ORIGINAL ARTICLE

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Vitamin-D status and metabolic syndrome in patients with type 2 diabetes mellitus

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Abstract

Introduction: Vitamin-D, besides its role in calcium and phosphorus homeostasis, has been increasingly recognized to affect various other metabolic processes including insulin secretion and sensitivity. Thus, Vitamin-D has a potential role in development of type 2 diabetes mellitus and metabolic syndrome. This study aims to evaluate the status of Vitamin-D and metabolic syndrome among patients with type 2 DM.

Method: This is a hospital based cross-sectional observational study conducted at Bir Hospital, Kathmandu, Nepal from October 2017 to March 2018. Adult patients above 18 years with newly diagnosed type 2 diabetes or those already diagnosed and under medication were included in this study. Baseline characters, Vitamin-D status, metabolic syndrome were evaluated. Statistical package for social sciences (SPSS) version 20 was used for data analysis.

Result: Fifty-eight participants; 38 (65.52%) males and 20 (34.48%) females were enrolled. Fifty-two (89.67%) participants had low Vitamin-D levels (either deficiency or insufficiency). The mean vitamin D level was 18.78 ng/ml. Metabolic syndrome was seen among 37 (63.8%) participants. Low Vitamin-D (deficient or insufficient) was more common among those with metabolic syndrome (97.3%) compared to those without metabolic syndrome (76.19%).

Conclusion: Type 2 diabetes patients have high prevalence of hypovitaminosis-D and metabolic syndrome. Vitamin-D deficiency is more common in those with metabolic syndrome.

Keywords: Metabolic Syndrome, Type 2 Diabetes Mellitus, Vitamin-D

INTRODUCTION

Vitamin-D, besides its role in calcium-phosphorus homeostasis and bone health, is being increasingly recognized to have role in development of diabetes and metabolic syndrome.[1–3] Studies have shown higher prevalence of hypovitaminosis-D in diabetes.[3] Vitamin-D enhances insulin response to glucose stimulation,[1,4] and stimulates insulin receptor expression and insulin responsiveness for glucose transport in tissues.[5] Thus hypovitaminosis-D could contribute to insulin resistance, diabetes and metabolic syndrome.

Analysis of data from third US National Health and Nutrition Examination Survey (NHANES) showed highest quartile of Vitamin-D was protective against diabetes with odds ratio of 0.25 compared with lowest quartile.[6] It also showed an inverse association between Vitamin-D level and metabolic syndrome. In a cross-sectional study in China,[7] Vitamin-D level was significantly lower in those with metabolic syndrome than in those without metabolic syndrome. Hypovitaminosis-D was associated with higher waist and hipline circumference, body-mass index (BMI), blood pressure, triglycerides, and insulin resistance. Though large scale data are not available from Nepal, a few studies have shown high prevalence of Vitamin-D deficiency.[8,9,10] Literature regarding Vitamin-D status in diabetes patients with and without metabolic syndrome in Nepal is scarce. According to WHO, the prevalence of diabetes in Nepal has increased from 4% in 1980 to 9.1% in 2014.[11] With a high prevalence of hypovitaminosis-D and rising prevalence of diabetes, status of Vitamin-D in Nepalese diabetic patients and its relation with metabolic syndrome merits evaluation.

Thus, this study aims to evaluate the status of Vitamin-D in patients with type 2 DM with and without metabolic syndrome.

METHOD

This is a hospital-based cross-sectional observational study conducted at the Department of Internal Medicine and the Endocrinology Unit, Bir Hospital, Kathmandu, Nepal from October 2017 to March 2018. Participants were selected by convenience sampling during the study period.

Adult patients above 18 years with newly diagnosed type 2 diabetes mellitus (DM) or those already diagnosed and under medication for the same were included in this study. The American Diabetes Association (ADA) diagnostic criteria[12] was used to label the diagnosis of diabetes. Exclusion criteria were: those below 18 years, patients with chronic kidney disease (CKD), patients with any known malignant disorder and those taking Vitamin-D and/or calcium supplementation.

Eligible patients in OPD or ward were explained about the study and an informed written consent was obtained.

History, general and systemic examination was done. Blood pressure, height, weight, BMI, and waist circumference were measured as per AHA 2017 guidelines and international norms.

For waist circumference cutoff, the NCEP/ATP-III criteria with South Asian Modification (SAM) was used (Table 3). BMI was calculated by dividing weight in kg by square of height in metres. For South Asian population, a BMI of 18.5-22.9 kg/m^2 is considered normal while ≥23 kg/m^2 is considered high.

Investigations including fasting blood sugar (FBS), post-prandial blood sugar (PPBS), HbA1C, Lipid profile and vitamin D level were sent.

For diagnosis of metabolic syndrome, the National Cholesterol Education Program/Adult Treatment Panel (NCEP/ATP)-III criteria[13] with south Asian modification[14] was used. Similarly, South Asian cutoff value was also used for BMI: 18.5-22.9 kg/m^2 is considered normal while ≥23 kg/m^2 is considered high.

Vitamin-D status was defined by the US Endocrine Society (USES) guidelines as: <20 ng/ml (50 nmol/L): Deficient; 21–29 ng/L: insufficient, ≥30 ng ml/ were considered sufficient.[15] For the purpose of analysis in this study, those with deficiency and insufficiency were considered to have low VItamin-D levels and those with sufficient levels were considered to have normal Vitamin-D levels.

Data was collected using a structured proforma and entered in the statistical package for social sciences (SPSS) software version 20 and the same was used for data analysis. Demographic and baseline variables (age, duration of diabetes, BMI, comorbidities, smoking and alcohol consumption status, proteinuria, retinopathy, and foot ulcer); occurrence of metabolic syndrome and status of Vitamin-D in those with and without metabolic syndrome were assessed. Descriptive statistics were used and expressed in terms of number and percentage.

Approval from the Institutional Review Board (IRB) of National Academy of Medical Sciences (NAMS) was obtained before commencement of the study.

RESULT

Demographic and baseline characteristics

A total of 58 participants were enrolled during the study period with 38 (65.52%) males and 20 (34.48%) females. The demographic and baseline characteristics of the participants are shown in Table 1. The mean, standard deviation and range of some relevant test variables are shown in Table 2.

Metabolic syndrome

Metabolic syndrome was seen among 37 out of 58 (i.e.

63.8%) participants with similar distribution among males [24 out of 38 (63.2%)] and females [13 out of 20 (65%)].

Among the components of metabolic syndrome, all had diabetes as this study was conducted among diabetics. Besides that, the most common component was elevated triglycerides which was seen among three fourths of the participants. Other components in decreasing frequency were high blood pressure, low HDL cholesterol level, and high waist circumference (Table 3). Among the baseline variables, smoking status [Odds ratio 5.908 (Smoker, current or former, compared to never smoker)] and high BMI [Odds ratio 5.683 compared to normal or low BMI] had significant correlation with metabolic syndrome (Table 4).

Vitamin D status
The mean vitamin D level was 18.78 ng/mL (males: 20.65 mg/mL, females: 15.21 ng/mL) with lowest value of 8 ng/mL and highest value of 52.9 ng/mL. As shown in Table 5, only six of the participants had sufficient vitamin D levels with 52 out of 58 (89.67%) participants having low vitamin D levels (either deficiency or insufficiency).

Mean Vitamin-D level among patients with and without metabolic syndrome was 17.79 ng/mL and 20.51 ng/mL respectively. Low vitamin D (deficient or insufficient) was more common among those with metabolic syndrome (36 out of 37; 97.3%) compared to those without metabolic syndrome (16 out of 21; 76.19%). The odds ratio of vitamin D deficiency in metabolic syndrome was 11.250.

DISCUSSION
In this study involving 58 type 2 diabetes mellitus patients, majority of participants had high BMI, poor glycemic control, low Vitamin-D level and metabolic syndrome.

There is accumulating evidence to suggest that altered vitamin D homeostasis may also play a role in the development of type 2 DM and metabolic syndrome.[1–3]

Potential mechanisms for the effects of vitamin D on type 2 DM and metabolic syndrome include:

A. Effect in pancreatic β cell function:
    Vitamin D affects insulin response to glucose

Table 1. Demographic and baseline characteristics of the participants, (N=58)

Variables	Number (%)	Variables	Number (%)
Age (years)		History of Hypertension	22 (37.9%)
18-30 years	1 (1.7%)	Hypothyroidism	2 (3.4%)
31-45 years	12 (20.7%)	Coronary artery disease	0 (0.0%)
46-60 years	26 (44.8%)	Stroke	5 (8.6%)
>60 years	19 (32.8%)		
Mean age (±SD) : 55.88 (±13.50) years		Diabetic foot ulcer	1 (1.70%)
Duration of DM (years)		Diabetic retinopathy	12 (20.7%)
≤5 years	29 (50.0%)	Proteinuria	19 (32.8%)
6-10 years	7 (12.1%)	**Smoking status**	
>10 years	22 (37.9%	Never	29 (50.0%)
Mean duration (±SD): 7.17 (±5.77) years		Former	26 (44.8%)
BMI		Current	3 (5.2%)
<18.5 kg/m2	2 (3.4%)		
18.5-22.9 kg/m2	15 (25.9%)		
≥23.0 kg/m²	41 (70.7%)		
Mean BMI (±SD): 25.27 (±4.10) kg/m²		Alcohol consumption	25 (43.1%)

Table 2. Test variables among participants (n=58 unless otherwise specified)

Variable	Mean	Standard deviation	Range
Fasting blood glucose (mg/dL)	204	83.94	107-445
Post prandial blood glucose (mg/dL)	299.31	135.31	101-647
HbA1C (%)	9.37	2.38	6.0-17.4
Waist circumference (cm)	86.26	12.36	61-117
Male (n=38)	88.57	11.42	70-117
Female (n=20)	81.85	13.16	61-112
Systolic BP (mmHg)	121.7	14.28	90-160
Diastolic BP (mmHg)	78.45	10.05	60-100
Total cholesterol (mg/dL)	180.64	46.23	76-277
HDL cholesterol (mg/dL)	44.81	12.76	14-73
Male (n=38)	44.21	11.99	14-73
Female (n=20)	45.95	14.36	24-70
LDL cholestrerol (mg/dL)	100.00	36.52	37-179
Triglycerides (mg/dL)	203.91	96.27	65-443
Vitamin D (ng/mL)	18.78	8.42	8-52.9

Table 3. Prevalence of metabolic syndrome and its components, (N=58)

Metabolic Syndrome	Number (%)
Overall prevalence (any three of five components)	37 (63.8%)
Waist circumference ≥90 cm (male), ≥80 cm (female).	23 (39.7%)
Serum triglyceride (TG) ≥150 mg/dL or drug treatment for elevated TG.	42 (72.4%)
Serum HDL cholesterol <40 mg/dL in male and <50 mg/dL in female or drug treatment for HDL cholesterol.	24 (41.7%)
Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure.	32 (55.2%)
Fasting plasma glucose (FPG) ≥100 mg/dL or drug treatment for elevated blood glucose	58 (100%)

Table 4. Distribution of baseline characteristics according to metabolic syndrome

Variables	Metabolic syndrome		Variables	Metabolic syndrome	
	Present (n=37)	Absent (n=21)		Present (n=37)	Absent (n=21)
Age			**Smoking**		
18-30 years	1	0	Never	13	16
31-45 years	8	4	Former	22	4
46-60 years	16	10	Current	2	1
>60 years	12	7			
Gender			**Alcohol consumption**		
Male	24	14	Yes	14	11
Female	13	7	No	23	10
Duration of DM			**Diabetic retinopathy**		
≤5 years	20	9	Present	5	7
6-10 years	5	2	Absent	32	14
>10 years	12	10			
BMI			**Proteinuria**		
<18.5 kg/m2	0	2	Present	14	5
18.5-22.9 kg/m2	6	9	Absent	23	16
≥23.0 kg/m2	31	10			

Table 5. Distribution of vitamin D status with baseline characteristics and metabolic syndrome components

Variables	Vitamin D Status		Variables	Vitamin D Status	
	Deficient/ Insufficient (n=52)	Sufficient (n=6)		Deficient / Insufficient (n=52)	Sufficient (n=6)
Age			**Proteinuria**		
18-30 years	1	0	Present	36	3
31-45 years	11	1	Absent	26	3
46-60 years	22	4			
>60 years	18	1			
Gender			**Metabolic syndrome**		
Male	34	4	Present	36	1
Female	18	2	Absent	16	5
Duration of DM	26	3	**Waist circumference criteria***		
≤5 years	7	0	Present	23	0
6-10 years	19	3	Absent	29	6
>10 years					
BMI	1	1	**Serum triglyceride criteria ****		
<18.5 kg/m2	12	3	Present	41	1
18.5-22.9 kg/m2	39	2	Absent	11	5
≥23.0 kg/m^2					
Smoking			**Serum HDL cholesterol criteria†**		
Never	25	4	Present	20	4
Former	24	2	Absent	32	2
Current	3	0			
Alcohol consumption	22	3	**Blood pressure criteria‡**		
Yes	30	3	Present	30	2
No			Absent	22	4
Diabetic retinopathy			**Blood sugar criteria$^^$**		
Present	10	2	Present	52	6
Absent	42	4	Absent	0	0

*Waist circumference ≥90 cm (male), ≥80 cm (female); ** Serum triglyceride (TG) ≥150 mg/dL or drug treatment for elevated TG; †Serum HDL cholesterol <40 mg/dL in male and <50 mg/dL in female or drug treatment for HDL cholesterol; ‡Blood pressure ≥ 130/85 mmHg or drug treatment for elevated blood pressure; ^Fasting plasma glucose (FPG) ≥100 mg/dL or drug treatment for dia-betes

stimulation but not basal insulinemia[1,4] by both direct (stimulation of insulin release and transcriptional activation of insulin gene[16,17]) and indirect mechanisms (maintenance of adequate intracellular pool of calcium which is essential for insulin secretion[18]).

B. Effect on insulin resistance: Vitamin-D stimulates insulin receptor expression, enhances insulin responsiveness for glucose transport,[5] and activates peroxisome proliferator activator receptor-δ, thus maintaining insulin sensitivity in peripheral tissue.

C. Effect on Inflammation:
Type 2 DM is known to be associated with systemic inflammation.[19] Systemic inflammation has been linked to insulin resistance; and elevated cytokine levels are supposed to play role in β cell dysfunction by triggering β cell apoptosis.[1]

Vitamin-D interacts with Vitamin-D response elements in the promoter region of cytokine genes to interfere with nuclear transcription factors implicated in cytokine generation and action.[1,20] By directly modulating the generation and effects of cytokines, vitamin D may improve insulin sensitivity and promote β cell survival.

D. Vitamin D and obesity:
Vitamin D receptors are highly expressed in adipocytes. A causal relationship between obesity and vitamin D deficiency has been shown in a bi-directional Mendelian randomization analysis of 21 cohorts.[21] Various mechanisms may be responsible for such association[22]: (1) reduced cutaneous synthesis (reduced cutaneous synthetic capacity as well as reduced sun exposure due to more sedentary lifestyle); (2) reduced intestinal absorption; (3) sequestration of vitamin D and its metabolites in adipose tissue; (4) reduced activation of vitamin D and/or increased catabolism.

In this study, Vitamin-D level was found to be low in most of the participants (52 out of 58; 89.65%) with the mean level of 18.78 ng/mL. A population based study in eastern Nepal showed 55.9% were Vitamin-D deficient, 30.2% were insufficient, and 13.9% had sufficient levels.[23] Another study done in women of Kavre district showed 48.7% had Vitamin-D <50 nmol/L (<20 ng/mL).[8] Mean Vitamin-D level in that study was 51.6 nmol/L (20.64 ng/mL) which is similar to this study. This study shows a higher prevalence of low Vitamin-D levels among diabetics compared to general population values. Other studies conducted among diabetes patients also show higher prevalence than the population-based data. A study in India showed 74.14% of diabetics had low Vitamin-D level.[24] Another study in Arab countries showed that prevalence of Vitamin-D deficiency among diabetics was 93.75% compared to 50% among non-diabetics.[25] All these finding are in keeping with the notion that Vitamin-D deficiency is more common in patients with diabetes.

Prevalence of metabolic syndrome in this study was found to be 63.8%. A few studies conducted in Nepal among general population have shown prevalence of 12 to 21%.[26,27] Higher prevalence among diabetics is expected because diabetes is itself a component of metabolic syndrome and also contributes to other components like obesity, dyslipidemia. Other studies conducted among diabetic patients have shown prevalence of metabolic syndrome among diabetics to be 58-74%,[28,29] which is similar to this study.

Prevalence of hypovitaminosis-D in diabetic patients with and without metabolic syndrome were 97.3% and 76.19% respectively. The mean Vitamin-D level in patients with and without metabolic syndrome was 17.79 ng/mL and 20.51 ng/mL respectively. The odds ratio of vitamin D deficiency in metabolic syndrome was 11.250. Similar results have been shown in prior cross sectional studies done in Qatar and China.[30,7] These studies showed that lower level of vitamin D was associated with higher waist circumference, hipline circumference, BMI, blood pressure, triglycerides, and insulin resistance and lower HDL cholesterol. A prospective analysis of the nation-wide Australian Diabetes, Obesity and Lifestyle Study (AusDiab) study[31] also showed that low vitamin D level is associated with increased incidence of metabolic syndrome as well. They prospectively analyzed five year follow up data of 6,537 adults ≥25 years and found that metabolic syndrome risk was significantly higher in people with vitamin D in the first (<18 ng/mL) and second (18-23 ng/mL) quintiles compared to those in the highest quintile (≥34 ng/mL); odds ratio 1.41 and 1.74 respectively. Vitamin D level was inversely associated with waist circumference, triglycerides, fasting glucose and homeostatic model assessment for insulin resistance. Another nationally representative population based cross sectional study in US showed inverse relation of vitamin D level and metabolic syndrome with the Odds ratio for metabolic syndrome in the highest quintile of vitamin D compared to the lowest quintile 0.27 (95% CI 0.15 to 0.46, p value <0.001).[32] Such correlation between vitamin D status and metabolic syndrome indicates that vitamin D deficiency could be an important risk factor for metabolic syndrome among diabetics. However, definite causality and direction of the effect between vitamin D and metabolic syndrome cannot be ascertained from this study. Prior studies examining the direction of such association suggest that lipid levels and BMI may be a cause for decreased vitamin D while some other studies show bidirectional association between them.[21] As elaborated earlier, vitamin D is linked to various aspects of insulin synthesis, release, sensitivity, action, obesity, endothelial function, chronic inflammation and lipid metabolism. All these mechanisms are linked to various components of metabolic syndrome in one or more ways. Thus, the association between vitamin D level and

metabolic syndrome seems biologically plausible.

There were several limitations of this study. First, being a small study, many of the potential associations could not be properly demonstrated.

Second, being a hospital-based study, it is very liable to Berkesonian bias. Most of the patients enrolled had uncontrolled diabetes. Thus generalizability of its findings to overall diabetic patients could be questioned. But at the same time, since individuals with uncontrolled diabetes are the ones who are more likely to develop metabolic complications, pertinent findings in this group of patients is certainly of significance.

Third, since this is a cross sectional study, definite causality and direction of association between adiposity, vitamin D, diabetes mellitus and metabolic syndrome could not be established.

CONCLUSION
This study has demonstrated high prevalence of Vitamin-D deficiency and high prevalence of metabolic syndrome among diabetics. Obesity was closely associated with both these conditions. Vitamin-D deficiency was more common in those with metabolic syndrome.

DECLARATIONS
Acknowledgement
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Conflict of Interest
None

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None

Ethical Clearance
Ethical clearance was obtained from Institutional Review Board of National Academy of Medical Sciences (NAMS) before commencement of the study.

Consent
Informed written consent was obtained from each participant.

Consent for Publication
Consent for publication was obtained from all the authors.

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