International Surgery Journal
Kamble A et al. Int Surg J. 2019 May;6(5):1654-1658
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: http://dx.doi.org/10.18203/2349-2902.isj20191886

Original Research Article

A study of the prevalence and severity of vitamin D deficiency in patient with diabetic foot and its association with vascular calcification and effect on healing

Ajonish Kamble, Manish Swarnkar*

Department of Surgery, Jawaharlala Nehru Medical Collage, Sawangi, Meghe, Wardha, Maharashtra, India

Received: 07 February 2019
Revised: 15 March 2019
Accepted: 23 March 2019

***Correspondence:**
Dr. Manish Swarnkar,
E-mail: mswarnkar1971@gmail.com

ABSTRACT

Background: With the increasing prevalence of diabetes mellitus (DM), vitamin D (vit D) deficiency and vascular calcification is frequently observed in DM and is an indicator of diabetic peripheral vascular disease with variable implications. Due to the current limited understanding, this research was initiated. Aims and objective was to critically assess the prevalence and severity of vitamin D deficiency in patients with diabetic foot infection, the association between vascular calcification and vitamin D deficiency and effect on healing in diabetic foot patient with and without vitamin D deficiency.
Methods: This observational study was conducted on 50 patients with diabetes mellitus. A detailed clinical history was recorded. Infection was confirmed by culture positivity and Doppler was used to detect vascular calcification. A follow-up for 3 weeks was done after which wound healing rate was assessed by change in wound surface area. Data was analyzed by Chi-square test and multivariate regression analysis.
Results: 58% patients were diagnosed with vitamin D deficiency. 40% of patients found to have VC associated with DM. 100 % association of VC was found in patients with severe vitamin D deficiency. Vitamin D deficiency significantly correlated with vascular calcification (p=0.0001). A significant difference was observed in wound healing between the patients with and without vitamin D deficiency i.e. 3.14±2.04mm.sq and 4.36±1.39mm.sq.
Conclusions: This study opens up an issue of recognizing vitamin D deficiency as a possible risk factor for diabetic foot infections and suggests the need for vitamin D supplementation.

Keywords: Diabetic foot infection, Vascular calcification, Vitamin D deficiency, Wound healing

INTRODUCTION

Vitamin D is a pleiotropic hormone known to play an immunomodulatory role in addition to Calcium and bone metabolism.[1,2] Receptors for its activated form have been identified on pancreatic β cells and immune cells.[3,4] Studies have proven association of vitamin D deficiency with viral and bacterial infection Foot infection accounts for 20% of hospitalization of diabetic patients annually.[5,6] Pathogenesis of diabetic foot and subsequent infections is related to immunological defects along with neuropathy and vascular abnormalities being the major contributors.[7]

Different studies have shown that deficiency of vitamin D leads to immune cell dysfunction, β cell damage and impaired insulin production.[3,8] 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.

Vascular calcification, long thought to be result of passive degeneration, involves a complex, regulated process of bio mineralization resembling osteogenesis. Vascular calcification is an important development in progression of vasculopathy. Diabetes mellitus contributes significantly to high prevalence of peripheral vascular disease and lower extremity amputation in these subjects. Vascular calcification is also associated with other manifestation of cardiovascular diseases like hypertension, coronary insufficiency and increased mortality in patients with diabetes mellitus.

Traditionally, medial arterial calcification has been associated with ageing, advanced chronic kidney disease and long-standing diabetes mellitus with diabetic neuropathy. Factors that potentiate medial arterial calcification in diabetes mellitus may include metabolic and hormonal along with activation of receptor activator of nuclear factor Kappa B ligand/osteoprotegerin (RANK-L/OPG) signalling pathway.[6] Interleukins, 25(OH) vitamin D, sex, parathyroid hormone (PTH), lipoprotein, steroids, thyroid etc. directly or indirectly regulate RANK-L/OPG pathway.[7]

The literature on the role of 25(OH) vitamin D in vascular calcification is ambiguous. Experimentally higher 25(OH) vitamin D level have been associated with increased vascular calcification while *in vivo*, lower level of 25(OH) vitamin D seems to have this effect. This suggests that 25 (OH) vitamin D may have a biphasic relation with risk promoting Vascular Calcification in both excess and deficiency.[8] Authors hence designed the present study to find out the prevalence and severity of vitamin D deficiency in patients with diabetic foot infection and vascular calcification in diabetic foot patient and its effect on healing.

METHODS

This observational study was conducted in Department of General Surgery in the tertiary health care Centre of ACHARYA VINOBHA BHAVE RURAL HOSPITAL (AVBRH) attached to Jawaharlal Nehru Medical College (JNMC) from October 2016 TO October 2018 after obtaining Institutional Ethical Committee clearance (DMIMS(DU)/IEC/2016-17/5001). Total 50 patients of Diabetes Mellitus with grades I/ II/III foot ulcer were included in the study. Patients with non-diabetic ulcer, chronic kidney disease (CKD), patients on drugs that interfere with vitamin D metabolism, Wagner's grade IV and V ulcer and patients lost to follow up were excluded from the study. The sample size was calculated using

$n = 2SP^2 [Z_{\alpha/2} + Z_{\beta}]^2/d^2$.

There were 50 patients satisfying all the criteria were selected after obtaining written informed consent and data was collected. A detailed clinical history, including age, sex, duration of diabetes, and concomitant and anti-diabetic medications and wound surface area on admission was recorded was recorded on a present proforma. Blood samples with and without anti-coagulant were collected for estimating glycosylated HbA1c and serum 25-hydroxyvitamin D (25(OH) D) by radioimmunoassay. Different cut-offs of vitamin D level for deficiency were chosen, i.e., ≤25 (severe), ≤50 (moderate) and ≤75(mild) nmol/l in accordance with the recommendations of endocrine society practice guidelines and institute of medicine definitions.[7,8] Infection was confirmed by culture positivity or fever with leucocytosis and Doppler was used to detect vascular calcification. After a period of 3 weeks (on 21st day) wound healing rate was assessed by change in surface area and calculated (Table 1).

Table 1: Formula to calculate rate of wound healing.

Change in Surface area (ΔA) = Aa - Ab
Aa = wound surface area on admission
Ab=wound surface area on 21st day
Surface area change per week (ΔA_W)= ΔA/Number of Weeks

Statistical analysis

Data was presented as means and standard deviations. Statistical analysis was done by using descriptive and inferential statistics using chi-square test and multivariate regression analysis. Software used in the analysis were SPSS 22.0 version and GraphPad Prism 6.0 version and $p<0.05$ was considered as the level of significance.

RESULTS

In the present study, out of 50 patients, 42 were males and 8 were females with mean age of 52.90 years and standard deviation of 16.88 years. The mean duration of DM was 8.70 with standard deviation of 6.60 and 10 patients were diagnosed diabetes mellitus on admission. Majority of patients had grade I ulcer (50%) followed by Grade III ulcer (26%) and Grade II ulcer (24%). 42% of patients had no vitamin D deficiency followed by moderate (28%), mild (18%) and severe (12%) vitamin D deficiency. Vascular calcification was present in 40 % of patients with mean HbA1C was found to be 8.89 (Table 2).

In multivariate regression analysis (Table 3), wound surface area change per week is dependent variable, correlated with independent variable i.e. age, gender, duration of diabetes mellitus, grades of ulcer, glycosylated hemoglobin, vitamin D deficiency, vascular calcification and wound surface area on admission. On multivariate regression analysis only duration of DM, vitamin D deficiency and wound surface area on admission found to have significant impact on wound surface area change per week (healing rate) ($p<0.5$).

In multivariate regression analysis (Table 4), vascular calcification is dependent variable correlated with

independent variable i.e. age, gender, duration of diabetes mellitus, grades of ulcer, glycosylated hemoglobin, vitamin D deficiency and wound surface area on admission. On multivariate regression analysis only gender and vitamin D deficiency found to have significant impact on vascular calcification (p<0.5).

Table 2: Comparison of clinical and biochemical characteristics of diabetic foot patients.

Parameters	Values
Total No of patients	50
Age (Mean ±SD)	52.90±16.88
Sex (M/F) no.	42/8
Duration of DM (Mean ±SD)	8.70±6.60 (10 patients diagnosed on admission)
Grades of ulcer	Grade I 50%, Grade II 24% , Grade III 26%
Vitamin D deficiency	No deficiency 42%, mild 18%, moderate 28%, severe 12%
Vascular calcification	Present in 40% (20 patients)
HbA1C(%) mean	8.89

Table 3: Multivariate regression analysis for predicting association of different independent variable on healing rate (response variable).

	Unstandardized Coefficients		t	P value
	B	Std. error		
Wound surface area change per week (mm.sq)	7.088	2.123	-	-
Age	0.324	0.019	1.651	0.106, NS
Gender	0.455	0.588	0.773	0.443, NS
Duration of DM	0.113	0.050	2.272	0.028, S
Grades of ulcer	0.674	0.505	1.335	0.189, NS
Glycosylated Hb%	0.182	0.178	1.027	0.310, NS
Vitamin D deficiency	0.897	0.378	2.374	0.022, S
Vascular calcification	0.347	0.903	0.385	0.701, NS
Wound surface area on admission	0.046	0.0148	3.100	0.003, S

In multivariate regression analysis (Table 5), vitamin D deficiency is dependent variable correlated with independent variable i.e. age, gender, duration of diabetes mellitus, grades of ulcer, glycosylated hemoglobin, vascular calcification and wound surface area on admission. On multivariate regression analysis only gender, grades of ulcer, glycosylated hemoglobin and vascular calcification found to have significant impact on vitamin D deficiency (p<0.5).

Table 4: Multivariate regression analysis for predicting association of different independent variable on vascular calcification (response variable).

	Unstandardized coefficients		t	P value
	B	Std. error		
Vascular calcification	1.547	0.273	-	-
Age	0.002	0.003	0.901	0.372, NS
Gender	0.246	0.093	2.647	0.011, S
Duration of DM	0.009	0.008	1.155	0.254, NS
Grades of ulcer	0.234	0.078	2.960	0.005, S
Glycosylated Hb %	0.045	0.029	1.525	0.134, NS
Vitamin D deficiency	0.326	0.040	8.096	0.001, S
Wound surface area on admission	0.001	0.002	0.500	0.619, NS

Table 5: Multivariate regression analysis for predicting association of different independent variable on vitamin D deficiency (response variable).

	Unstandardized coefficients		t	P value
	B	Std. error		
Vitamin D deficiency	2.479	0.777	-	-
Age	0.006	0.007	0.847	0.401, NS
Gender	0.458	0.228	2.129	0.039, S
Duration of DM	0.007	0.020	0.365	0.716, NS
Grades of ulcer	0.461	0.193	2.385	0.021, S
Glycosylated Hb%	0.161	0.068	2.366	0.022, S
Vascular calcification	1.864	0.230	8.096	0.001, S
Wound surface area on admission	0.000	0.006	0.032	0.975, NS

DISCUSSION

In the present study, according to recommendation of endocrine society practice guideline three ranges were chosen for evaluation of vitamin D deficiency i.e. mild, moderate and severe. According to recommendation of endocrine society practice guideline, i.e. mild is less than 75nmol/l, moderate is less than 50nmol/l and severe is less than 25nmol/l as per Tiwari S et al.[1] In our study we found that 18% patients reported with mild, 28% with moderate, 12% with severe vitamin D deficiency. Patient with no vitamin deficiency were 42%. Majority of patients had moderate vitamin D deficiency in our study. Prevalence of vitamin D deficiency in diabetic foot patients was significantly higher.

It was found that 40% of patients had vascular calcification with Vitamin D deficiency (p=0.0001). Patients with no vitamin D deficiency had no vascular calcification. Suggesting significant association between vitamin D deficiency and vascular calcification in diabetic foot patients.

It was found that wound surface area change per week is dependent variable, correlated with independent variable i.e. age, gender, duration of diabetes mellitus, grades of ulcer, glycosylated haemoglobin, vitamin D deficiency, vascular calcification and wound surface area on admission. On multivariate regression analysis only duration of DM, vitamin D deficiency and wound surface area on admission found to have significant impact on wound surface area change per week (healing rate). (p<0.5) Margolis et al, found in his study that Logistic regression odds ratios (ORs; 95% confidence intervals [95%CIs]) revealed that those patients with a diabetic neuropathic foot ulcer that healed within 20 weeks using standard care were more likely to have a smaller wound (OR = 0.67; 95% CI, 0.55-0.81), a wound that existed for a shorter period (OR = 0.73; 95% CI, 0.61-0.87), and be non-white (OR = 0.64; 95% CI,0.43-0.96) compared with patients whose wounds did not heal within 20 weeks.[13] The patient's age (OR = 0.99; 95% CI, 0.89-1.01), serum level of glycosylated haemoglobin at the start of the study (OR = 1.03; 95% CI, 0.97-1.10), and sex (OR = 1.02; 95% CI, 0.69-1.50) were associated with the probability of wound healing.

Similarly in study by Margolis et al (2002) demonstrated that The risk factors or wound characteristics that most dramatically are associated with a wound failing to heal are increasing wound size, increasing wound duration, and the grade of the wound.[14] In a study by Oyibo et al (2001) diabetic medicine, 18: 133-138) Found that Ulcer area correlated with healing time (rs = 0.27, P<0.0001) and predicted healing (P = 0.04). Patient's age, sex, duration/type of diabetes, and ulcer site had no effect on outcome.[15]

It was found that vascular calcification is dependent variable correlated with independent variable i.e. age, gender, duration of diabetes mellitus, grades of ulcer, glycosylated haemoglobin, vitamin D deficiency and wound surface area on admission. On multivariate regression analysis only gender and vitamin D deficiency found to have significant impact on vascular calcification (p<0.5). In a study by Sharma et al (2010) it was found that the only factor independently associated with calcification was duration of known diabetes (P = 0.004).[16] Similarly Moon et al (2010) found advancing age, male sex were the significant risk covariates for MAC of legs.[17]

It was found that vitamin D deficiency is dependent variable correlated with independent variable i.e. age, gender, duration of diabetes mellitus, grades of ulcer, glycosylated haemoglobin and vascular calcification and wound surface area on admission. On multivariate regression analysis only gender, grades of ulcer, glycosylated haemoglobin and vascular calcification found to have significant impact on vitamin D deficiency (p<0.5). Similar results were also shown in a study by Zubair M et al (2012) that A significant correlation exists between 25(OH)D level and ulcer grades [r = 0.012, p<0.002], H bA1c (>6.9%) [r = 0.342, p < 0.032].[18] In study by Zhou et al (2015) the correlation analysis results suggested that the level of 25(OH)D was inversely associated with duration (r=-0.663,p‹.05), HbA1c (r= -0.482, p<0.05).[19]

CONCLUSION

Present study supports the proposition that vitamin D deficiency is more dominant in diabetic foot infection. Wound healing is impaired in diabetic patients while vitamin D is essential for a normal functioning immune system. The most active vitamin D metabolite, 1,25-dihydroxyvitamin D3, induces antimicrobial peptides production in keratinocytes from diabetic foot ulcers. This study opens up an issue of recognizing vitamin D deficiency as a possible risk factor for diabetic foot infections and suggests the need for vitamin D supplementation in such patients to prevent or to adjuvant the antibiotic therapy for control of infection. Our data also raise the possibility that 25(OH)D might provide an adjunctive method for early detection of risk for foot complications in diabetes.

ACKNOWLEDGEMENTS

Authors would like to thank the institution and patients which helped in completion of research project.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of Datta Meghe Institute of Medical Sciences, Wardha, Maharashtra, India (DMIMS(DU)/IEC/2016-17/5001)

REFERENCES

1. Tiwari S, Pratyush DD, Gupta B, Dwivedi A, Chaudhary S, Rayicherla RK, et al. Prevalence and severity of vitamin D deficiency in patients with diabetic foot infection. Br J Nutr. 2013 Jan;109(01):99-102.
2. Swain J, Tiwari S, Dd P, Dwivedi A, Gupta B, Shukla RC, et al. Vascular calcification in diabetic foot and its association with calcium homeostasis. Indian J Endocrinol Metab. 2012;16:S450-2.
3. Baeke F, Etten EV, Overbergh L, Mathieu C. Vitamin D3 and the immune system: maintaining the balance in health and disease. Nutr Res Rev. 2007 Jun;20(1):106-18.
4. Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D3, and the

immune system. Am J Clin Nutr. 2004;80(6 Suppl):1717S-20S.
5. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr. 2004 May;79(5):820-5.
6. Veldman CM, Cantorna MT, DeLuca HF. Expression of 1,25-dihydroxyvitamin D(3) receptor in the immune system. Arch Biochem Biophys. 2000 Feb 15;374(2):334-8.
7. Kawaura A, Takeda E, Tanida N, Nakagawa K, Yamamoto H, Sawada K, et al. Inhibitory effect of long term 1α-hydroxyvitamin D3 administration on Helicobacter pylori infection. J Clin Biochem Nutri. 2006;38(2):103-6.
8. Sabetta JR, DePetrillo P, Cipriani RJ, Smardin J, Burns LA, Landry ML. Serum 25-hydroxyvitamin d and the incidence of acute viral respiratory tract infections in healthy adults. PloS one. 2010;5(6):e11088.
9. Pfeifer M BJ. Levin and O'Neal's The Diabetic Foot. 7th ed. Elsevier; 2007:203-205.
10. Jeffcoate WJ, Rasmussen LM, Hofbauer LC, Game FL. Medial arterial calcification in diabetes and its relationship to neuropathy. Diabetologia. 2009;52(12):2478-88.
11. Hofbauer LC, Heufelder AE. Role of receptor activator of nuclear factor-kappaB ligand and osteoprotegerin in bone cell biology. J Mol Med Berl Ger. 2001;79(5-6):243-53.
12. Hsu JJ, Tintut Y, Demer LL. Vitamin D and osteogenic differentiation in the artery wall. Clin J Am Soci Nephrol. 2008;3(5):1542-7.
13. Margolis DJ, Kantor J, Santanna J, Strom BL, Berlin JA. Risk factors for delayed healing of neuropathic diabetic foot ulcers: a pooled analysis. Arch Dermatol. 2000;136(12):1531-5.
14. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: the association of wound size, wound duration, and wound grade on healing. Diabetes Care. 2002 Oct;25(10):1835-9.
15. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Armstrong DG, Harkless LB, et al. The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. Diabet Med J Br Diabet Assoc. 2001;18(2):133-8.
16. Sharma A, Scammell BE, Fairbairn KJ, Seagrave MJ, Game FL, Jeffcoate WJ. Prevalence of Calcification in the Pedal Arteries in Diabetes Complicated by Foot Disease. Diabetes Care. 2010;33(5):e66-e66.
17. Moon JS. A controlled study of medial arterial calcification of legs: implications for diabetic polyneuropathy. Arch Neurol. 2011;68(10):1290.
18. Akther JM, Khan IA, Shahpurkar VV, Khanam N, Syed ZQ. Evaluation of the diabetic foot according to Wagner's classification in a rural teaching hospital. Br J Diabetes Vasc Dis. 2011;11(2):74-9.
19. Zhou W, Ye SD. relationship between serum 25-hydroxyvitamin d and lower extremity arterial disease in type 2 diabetes mellitus patients and the analysis of the intervention of vitamin D. J Diabetes Res. 2015;2015:1-6.

Cite this article as: Kamble A, Swarnkar M. A study of the prevalence and severity of vitamin D deficiency in patient with diabetic foot and its association with vascular calcification and effect on healing. Int Surg J 2019;6:1654-8.