluorescence method and the exclusive Kit of the manufacturer.

Statistical data analysis

SPSS-17 software was used to analyze the data and the results were expressed as Mean ± SD. To determine the quantitative data, Kolmogrov-Smirnov test was run and to analyze the qualitative variables between groups, chi square test and Fisher's exact test were applied. To compare the study variables and some demographic characteristics between the two groups before intervention, student T-test was used. Paired T-test was applied to compare the mean quantitative variables before and after intervention in each group. Also, student t-test was run to compare the mean quantitative variables between groups. $P<0.05$ was considered significant.

Ethical considerations

Informed consent was taken from the participants and they freely volunteered to participate in this study and could withdraw from the study whenever they wished. Moreover, the study proposal was approved and confirmed by the Ethics-in-Research Commission of Shahid Sadoughi University of Medical Sciences and clinical trial code was taken from the trial registration center of deputy of research and technology of ministry of health (www.irct.ir, clinical trial code: IRCT1394041321740N1).

Results

In this study, 47 patients, including 23 patients in G150 with the mean age of 56.52±7.61 and 24 patients in G300 with the mean age of 57.46±8.68 years were recruited and they fully completed the study period (Figure 1). Table 1 presents the demographic information of the participants before intervention. As indicated, the means of quantitative characteristics, including age, BMI, diabetes duration and other qualitative characteristics such as gender and ulcer type showed no statistically significant difference between the study groups.

According to Table 2, serum vitamin D level after four weeks of intervention reached an adequate level. The mean of serum vitamin D level in both groups was significantly increased compared to the baseline (P<0.01). So that, the mean of changes 12.6±5.0 and 18.4±6.4 ng/ml (P=0.001) in G150 and in G300, respectively.

As indicated in Table 2, the ulcer area in both groups was significantly decreased compared with the baseline (P<0.01). The mean of changes of ulcer area were 2.36±0.97 and 2.8±1.29cm in G150 and G300 (P=0.05), respectively. Thus, it seemed that reduced ulcer area in G300 was more than that of G150.

According to Table 2, serum CRP, WBC, ESR and FBS levels were significantly reduced in both groups compared to the baseline (P<0.001). The mean of serum CRP, ESR and FBS concentrations were found a significant difference between groups (P<0.05) and the mean changes of serum FBS and CRP concentrations were found to be significantly different between groups so that their serum levels in G300 were significantly decreased than those of G150 after intervention.

Discussion

The findings showed that administration of 150,000 and 300,000 IU of vitamin D ameliorated the ulcer and vitamin D status and reduced ESR, CRP, WBC and FBS in the patients with diabetic foot ulcer. In addition, the 300,000 IU is significantly more effective than 150,000 IU.

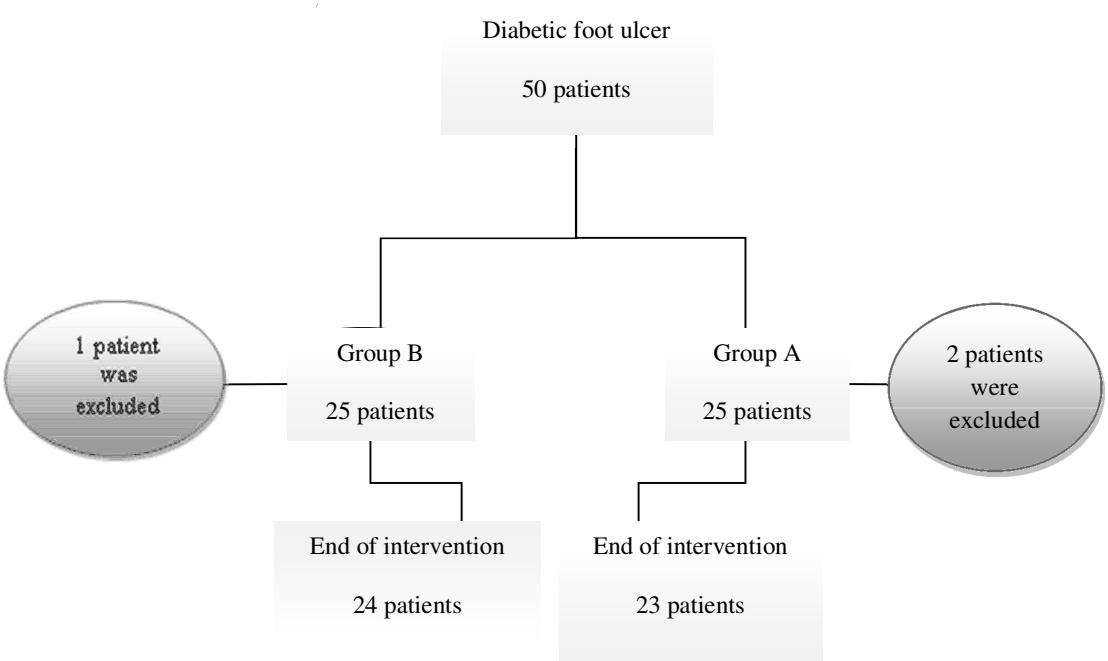

Figure 1.Study Design

The results of this study showed that vitamin D can improve the diabetic foot ulcer, which is similar to the results of other studies (7,12). The findings of Iao Q. Tian et al (23) demonstrated that daily administration of 1- and 25-dehyroxyvitamin D (5 ng and 50 ng) significantly improved the ulcer in mouse. In the study carried out by Johan D. Heilborn et al (7), the effect of local treatment with vitamin D analogue calcipotriol on increasing the expression of hCAP18 protein was analyzed in vivo during the skin ulcer period. A total of 10 patients participated in this study voluntarily and were randomly divided into case and control groups. One side of the treatment area was considered as control in which Vaseline was used for treatment and the other side went through treatment with 24 mg calcipotriol in the form of 5% g ointments. The results showed that 24 hours after ulcer

Table 1. Frequency of qualitative and mean of quantitative variables in the study groups at the beginning of intervention

Variables	150000IU (n=23) Mean ± SD	300000IU (n=24) Mean ± SD	*P*-value*
Age (year)	56.52±7.61	57.46±8.68	0.7
Body mass index (kg/m^2)	27.0±2.17	26.41±2.4	0.3
Diabetes duration (years)	11.3±3.77	11.29±3.95	0.9
Gender	**N (%)**	**N (%)**	***P*-value****
Male	14 (60.9)	13 (54.2)	0.6
Female	9 (39.1)	11 (45.8)	
Body mass index classification			
Normal (18.5-24.9)	5 (21.7)	10 (41.7)	0.1
Overweight (25-29.9)	16 (69.6)	12 (50)	
Obese (>30)	2 (8.7)	2 (8.3)	
Vitamin D status (ng/ml)			
Deficient (<20)	11 (47.8)	13 (54.2)	0.7
Sufficient (>20)	12 (52.2)	11 (45.8)	
Ulcer type (Wagner)			
Wagner 1	6 (26.1)	4 (16.7)	0.5
Wagner 2	17 (73.9)	20 (83.3)	

: Student t-test; **: Chi square test

Table 2. Mean of quantitative variables before and after the intervention for two groups

Variables	Baseline	After	Changes	*P*-value*
25-hydroxyvitamin D (ng/ml)				
1500000IU (n=23)	27.91±19.7	40.53±15.49	12.6±5.0	<0.001
300000IU (n=24)	23.03±15.98	41.62±13.93	18.4±6.4	<0.001
P*-value*	0.56	0.80	0.001	
Fasting blood sugar (mg/dl)				
1500000IU (n=23)	166.09±28.44	154.17±28.53	-11.9±6.9	<0.001
300000IU (n=24)	158.5±32.34	137.21±25.68	-21.3±11.1	<0.001
***P*-value**	0.95	0.03	0.001	
Ulcer area (cm)				
1500000IU (n=23)	8.2±1.38	5.84±0.97	-2.3±0.6	<0.001
300000IU (n=24)	7.92±1.9	5.23±1.29	-2.8±1.0	<0.001
***P*-value**	0.22	0.07	0.05	
Serum CRP (mg/l)				
1500000IU (n=23)	7.3±2.2	5.52±2 0	-1.7±1.0	<0.001
300000IU (n=24)	7.25±2.85	4.38±1.41	-2.9±1.7	<0.001
***P*-value**	0.71	0.02	0.01	
Serum ESR (mg/h)				
1500000IU (n=23)	31.52±6.18	20.52±6.11	-11.0±3.1	<0.001
300000IU (n=24)	29.00±6.97	16.37±5.31	-12.6±3.2	<0.001
***P*-value**	0.46	0.01	0.08	
Serum WBC (µl)×10^3				
1500000IU (n=23)	8.10±1.05	7.94±1.05	-0.15±0.1	<0.001
300000IU (n=24)	8.12±0.87	7.91±0.90	-0.22±0.1	<0.001
***P*-value**	0.83	0.80	0.2	

*:Paired-Samples T-test; **: Student T-test

was created, expression of hCAP18 mRNA was significantly enhanced in the ulcers treated with calcipotriol in comparison with control ulcers, which was in line with the results obtained in the current research which showed vitamin D could effectively improve the diabetic foot ulcer.

Further, the study by Wang TT et al (24) indicated that treatment with vitamin D increased the production of hCAP18 in keratinocytes which is accompanied by restoration of skin cells in human. Human studies conducted on the administration of vitamin D supplement showed the beneficial effects of this supplement among the patient population (25,26). In addition to regulation of calcium and phosphorus, vitamin D has also been reported to have several physiologic functions. Vitamin D can reduce the insulin resistance via regulation of inflammatory and immune processes. Recently, vitamin D has been introduced as a transcription inducer of hCAP18/LL37 genes, which play a significant role in epithelial cells and restoration of tissues (27). Vitamin D is bonded to its hormonal receptors (VDR) in the skin and increases the secretion of hCAP18, followed by enhanced restoration of skin cells (28).

Moreover, Burkiewicz CJ et al (13) performed a study in 2012 and investigated the correlation of vitamin D with skin health improvement. The study participants received 50000 IU of vitamin D for two weeks. After treatment, the mean of ulcer area was reduced from 25 cm to 18 cm in the case group and from 27 cm to 24.5 cm in the placebo group (P=0.78 and 0.70, respectively), indicating no difference between the groups with and without vitamin D deficiency. However, a positive trend was observed between vitamin reserve and ulcer improvement in both groups. These results are in contrast with the findings of the present study. In fact, in the current study 150,000 and 300,000 IU of vitamin D could significantly reduce the ulcer area; therefore administration megadoses of vitamin D are believed to be more effective in diabetic patients.

In addition, Al-Ahmady et al (12) carried out a study in 2013 and evaluated diabetic foot ulcer in four weeks period. The patients were randomly assigned to three groups. The first group received 50 mg zinc gluconate daily after the meal, the second group received 1000 IU of vitamin D twice a day after the meal and the third group was considered the control group. The changes were determined after treatment. The percentage of ulcer reduction in the Zn, vitamin D and placebo groups were reported to be 73.83±6.08, 71.86±4.79 and 32.6±4.28, respectively (P<0.01). This was similar to the current study in that vitamin D improved diabetic foot ulcer.

In the study of Von Hurst et al (26) conducted in 2010 on the insulin-resistant women with vitamin D deficiency, 4000 IU of vitamin D was administered daily over a six-month period and blood parameters were analyzed after 3 and 6 months in CRP group. The testing and non-testing blood levels were slightly decreased and increased, respectively, indicating no statistically significant differences between the study groups. In the current study, CRP level was reported to show no significant difference between groups at baseline and end of the study, but it was significantly reduced in both groups. As a non-specified inflammatory marker, CRP is indicative of general illness and is increased with mild chronic infection or tissue damage in the body.

Also, Mozaffari-Khosravi et al (29) conducted a study in 2011 on the effect of high-dose vitamin D on pro-inflammatory factors in the women with gestational diabetes. A total of 45 patients with gestational diabetes were randomly divided into case and control groups. The case group received a single dose of 300000 IU of vitamin D through intramuscular injection. The findings revealed that about 80% of the mothers had vitamin D deficiency before treatment. They concluded that injection of high-dose vitamin D increased serum vitamin D to 50-80 nmol/l, creating a favorable and immune level for the mothers, reducing insulin resistance and decreasing

diabetes type 2 by preserving it in a favorable condition for a long time.

Yuen-fungYiu et al (30) examined the effect of vitamin D on the endothelial performance in patients with diabetes type 2. The patients in the case group received daily vitamin D supplement (500 ID) for 12 weeks. Their results showed that vitamin D significantly affected the vascular efficiency, inflammatory biomarkers and oxidative stress among the patients with diabetes type 2, whereas no significant reduction was reported for inflammatory markers in the present study.

Another study conducted by Talaei et al (31) investigated the effect of vitamin D on insulin resistance among the diabetic patients. The patients received 50000 IU of vitamin D tablets weekly for a period of two months. The findings showed that 24% of patients were suffering from vitamin D deficiency at baseline. Insulin and serum FPG were significantly reduced after treatment with vitamin D, so they concluded that vitamin D can improve diabetes control.

Finally, the results of this study indicated that vitamin D supplement improved diabetic foot ulcer in the patients with diabetes. Other studies have also reported a positive correlation between vitamin D and ulcer amelioration (13,14). Low level of serum vitamin D has also been demonstrated in the patients with diabetes type 2 (12,32). The limitations of the current research included lack of control group, short follow-up period of four weeks and inclusion of patients with Wagner1 and 2 ulcer. Future studies are recommended to use similar doses with a control group and a longer period to analyze the longer efficacy mega doses of vitamin D in improving the diabetic foot ulcer. Moreover, the effects of vitamin D suggested to be investigated in different types of diabetic ulcer.

Conclusions

The present trial showed that injection of a single dose of 150,000 or 300,000 IU of vitamin D, especially 300,000 IU improves the ulcer and vitamin D status. Therefore, vitamin D status is recommended to be assessed in the clinical care of patients with diabetic foot.

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