



INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation

Journal Home Page: www.pharmascope.org/ijrps

To study the effect of oral vitamin D supplements on wound healing in patient with diabetic foot ulcer and its effect on lipid metabolism

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Article History:

Received on: 14 Apr 2020
 Revised on: 02 May 2020
 Accepted on: 14 May 2020

Keywords:

Vit D,
 TCH,
 TG,
 HDL and diabetic foot
 ulcer

ABSTRACT

To Critically Assess the effect of oral vitamin D supplements on wound healing in patient with diabetic foot ulcer and its effect on lipid metabolism. This is a single-Centre prospective randomized, control-controlled study was conducted in Department of Surgery Datta Meghe Medical College, Hingana, Nagpur, in collaboration with Datta Meghe Institute of Medical Sciences (DMIMS) Deemed to be University from June 2019 TO March 2020. Total 60 patients were included in this study randomized grouping were done, group A vitamin d supplements and group B as control group. In group A vitamin D levels were significantly increased after 12 weeks of intervention as compared to baseline while in group B no change was seen after intervention. After 12 week of intervention, comparison of group A vs. group B, we found that Vitamin D HbA1c, TC, HDL and Wound surface area, significantly improved while there was no change seen in triglycerides levels in both the group. After intervention with vitamin D supplements for 12 weeks among patients with diabetic foot ulcer had good result and beneficial effect on glucose metabolism, vitamin D levels, lipid profile and wound healing.



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ISSN: 0975-7538

DOI: <https://doi.org/10.26452/ijrps.v11i2.2290>

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INTRODUCTION

Diabetes mellitus is major problem in worldwide in year 2015, 415 million population were known

to have diabetes mellitus. There is increase in diabetic population around 642 million approximately by year 2040. ([International Diabetes Federation, 2015](#)) 69.2 million Population are affected in India, according to recent estimate. ([International Diabetes Federation, 2015](#)) Complication of diabetes mellitus leading to 5 million deaths globally in 2015. ([WHO, 2017](#)) As complication of diabetes mellitus leads to increase morbidity, mortality and health expenditure ([Alexiadou and Doupis, 2012](#)).

Diabetic foot is one of the most significant and devastating complications of diabetes and is characterized as a group of syndromes with neuropathy, ischemia and infection leading to tissue breakdown and eventual amputation. ([Forlee, 2010](#)) Diabetic patients are at greater risk of developing Dia-

betic foot infection and ulcer formation and leading to non-traumatic amputation of foot. It is estimated that approximately 45,000 lower limbs are amputated every year in India and the vast majority of these are probably preventable. (Jain and Viswanath, 2015) Vitamin D has immunomodulatory role with homeostasis of calcium and bone metabolism. (Baeke *et al.*, 2007; Cantorna *et al.*, 2004) Vitamin D has direct effect on the function of the pancreatic cells and treatment with vitamin D supplements would improve in glucose induce insulin secretion. (Lee *et al.*, 1994) Foot infection accounts for 20 % of hospitalisation of diabetic patients annually (Lavin and Neal, 1988). Immunological defects in addition to neuropathy and vascular abnormality are the prime contributors in the pathogenesis of diabetic foot and subsequent infections. (Geerlings, 1999) Different studies have shown that deficiency of vitamin D leads to immune cell dysfunction, b cell damage and impaired insulin production. In addition to hyperglycaemia, vitamin D deficiency could also be linked to an altered immune system of patients with diabetes, rendering them susceptible to foot infection and unfavourable prognosis (Hayes *et al.*, 2003; Mattila *et al.*, 2007; Holick *et al.*, 2011).

So we design this study to evaluate the effect of vitamin D supplements for 12 week in diabetic foot ulcer patient with grade II and grade III wagner diabetic foot ulcer classification comparing with control group.

Aim

To Critically Assess the effect of oral vitamin D supplements on wound healing in patient with diabetic foot ulcer and its effect on lipid metabolism.

Objective

This study is conducted to evaluate the effect of oral vitamin D supplements on wound healing inpatient with diabetic foot ulcer.

To study the effect of oral vitamin D supplements on lipid profile.

MATERIALS AND METHODS

Study Setting

This is a single-Centre prospective randomized, control-controlled study was conducted in Department of Surgery Datta Meghe Medical College Hingna, Nagpur in collaboration with Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi, Wardha, Maharashtra, come under Datta Meghe Institute of Medical Sciences (DMIMS) Deemed to be University.

Duration of study

June 2019 TO March 2020.

Sample size

Total 60 patients were included in this study.

Grouping

Randomized Grouping.

Group A- vitamin D supplements

Group B- control group

Selection criteria

Inclusion Criteria for the Study

Diabetic patients with grades II/ III-foot ulcer

Exclusion Criteria for the Study

Nondiabetic ulcer

Patients with chronic kidney disease (CKD)

Taking immunosuppressant, Calcium supplements and drugs that interfere with vitamin D metabolism.

Liver diseases.

Wagner's grade I, IV and V ulcer.

Lost to follow up.

Trial design

The current study was a prospective randomized controlled clinical trail

Participants

60 patients with grade II/III patients, between 2019 to 2020.

Study design

All participants were stratified for gender, type and duration of DM. Participants were randomly divided into two groups group A received vitamin D supplements every weekly for 12 weeks. Participants were followed-up at every weekly for 12 weeks for assessment of wound healing and vitamin D supplements. Group B were monitored every weekly and no medication were given that would interfere in vitamin D metabolism.

Intervention

Patient received supplements every weekly for 12 weeks. Group A received cholecalciferol 60000 IU sachet and no medication were given to control group that would interfere the vitamin D metabolism.

The data was collected from 60 patients with diabetic ulcers satisfying all the inclusion criteria mentioned above. Selection of patients was done from

Table 1: General characteristics of study participants

| | Group A Vitamin D group(n=30) | Group B control group(n=30) |
|--|-------------------------------------|-----------------------------------|
| Gender (%) | | |
| Male | 25(80%) | 23 (69.57%) |
| Female | 5 (20%) | 7 (30.43%) |
| Age (years) | 60.2±9.3 | 59.7±8.4 |
| Height (cm) | 172.7±14.7 | 169.4±12.5 |
| Weight at start of trial (kg) | 78.6±12.9 | 74.2±15.5 |
| Weight at end of trial (kg) | 78.5±12.8 | 74.1±15.6 |
| Weight change (kg) | 0.01±0.6 | 0.01±1.1 |
| BMI at start of trial (Kg/m ²) | 26.4±4.2 | 25.9±3.8 |
| BMI at end if trial (Kg/m ²) | 26.4±4.1 | 25.9±3.9 |
| BMI change | 0.001±0.04 | 0.006±0.02 |

Table 2: Wound healing, metabolic bio markers, at baseline and 12 weeks of intervention in patients with diabetic foot ulcer

| | Group A [Vitamin D group (n=30)] | | | |
|-------------------|----------------------------------|--------------|------------|---------|
| | Baseline | End of trial | Change | P Value |
| Vitamin D (ng/ml) | 18.5±11.6 | 31±9.8 | -12.5±10.1 | 0.0001 |
| HbA1c (%) | 9.1±2.1 | 7.9±2.7 | 1.2±0.03 | 0.008 |
| TG (mg/dl) | 169.6±54.4 | 150.7±50.3 | 18.8±51.6 | 0.167 |
| T C (mg/dl) | 180.8±30.3 | 165.5±30.7 | 15.1 0.07 | 0.05 |
| HDL (mg/dl) | 34.8±3.8 | 36.1±2.4 | -1.3±1.2 | 0.118 |
| WSA | 29.83±15.02 | 21.76±11.30 | 8.06±6.82 | 0.02 |

Table 3: Wound healing, metabolic bio markers, at baseline and 12 weeks of intervention in control group

| | Group B [Control group (n=30)] | | | |
|---------------------------|--------------------------------|--------------|-----------|---------|
| | Baseline | End of trial | Change | P Value |
| Vitamin D (ng/ml) | 20.5±9.3 | 20.1±8.5 | 0.4±0.3 | 0.86 |
| HbA1c (%) | 9.8±3.5 | 9.9±4.8 | -0.1±0.8 | 0.92 |
| Triglycerides (mg/dl) | 159.4±68.8 | 155.9±70.5 | 3.8±6.4 | 0.846 |
| Total cholesterol (mg/dl) | 172.4±38.2 | 179.2±40.6 | -6.6±2.2 | 0.5 |
| HDL (mg/dl) | 37.6±4.6 | 32.6±5.1 | 5.1±1.3 | 0.002 |
| WSA | 25.06±14.02 | 21.3±13.19 | 3.76±1.73 | 0.28 |

consecutive series of prospective patients. Randomized grouping was done, Group A as a vitamin D supplements and group B as control. Informed written consent was obtained from all participants. A detailed clinical history, including age, sex, height, weight, BMI calculation done at start and end of trial, duration of diabetes, wound surface area was taken on baseline and end of trial and concomitant and anti-diabetic medications, was recorded on a preset proforma. Patient were followed or examined for 12 weeks after standard care and Wound healing rate

was assessed by change in surface area and calculated by below mentioned formula,

$$\text{Surface area change } \Delta A = A_a - A_b$$

Where, A_a = wound area on admission

A_b=wound area on 12 weeks

$$BMI (\%) = \frac{Kg}{m^2} \times 100$$

Where, kg= weight of patient

M^2 = height of patient (cm)

WSA = wound surface area

Sample collection

Blood samples with and without anti-coagulant was collected for estimating glycosylated HbA1c and serum 25-hydroxyvitamin D (25(OH) D), Lipid Profile, respectively.

Serum 25-hydroxyvitamin D assay

Serum 25(OH)D was estimated by Radioimmunoassay (RIA)

Adequacy of vitamin D

Different cut-offs of vitamin D level for deficiency is chosen, i.e., ≤ 25 (severe), ≤ 50 (moderate) and ≤ 75 (mild) nmol/l for evaluating the most appropriate risk factor in patients with diabetic foot infection. The three cut-offs of vitamin D deficiency chosen are in accordance with the recommendation of Endocrine Society practice guidelines (Holick *et al.*, 2011) and Institute of Medicine definitions (Institute Of Medicine, 2011).

The Wagner Diabetic Foot Ulcer Grade Classification System

The Wagner diabetic foot ulcer classification system assesses ulcer depth and the presence of osteomyelitis or gangrene by using the following grades:

1. Grade 0 – intact Skin
2. Grade 1 – superficial ulcer of skin or subcutaneous tissue
3. Grade 2 – ulcers extend into tendon, bone, or capsule
4. Grade 3 – deep ulcer with osteomyelitis, or abscess
5. Grade 4 – partial foot gangrene
6. Grade 5 – whole foot gangrene

Statistical Analysis

Data collected was entered into Microsoft Excel Worksheet and statistically analysed by using SPSS (Statistical Package for Social Sciences) version 20. For quantitative data mean, standard mean, standard deviation, t-test and Karl Pearson's Coefficient of Correlation were calculated. P value < 0.05 (0.01) will be considered as statically significant (highly significant) at 95% confidence interval.

Ethical Consideration

Informed and written consent (Marathi and English) was taken from each subject before collecting data and blood sample. Only those individuals, who volunteer to participate in the study, was included and the data was kept confidential. The study was not imposing any burden on the subjects and the Institute; therefore, the study is ethically justified. The proposed study was undertaken subject to approval by Institutional Ethical Committee.

RESULTS AND DISCUSSION

Table 1 shows the demographic characteristic of two groups. In vitamin D group males were 25 and females were 5 out of 25 while in control group males were 23 and females were 7 respectively. Mean age was 60.2 ± 9.3 in group A and 59.7 ± 8.4 in group B, height was 172.7 ± 14.7 in group A and 169.4 ± 12.5 in group B respectively. In group A mean weight of patient at baseline was 78.6 ± 12.9 and at the end of trial was 78.5 ± 12.8 , while in group B baseline was 74.2 ± 15.5 and at the end of trial was 74.1 ± 15.6 . Weight change was 0.01 ± 0.6 and 0.01 ± 1.1 in group A and B respectively. In group A, BMI at baseline and end of trial was 26.4 ± 4.2 and 26.4 ± 4.1 , while change was 0.001 ± 0.04 . In group B, BMI at baseline and end of trial was 25.9 ± 3.8 and 25.9 ± 3.9 , while change was 0.001 ± 0.04 respectively.

Table 2 shows in group A vitamin D levels were significantly increased after 12 weeks of intervention as compared to baseline (18.5 ± 11.6 vs. 31 ± 9.8 , $p=0.0001$). There was significant change in HbA1c level after intervention in group A (9.1 ± 2.1 vs. 7.9 ± 2.7 , $p=0.008$). Similar results were seen in total cholesterol levels after intervention in group A (180.8 ± 30.3 vs. 165.5 ± 30.7 , $p=0.05$). Wound surface area was (29.83 ± 15.02 vs. 21.76 ± 11.30 , $p=0.02$) in group A. The level of high-density lipoprotein in group A (34.8 ± 3.8 vs. 36.1 ± 2.4 , $p=0.118$) after 12 weeks of intervention. High density lipoprotein in group A was 34.8 ± 3.8 in baseline and at the end of trial was 36.1 ± 2.4 and change was -1.3 ± 1.2 and no significant change was observed p value is 0.118.

Table 3 shows in group B no change was seen after intervention (20.5 ± 9.3 vs. 20.1 ± 8.5 , $p=0.86$). HbA1c level after intervention in was group B (9.8 ± 3.5 vs. 9.9 ± 4.8 , $p=0.92$). Total cholesterol levels after intervention in group B (172.4 ± 38.2 vs. 179.2 ± 40.6 , $p=0.5$). Wound surface area was in group B (25.06 ± 14.02 vs. 21.3 ± 13.19 , $p=0.28$). The level of high-density lipoprotein in group B (37.6 ± 4.6 vs. 32.6 ± 5.1 , $p=0.002$) was significantly lower level after 12 weeks of intervention. No signifi-

Table 4: Changes in wound surface area and change in metabolic bio markers after intervention for 12 weeks

| Parameters | Group A Vitamin D group | Group B Control group | P Value |
|--------------------|----------------------------|--------------------------|---------|
| Vitamin D | 12.5±10.1 | 0.4±0.3 | 0.0001 |
| HbA1c | 1.2±0.03 | 0.1±0.8 | 0.0001 |
| Triglycerides | 18.5±51.6 | 3.8±6.4 | 0.126 |
| Total cholesterol | 15.1 0.07 | 6.6±2.2 | 0.0001 |
| HDL | 1.3±1.2 | 5.1±1.3 | 0.0001 |
| WSA after 12 weeks | 8.06±6.82 | 3.76±1.73 | 0.0014 |

icant changes were seen in triglycerides level group B.

Table 4 shows change after 12 weeks of intervention. After 12 week of intervention, comparison of group A vs. group B, we found that Vitamin D (12.5±10.1 vs. 0.4±0.3, p=0.0001), Glycoslated hemoglobin (1.2±0.03 vs. 0.1±0.8, p=0.0001), Total cholesterol (15.1 0.07 vs. 6.6±2.2, p=0.0001), High density lipoprotein (1.3±1.2 vs. 5.1±1.3, p=0.0001) and Wound surface area (8.06±6.82 vs. 5.1±1.3, p=0.0001), significantly improved while there was no change seen in triglycerides levels (18.5±51.6 vs. 3.8±6.4, p=0.126) in both the group.

In our study, we study the effect of vitamin D supplements in diabetic foot ulcer patients. We supplemented patients with oral cholecalciferol sachet (60,000-IU) every weekly for 12 week and patients were followed up every weekly for supplements and for examination. Control groups were not given any medication which will interfere with vitamin D metabolism. After 12 weeks of intervention, we evaluated wound surface area, lipid concentration (total cholesterol, triglyceride and high-density lipoprotein) and glycoslated hemoglobin.

Vitamin D levels (12.5±10.1 vs. 0.4±0.3, p=0.0001) significantly raised after intervention for 12 weeks. In this study we found that vitamin D supplements had beneficial effect on wound surface area as compared to control group (8.06±6.82 vs. 5.1±1.3, p=0.0001), there was marked reduction in size of wound surface area. There was significant decrease in level of glycoslated hemoglobin (1.2±0.03 vs. 0.1±0.8, p=0.0001) after intervention. We found significant decrease in total cholesterol levels (15.1 0.07 vs. 6.6±2.2, p=0.0001). Levels of high-density lipoproteins were elevated in group A as compared to group B (1.3±1.2 vs. 5.1±1.3, p=0.0001). No changes seen in triglycerides level in both groups.

In our study, we found that patients in group A, vitamin D, glycosylated hemoglobin total cholesterol, high density lipoprotein significantly improved and

significant reduction in wound surface area after intervention.

Silimar effect are seen in few studies rezza razaghi et al vitamin D supplementation for 12 weeks in patients with DFU had beneficial effects on glucose homeostasis, lipid profile and reduction in diabetic foot ulcer size ([Institute Of Medicine, 2011](#)).

Silimar effects were observed by Hassan Mozaffari-Khosravi et al after intervention with injectable vitamin d, wound size significantly reduced and improves glucose metabolism and vitamin D levels. (2020) ([Razzaghi et al., 2017](#)).

In our study we found that there was increase in vitamin D levels and decrease in glycosylated hemoglobin and decrease wound surface area after 12 week intervention, Hu, Zhiwei MM et al suggested that Vitamin D supplementation in diabetic mellitus patients can improve HbA1c, insulin resistance, and insulin in short-term intervention, suggesting that vitamin D can be considered as a therapeutic agent along with the other treatments for T2D. Studies have shown that vitamin D deficiency is associated with the development of T2D, T2D nephropathy, T2D microvascular or macrovascular disease, diabetic retinopathy, and diabetic peripheral neuropathy ([Mozaffari-Khosravi et al., 2016](#); [Hu et al., 2019](#)).

CONCLUSIONS

Present study supports that vitamin D deficiency is more prominent in diabetic foot patients and impaired wound healing and glucose metabolism. After intervention with vitamin D supplements for 12 weeks among patients with diabetic foot ulcer had good result and beneficial effect on glucose metabolism, vitamin D levels, lipid profile and wound healing. The only limitation was that, this study had small sample size and diabetic subjects with diabetic foot ulcer.

Conflict of Interest

Nil.

Source of Funding

Nil.

REFERENCES

Institute Of Medicine 2011. *Dietary Reference Intakes for Calcium and Vitamin D*. The National Academies Press, Washington, DC.

Alexiadou, K., Doupis, J. 2012. Management of Diabetic Foot Ulcers. *Diabetes Therapy*, 3(1).

Baeke, F., Etten, E. V., Overbergh, L., Mathieu, C. 2007. Vitamin D3 and the immune system: maintaining the balance in health and disease. *Nutrition Research Reviews*, 20(1):106–118.

Cantorna, M. T., Zhu, Y., Froicu, M., Wittke, A. 2004. Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. *The American Journal of Clinical Nutrition*, 80(6):1717S–1720S.

Forlee, M. 2010. What is the diabetic foot? The rising prevalence of diabetes worldwide will mean an increasing prevalence of complications such as those of the extremities. *Continuing Medical Education*, 28:152–156.

Geerlings, S. 1999. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunology and Medical Microbiology*, 26(3-4):259–265.

Hayes, C. E., Nashold, F. E., Spach, K. M., Pedersen, L. B. 2003. The immunological functions of the vitamin D endocrine system. *Cellular and Molecular Biology*, 49(2):277–300.

Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., Murad, M. H., Weaver, C. M. 2011. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, 96(7):1911–1930.

Hu, Z., Chen, J., Sun, X., Wang, L., Wang, A. 2019. Efficacy of vitamin D supplementation on glycemic control in type 2 diabetes patients. *Medicine*, 98(14).

International Diabetes Federation 2015. Update of mortality attributable to diabetes for the IDF Diabetes Atlas: Estimates for the year 2013. *Diabetes Research and Clinical Practice*, 109(3):461–465.

Jain, A., Viswanath, S. 2015. Studying major amputations in a developing country using Amit Jain's typing and scoring system for diabetic foot complications - time for standardization of diabetic foot practice. *International Surgery Journal*, 2(1):26–30.

Lavin, M. E., Neal, L. W. 1988. *The Diabetic Foot*. CW Mosby Co, St Louis.

Lee, S., Clark, S. A., Gill, R. K., Christakos, S. 1994. 1,25-Dihydroxyvitamin D3 and pancreatic beta-cell function: vitamin D receptors, gene expression, and insulin secretion. *Endocrinology*, 134(4):1602–1610.

Mattila, C., Knekt, P., Mannisto, S., Rissanen, H., Laaksonen, M. A., Montonen, J., Reunanen, A. 2007. Serum 25-Hydroxyvitamin D Concentration and Subsequent Risk of Type 2 Diabetes. *Diabetes Care*, 30(10):2569–2570.

Mozaffari-Khosravi, H., Haratian-Arab, M., Tavakkoli, H. M., Nadjarzadeh, A. 2016. 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 TT - IJDO*, 8(4):164–171.

Razzaghi, R., Pourbagheri, H., Momen-Heravi, M., Bahmani, F., Shadi, J., Soleimani, Z., Asemi, Z. 2017. 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. *Journal of Diabetes and its Complications*, 31(4):766–772.

WHO 2017. Top 10 causes of death.