Journal of Diabetes and Its Complications xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

The effects of vitamin D supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial

Reza Razzaghi [a], Hamideh Pourbagheri [a], Mansooreh Momen-Heravi [a,b], Fereshteh Bahmani [c], Jafar Shadi [c], Zahra Soleimani [a], Zatollah Asemi [c,*]

[a] Department of Infectious Disease, School of Medicine, Kashan University of Medical Sciences, Kashan, I.R. Iran
[b] Social Determinants of Health Research Center, Kashan University of Medical Sciences, Kashan, I.R. Iran
[c] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R. Iran

ARTICLE INFO

Article history:
Received 23 April 2016
Received in revised form 6 June 2016
Accepted 18 June 2016
Available online xxxx

Keywords:
Vitamin D supplementation
Wound healing
Insulin resistance
Inflammation
Diabetic foot

ABSTRACT

Objective: This study was conducted to evaluate the effects of vitamin D supplementation on wound healing and metabolic status in patients with diabetic foot ulcer (DFU).
Methods: This randomized, double-blind, placebo-controlled trial was performed among 60 patients with grade 3 DFU according to "Wagner–Meggitt's" criteria. Participants were randomly divided into two groups (each 30 participants) and received either 50,000 IU vitamin D supplements every 2 weeks for 12 weeks (group A) or placebo (group B). Fasting blood samples were taken at study baseline and after 12-week intervention to determine related markers.
Results: After 12 weeks of intervention, compared with the placebo, vitamin D supplementation resulted in a significant reduction in ulcer length (-2.1 ± 1.1 vs. -1.1 ± 1.1 cm, $P = 0.001$), width (-2.0 ± 1.2 vs. -1.1 ± 1.0 cm, $P = 0.02$) and depth (-1.0 ± 0.5 vs. -0.5 ± 0.5 cm, $P < 0.001$), and erythema rate (100% vs. 80%, $P = 0.01$). In addition, in supplemented patients changes in serum insulin concentration (-3.4 ± 9.2 vs. $+2.8 \pm 9.3$ μIU/mL, $P = 0.01$), homeostasis model of assessment-estimated insulin resistance (-1.5 ± 4.1 vs. $+1.7 \pm 5.1$, $P = 0.01$), the quantitative insulin sensitivity check index ($+0.006 \pm 0.02$ vs. -0.006 ± 0.02, $P = 0.03$) and HbA1c (-0.6 ± 0.6 vs. -0.1 ± 0.5%, $P = 0.004$) were significantly different from those of patients in the placebo group. Additionally, following supplementation with vitamin D, significant reductions in serum total- (-15.8 ± 18.9 vs. $+5.3 \pm 31.8$ mg/dL, $P = 0.003$), LDL- (-17.2 ± 19.8 vs. $+2.2 \pm 28.6$ mg/dL, $P = 0.003$), total-/HDL-cholesterol ratio (-1.1 ± 0.8 vs. -0.2 ± 1.1, $P = 0.001$), high sensitivity C-reactive protein (hs-CRP) (-0.4 ± 2.5 vs. $+1.9 \pm 4.2$ μg/mL, $P = 0.01$), erythrocyte sedimentation rate (ESR) (-34.7 ± 32.4 vs. -18.0 ± 26.6 mm/h, $P = 0.03$) and plasma malondialdehyde (MDA) concentrations (-0.7 ± 0.9 vs. -0.2 ± 0.5 μmol/L, $P = 0.008$) were seen compared with the placebo.
Conclusions: Overall, vitamin D supplementation for 12 weeks among patients with DFU had beneficial effects on glucose homeostasis, total-, LDL-, total-/HDL-cholesterol, ESR, hs-CRP and MDA levels. In addition, vitamin D may have played an indirect role in wound healing due to its effect on improved glycemic control.

1. Introduction

The diabetic foot ulcer (DFU) is a common complication of diabetes mellitus affecting 10%–25% of people with diabetes (Armstrong et al., 2014). The annual incidence of ulceration and amputation among patients with DFU is as high as 2.5%–10.7% and 0.25%–1.8%, respectively (Tiaka, Papanas, Manolakis, & Maltezos, 2011). Patients with diabetic foot ulcer have a higher mortality compared with patients with diabetes who have not developed food ulcer. DFU is a major cause of morbidity in diabetic patients, and the mortality rate is about twice that of diabetic patients without foot ulcer (Daousi et al., 2004). Diabetic neuropathy and peripheral vascular disease are the main etiological factors in DFU (Sinwar, 2015). Furthermore, insulin resistance, dyslipidemia, inflammation and oxidative stress play a significant role in the pathogenesis of DFU (Karadurmus et al., 2010; Sytze Van Dam, Cotter, Bravenboer, & Cameron, 2013).

Clinical trial registration number: http://www.irct.ir: IRCT201510315623N54.
Conflicts of interest: None declared.
* Corresponding author. Tel.: +98 31 55463378; fax: +98 31 55463377.
E-mail address: asemi_r@yahoo.com (Z. Asemi).

http://dx.doi.org/10.1016/j.jdiacomp.2016.06.017
1056-8727/

In recent years, there has been an effort to understand possible roles of vitamin D inadequacy including its role in pancreatic insulin secretion and insulin action, the immune system particularly on T cell medicated immunity and decreased inflammation and oxidative stress (Asemi, Hashemi, Karamali, Samimi, & Esmaillzadeh, 2013; Zubair, Malik, Meerza, & Ahmad, 2013). Circulating levels of 25(OH)D were low in patients with DFU (Asemi et al., 2013; Tiwari et al., 2013) and the beneficial effects of vitamin D supplementation on markers of insulin resistance, biomarkers of inflammation and oxidative among patients without DFU were reported. We have previously indicated that supplementation with 50,000 IU vitamin D/week among patients with major depressive disorder for 8 weeks had the beneficial effects on parameters of glucose homeostasis, and oxidative stress, but did not affect lipid profiles (Sepehrmanesh et al., 2016). However, improvement in vitamin D status following administration with 280 μg/day for 2 weeks and 140 μg/day for 10 weeks did not improve insulin resistance among patients with diabetes (Kampmann et al., 2014).

The favorable effects of vitamin D supplementations on wound healing, insulin resistance, biomarkers of inflammation and oxidative stress may be mediated by its impact on stimulating the phagocytosis and killing the bacteria by macrophages (van Etten, Decallonne, Bouillon, & Mathieu, 2004), suppressing interferon-g-mediated macrophage activation (Helming et al., 2005), activating insulin receptor expression, and the downregulation of cytokine generation (Pittas, Lau, Hu, & Dawson-Hughes, 2007). As there is evidence that vitamin D intake may accelerate wound healing and has anti-inflammatory and antioxidant effects, we hypothesized that vitamin D supplementation might help patients with DFU to heal their wound faster, and have better metabolic profiles, and biomarkers of inflammation and oxidative stress. The objective of this study was to evaluate the effects of vitamin D supplementation on wound healing and metabolic status in patients with DFU.

2. Methods

2.1. Trial design

The current study was a prospective randomized double-blind placebo-controlled clinical trial.

2.2. Participants

In the current study, 60 patients with grade 3 DFU aged 40–85 years who referred to the Shahid Beheshti Clinic in Kashan, Iran, between November 2015 and January 2016 were recruited. The Wagner–Meggitt's original system has six grades of lesions. This system assesses ulcer depth and the presence of osteomyelitis or gangrene by using the following grades: grade 0 (pre-or postulcerative lesion), grade 1 (partial/full thickness ulcer), grade 2 (probing to tendon or capsule), grade 3 (deep ulcer with abscess or osteomyelitis), grade 4 (partial foot gangrene), and grade 5 (whole foot gangrene) (Jain, 2012). In the current study, all patients had the same grade 3. Pregnant and breastfeeding patients, participants who consumed vitamin D supplements during the past 3 months, anticipated changes in medications throughout the study and patients with history of diseases which influence the development of DFU including chronic trauma were excluded.

2.3. Ethics statements

This trial was conducted in accordance with the Declaration of Helsinki and informed consent was received from all patients. The research was approved by the ethics committee of Kashan University of Medical Sciences (KUMS) and was recorded in the Iranian website for registration of clinical trials (http://www.irct.ir: IRCT201510315623N54).

2.4. Study design

At the onset of the study, all participants were stratified for gender (males: 22 and 8 females in each group), type and dosage of medications, duration of diabetes mellitus (DM), pre-intervention BMI (<25 and ≥25 kg/m^2) and age (<55 and ≥55 years). Participants were then randomly divided into two groups to receive either vitamin D supplements (n = 30) or placebo (n = 30) for 12 weeks.

In addition, all participants underwent a similar treatment protocol for the Diabetic Foot, based on the Infectious Diseases Society of America (IDSA) (Berbari et al., 2015). Participants were requested not to change their ordinary physical activity and not to take any nutritional supplements during the 12-week trial. All patients completed 3-day food records and three physical activity records at the study baseline, weeks 3, 6 and 9 of the intervention and end-of-the trial. Daily macro- and micro-nutrient intakes were analyzed by nutritionist IV software (First Databank, San Bruno, CA). In the current study, physical activity was described as metabolic equivalents (METs) in hours per day. To determine the METs for each patient, we multiplied the times (in hour per day) reported for each physical activity by its related METs coefficient by standard tables (Ainsworth et al., 2000).

2.5. Intervention

In the intervention group, patients received 50,000 IU vitamin D supplements every 2 weeks for 12 weeks. Vitamin D supplements and placebos capsules were similar in shape and size and manufactured by Zahravi (Tabriz, Iran).

2.6. Treatment adherence

Every four weeks, participants were given enough supplements to last until 3 days after their next scheduled visit and were instructed to return all the unused supplements at each visit. Patients were scheduled for the follow-up visits every 2 weeks at weeks 2, 4, 6, 8, 10 and 12 of the intervention for an intermediate evaluation and an ulcer debridement as well as to complete 3-day food records and three physical activity records at weeks 0, 3, 6, 9 and 12 of the intervention. To determine the compliance the remaining supplements were counted and subtracted from the amount of supplements provided to the participants. To increase compliance, all participants received short messages on their cell phones every day to remind them about taking the capsules.

2.7. Assessment of anthropometric measures

Weight and height of participants were determined in an overnight fasting status using a standard scale (Seca, Hamburg, Germany) at the onset of the study and after 12-weeks' intervention. BMI was calculated as weight in kg divided by height in meters squared.

2.8. Assessment of outcomes

In our study, wound healing and markers of insulin resistance were considered as the primary outcome and lipid profiles, and biomarkers of inflammation and oxidative stress were considered as the secondary outcomes.

2.9. Clinical assessment

Ulcer size was measured by multiplying the largest by the second largest perpendicular diameter of the skin lesion. Cumulative ulcer size (sum of the two largest perpendicular diameters and ulcer depth) was also computed for each patient. Depth of the ulcer was defined as

Please cite this article as: Razzaghi, R., et al., The effects of vitamin D supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized,...., *Journal of Diabetes and Its Complications* (2016), http://dx.doi.org/10.1016/j.jdiacomp.2016.06.017