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Original Article

Low Vitamin D Status is Linked to Cardiovascular Risk in Newly Diagnosed Type 2 Diabetes Mellitus

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ABSTRACT

Background and Aim: Vitamin D is linked to the prevalence and severity of cardiac autonomic neuropathy in Type 2 Diabetes Mellitus (T2DM). Autonomic dysfunctions are evident in newly diagnosed T2DM subjects. However, the association of Vitamin D level with autonomic dysfunction in newly diagnosed T2DM remains unclear. To study the relationship between Vitamin D status and cardiovascular autonomic function in newly diagnosed T2DM. **Methods:** One group descriptive study with 47 newly diagnosed T2DM patients (mean age 39±4 years, with 23 males and 24 females), recruited based on American Diabetes Association (ADA) criteria in outpatient clinic of Jawaharlal Institute of Post Graduate Medical Education and Research, Puducherry, India. Cardiovascular autonomic functions including heart rate variability, baroreflex sensitivity and other conventional autonomic function tests were measured. The level of 25-hydroxy Vitamin D[25(OH)D] was measured using chemiluminescence assay technique. **Results:** The mean serum 25(OH)D concentration was 17.49±7.10, and all patients had Low Vitamin D levels (<30 ng/mL). There were significant negative correlations of Vitamin D level with basal HR (P=0.006), LF(nu) (P=0.010), LF-HF ratio (P=0.023); and positive correlations with BRS (P=0.007), HF(nu) (P<0.001) and TP (P=0.002). **Conclusion:** There was decrease in Vitamin D level in all subjects and it showed association with markers of sympathovagal imbalance. This might increase the cardiovascular risk in them.

Keywords: Baroreflex sensitivity, Heart rate variability, Newly diagnosed T2DM, Sympathovagal imbalance, Vitamin D.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is one of the chronic endocrine disorders. In 2016, 65 million Indians were living with diabetes[1] and there would be 80 million diabetic individuals in India by 2030.[2] Even though T2DM is usually of adult type, now-a-days it is observed frequently in the younger age group, which is associated with high Cardiovascular (CV) and mortality risk.[3,4] Cardiovascular autonomic neuropathy is associated with increased major cardiovascular events in diabetic patients.[5] Cardiovascular Autonomic Function Tests (CAFT) including Heart Rate Variability (HRV), Baroreflex Sensitivity (BRS) and other conventional autonomic function tests have been reported as useful, non-invasive markers of CV risk in diabetes.[6,7] Autonomic dysfunction has also been reported in newly diagnosed T2DM of younger age group.[6,8] Vitamin D levels are significantly decreased in newly diagnosed T2DM.[9,10] Vitamin D deficiency has an adverse effect over cardiac autonomic functions, and hence can increase the CV risk, though the symptoms of autonomic imbalance need not be manifested in all individuals.[11-14] However, the link of Low Vitamin D level with CV risk in newly diagnosed T2DM has not been established. Therefore, in the present study, we have assessed the link between Vitamin D and Cardiovascular autonomic functions in newly diagnosed T2DM subjects.

MATERIALS AND METHODS

Study Population

The study was designed as one group descriptive study, and was conducted at the Department of Physiology in collaboration with the Department of Endocrinology, Department of Biochemistry and Department of Medicine in JIPMER, at Puducherry, India. Forty-seven untreated newly diagnosed T2DM patients of either gender between the age group of 18 to 45 years attending the

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Medicine/Endocrinology outpatient department in JIPMER, staffs and relatives of staffs of JIPMER comprised the study population. The patients with hypertension, heart diseases, musculoskeletal disorders, autonomic dysfunction, those receiving medication that can influence autonomic function, endocrine diseases other than T2DM, high blood sugar levels or with complications which require immediate blood sugar control, history of smoking and alcoholism were excluded. The study was approved by the Institute Ethics Committee for human studies – Approval No: JIP/IEC/2018/470, and was done as per guidelines from the declaration of Helsinki and ICMR guidelines. Written informed consent was obtained from all participants after explaining the details of the procedure in the patient's language.

Assessment of Anthropometric Parameters

Height was measured to the nearest centimetre using a stadiometer (V.M. Electronics Hardware Ltd.,) which was mounted on a wall. Weight was measured using a weighing machine (Charder Electronic Co. Ltd., Taichung, Taiwan) to the nearest kilogram. Body Mass Index (BMI) was calculated using Quetelet's index (BMI = weight (kg)/[height (m)]^2). Asian criteria for BMI were followed.

Assessment of Basal Cardiovascular Parameters

The study participants were asked to report to autonomic function testing laboratory in the Physiology department in loose clothing, 2 hr after a light breakfast. The participant's basal parameters and CAFT parameters were recorded. Basal BP and HR were recorded after 10 min of rest in sitting posture by oscillometric method using automated blood pressure monitor Omron (SEM 1 Model, Omron Healthcare Co. Ltd., Kyoto, Japan).

Assessment of Cardiovascular Autonomic Function Tests

The participants were advised to avoid caffeine, nicotine products and alcohol, 24 hr before the procedure. The drugs affecting cardiovascular system and Autonomic Nervous System (ANS) were withheld after consultation with the physician. The participants were advised not to perform any strenuous exercise before the procedure. Short-term HRV and BRS were recorded following standard operating protocols. HR response to standing (30:15 ratio), HR changes with deep breathing (E:I ratio), BP response to Isometric Hand-Grip (IHG) and BP changes with the cold pressor test were recorded with adequate rest in-between.

For the purpose of recording HRV, lead II Electrocardiogram (ECG) was acquired at 200 samples per second using BIOPAC MP150 system. The series of RR intervals for 5 min, free of ectopic beats and artefacts, were analyzed using Kubios HRV software to obtain HRV analysis, and all the parameters of HRV were studied. The BRS was recorded using Finapres (Finometer model-1, Finapres Medical Systems B.V, Amsterdam, The Netherlands), and Beatscope easy software was used for analysis.

In brief, the conventional autonomic function tests such as HR response to standing and deep breathing were studied from the data recorded on BIOPAC MP150 system, which was digitalized and analysed using Acknowledge software. The maximum RR interval at 30th beat was divided by minimum RR interval at 15th beat during standing to obtain 30:15 ratio. The values of maximum and minimum RR intervals of each cycle of deep respiration were noted, and the average was taken for 6 cycles, from which Expiration:Inspiration (E:I) ratio was derived. The IHG test and cold pressor test are sympathetic function tests, in which acute stressor was given after recording basal BP. In IHG test, the subject was asked to use dominant hand, and by using handgrip dynamometer, maximum voluntary contraction was noted. The subject was then asked to hold the dynamometer at 1/3rd of maximum voluntary contraction and sustain it for 3-5 min. Immediately on completion of exercise, a BP reading was taken and compared with baseline for the rise in diastolic BP. In cold pressor test, the subject was asked to keep the hand up to wrist immersed under the cold water of 10°C for 1 min. BP was taken at the end of 1 min of immersion and compared with the baseline BP.

Sample Size Calculation

The required sample size was calculated as 47 using the statistical formula for one group descriptive study estimating a mean, http://www.sample-size.net/sample-size-conf-interval-mean/. The sample size was estimated at 95% confidence level and 5% precision, with a standard deviation of LF/HF ratio of HRV as 8.7.[15]

Statistical Analysis of Data

The normality of the continuous data was assessed using the Kolmogorov-Smirnov test. Normally distributed data were represented as mean and standard deviation. Non-normally distributed data were represented as median and range. Correlation between the variables was analysed using the Pearson's correlation test for parametric data and Spearman's Rank correlation test for non-parametric data. All statistical analyses were carried out for two-tailed significance and a P value <0.05 was considered as statistically significant. Statistical analysis was performed using IBM SPSS software version 21.0.

RESULTS

We recruited newly diagnosed T2DM patients (n=47) of either gender between the age group of 18 to 45 years who were not under treatment. The mean age of the patients at diagnosis was 39 ± 4 years and the mean BMI was 24 ± 3kg/m^2. Distribution of baseline parameters is shown in Table 1 and 2. In the correlation analysis (Table 3), Vitamin D was found to be negatively correlated with basal HR (r=-0.393, P=0.006), and positively correlated with BRS (r=0.385, P=0.007). Among cardiovascular autonomic function tests parameters, ΔDBP - cold pressor test

Table 1: Distribution of baseline parameters and biomarkers in newly diagnosed T2DM (n=47).

Sl. No.	Parameters	Newly diagnosed T2DM (n=47)
General characteristic and Anthropometry parameters		
1	Age (Years)	38.98 ± 4.13
2	Height (cm)	160.28 ± 8.77
3	Weight (Kg)	62.38 ± 11.37
4	BMI (Kg/m^2)	24.14 ± 2.97
Cardiovascular Parameters		
1	Basal HR (beats per minute)	72.85 ± 8.61
2	SBP (mm Hg)	121.51 ± 8.85
3	DBP (mm Hg)	80.55 ± 6.19
4	BRS (ms/mmHg)	15.20 ± 6.80
Biochemical Parameters		
1	Vitamin D (ng/mL)	17.496 ± 7.105
2	FPG (mg/dL)	152.66 ± 19.33

Values are expressed as mean±SD.HR: Heart Rate; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BRS: Baroreflex Sensitivity; FPG: Fasting Plasma Glucose.

Table 2: Distribution of cardiac autonomic function and heart rate variability parameters in newly diagnosed T2DM (n=47).

Sl. No.	Parameters	Newly diagnosed T2DM (n=47)
Cardiac autonomic function tests parameters		
1	30:15 Ratio	1.08 ± 0.102
2	E:I Ratio	1.20 ± 0.12
3	ΔDBP_{IHG} (mm Hg)	24.04 ± 4.80
4	ΔDBP-Cold Pressor Test (mm Hg)#	26.00 (22.00 – 28.00)
HRV Parameters – Time Domain Indices		
1	Mean HR	75.71 ± 10.34
2	SDNN (ms)	30.60 ± 13.35
3	RMSSD (ms)	29.22 ± 14.07
4	NN50 (beats)#	8.00 (4.00 – 90.00)
5	pNN50 (%)#	2.10 (0.76 – 28.00)
HRV Parameters – Frequency Domain Indices		
1	LF (ms^2)	225.70 ± 178.23
2	HF (ms^2)	226.04 ± 163.93
3	LF (nu)	51.16 ± 16.11
4	HF (nu)	50.19 ± 16.03
5	LF:HF Ratio	1.216 ± 0.896
6	Total Power (ms^2) $	641.06 ± 337.55

Values are expressed as mean±SD; and # - median (range) for non-parametric data.HR: Heart Rate, SDNN: Standard Deviation of NN intervals; RMSSD: Root Mean Square of Standard Deviation; NN50: consecutive NN intervals with difference more than 50ms; pNN50: percentage of NN50 intervals; LF: Low Frequency; HF: High Frequency; LF: HF ratio: Low Frequency: High Frequency ratio.

Table 3: Correlation Analysis of Vitamin D on study parameters in newly diagnosed T2DM (n=47).

Sl. No.	Parameters	Newly diagnosed T2DM (47)	
		r	p
Cardiovascular Parameters			
1	Basal HR (beats per minute)	-0.393	0.006**
2	SBP (mm Hg)	-0.059	0.693
3	DBP (mm Hg)	-0.242	0.102
4	BRS (ms/mmHg)	0.385	0.007**
Cardiac autonomic function tests parameters			
1	30:15 Ratio	0.209	0.158
2	E:I Ratio	0.098	0.513
3	ΔDBP_{IHG} (mm Hg)	-0.103	0.489
4	ΔDBP - Cold Pressor Test (mm Hg) #	-0.344	0.018*
HRV Parameters – Time Domain Indices			
1	RMSSD (ms)	0.097	0.517
2	SDNN (ms)	0.151	0.310
3	NN50 #	0.088	0.557
4	pNN50 #	0.107	0.472
HRV Parameters – Frequency Domain Indices			
1	LF (nu)	-0.371	0.010*
2	HF (nu)	0.573	<0.001***
3	LF:HF Ratio	-0.331	0.023*
4	Total Power (ms^2)	0.435	0.002**

Pearson's correlation test was used for parametric data.# - Spearman's correlation test was used for non-parametric data.The P value <0.05 was statistically considered significant.***: p-value <0.001; **: p-value <0.01; *: p-value < 0.05.HR: Heart Rate; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BRS: Baroreflex Sensitivity; FPG: Fasting Plasma Glucose. SDNN: Standard Deviation of NN intervals; RMSSD: Root Mean Square of Standard Deviation; NN50: consecutive NN intervals with difference more than 50ms; pNN50: percentage of NN50 intervals; LF: Low Frequency; HF: High Frequency; LF: HF ratio: Low Frequency: High Frequency ratio.

showed significant negative correlation with Vitamin D (r=-0.344, P=0.018). Statistically significant negative correlations were found between Vitamin D and LF (nu) (r=-0.371, P=0.010) and LF:HF ratio (r=-0.331, P=0.023). Statistically significant positive correlations were found between Vitamin D and HF (nu) (r=0.573, P<0.001) and total power $(ms)^2$ (r=0.435, P=0.002).

DISCUSSION

Vitamin D level was found to be lower in newly diagnosed T2DM. Apart from maintaining the musculoskeletal health, the important function of Vitamin D is to stimulate the nervous system to keep the sympathetic and parasympathetic nervous systems in balance with each other.[11] It was found that autonomic functions are impaired in newly diagnosed T2DM.[6] However, the link of Vitamin D level with autonomic functions in newly diagnosed T2DM was not known. This study was conducted to assess the relationship between Vitamin D level and autonomic functions. Subjects with hypertension were excluded from the study, as hypertension is known to affect autonomic functions.

The CV parameters, CAFT parameters, and HRV parameters were comparable with earlier reports in newly diagnosed diabetics (Tables 1, 2, 3).[6] HRV is stated to represent a nonspecific predictor of mortality with a lower value corresponding to a higher risk of mortality.[16] The overall vagal drive of cardiac modulation is represented by TP.[6] The TP was only 641.06 ms^2, which is less as it should be around 1000 ms^2 for a normal individual. Reduced TP indicates decreased parasympathetic tone in these subjects. The 30:15 ratio (1.08 ±0.10) was less than normal (normal = 1.12 - 1.10). As the 30:15 ratio is an indicator of parasympathetic function, decrease in this ratio than the normal range in the study population shows that they have reduced parasympathetic reactivity. Thus, there was decreased parasympathetic activity and reactivity in these subjects, which could increase the possibility of CVD risk in them, as reduced vagal function has been shown to be associated with increased cardiovascular morbidity and mortality.[17]

The baroreflex's effectiveness to regulate HR and BP on beat-to-beat basis is determined mainly by vagal activity. CVDs are

usually featured with impairment of baroreflex activity and associated with an imbalance in the sympathovagal outflow from the central nervous system to heart and blood vessels.[6] BRS has been shown to predict cardiovascular events in T2DM patients without structural heart disease.[18] In our study, the BRS was towards the lower range (15.20±6.80 ms/mm of Hg) as normal BRS ranges from 15-25 ms/mm of Hg. Low BRS indicates poor vagal tone and increased cardiovascular risk.[17,19]

Vitamin D was found to be much lesser than the normal range of 30-100ng/mL. Though the duration of disease was not assessed in our study, this finding is similar to that of Laway *et al*., who noted low Vitamin D in newly diagnosed T2DM in the age group of >25 years and duration of less than six months.[20] Vitamin D level was negatively associated with basal HR and positively associated with BRS, suggesting that with a decrease in Vitamin D level, there was a concomitant decrease in vagal tone which might increase cardiovascular risk in these subjects. Among the cardiac autonomic function test parameters, Vitamin D showed a negative association with ΔDBP-cold pressure test. As the cold pressure test is a pure sympathetic function test, this finding indicates that with a decrease in Vitamin D level, there occurs higher sympathetic reactivity in T2DM patients. This was further supported by the significant negative association of Vitamin D with LFnu. The LFnu represents the resting sympathetic tone. Thus, a decrease in Vitamin D level was accompanied by increased sympathetic activity and reactivity. Further, Vitamin D level showed a positive correlation with HFnu and TP, indicating that with a decrease in Vitamin D level, the parasympathetic tone reduces, since both HFnu and TP reflect the resting vagal tone. This rise in sympathetic tone along with reduced parasympathetic tone and their association with fall in Vitamin D level was evident by the negative correlation of Vitamin D with LF:HF ratio, since LF:HF ratio represents the sympathovagal balance. A higher LF:HF ratio indicates sympathovagal imbalance, either due to higher sympathetic or lower parasympathetic or both. Thus, a decrease in Vitamin D level was accompanied by increased sympathetic activity and reactivity as well as a higher sympathovagal imbalance. Greater sympathetic response leading to sympathovagal imbalance exerts pressure on the heart and impairs cardiac function over a period of time. Thus, Vitamin D deficiency status was associated with decreased parasympathetic activity and increased sympathetic activity as well as reactivity, along with higher sympathovagal imbalance. This might increase the cardiovascular risk in newly diagnosed T2DM.

Limitations of the Study

The study should be performed on a larger sample size to get more accurate results. A more detailed study of cardiac autonomic functions should include 24 hr HRV analysis and reactivity tests such as valsalva ratio, which were not assessed in our study.

CONCLUSION

Sympathovagal imbalance in the form of decreased parasympathetic activity and reactivity was observed in newly diagnosed T2DM.One of the cardiovascular markers is BRS, which suggested that cardiovascular risk increases in newly diagnosed T2DM in the form of decreased vagal tone. Also, a decrease in Vitamin D levels in all subjects and its association with markers of sympathovagal imbalance suggested the increase in cardiovascular risk. Being a descriptive study, the cause-effect relationship could not be established. Vitamin D deficiency is a treatable condition which when treated earlier appropriately, can show improvement in sympathovagal imbalance, and decrease in cardiovascular risk in newly diagnosed T2DM. The sympathovagal imbalance might appear early in diabetes, and Vitamin D supplementation might be an additional therapy for reducing cardiovascular risk in DM. Hence more trials on patients are needed so that Vitamin D can be suggested as an adjunct for newly diagnosed diabetes mellitus patients in the future in addition to conventional therapy.

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CONFICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus; **CV:** Cardiovascular; **CAFT:** Cardiovascular Autonomic Function Tests; **HRV:** Heart Rate Variability; **BRS:** Baroreflex Sensitivity; **BMI:** Body Mass Index; **ANS:** Autonomic Nervous System; **HR:** Heart Rate; **IHG:** Isometric Handgrip; **BP:** Blood Pressure; **SBP:** Systolic Blood Pressure; **DBP:** Diastolic Blood Pressure; **FPG:** Fasting Plasma Glucose; **SDNN:** Standard Deviation of NN intervals; **RMSSD:** Root Mean Square of Standard Deviation; **NN50:** Consecutive NN intervals with difference more than 50ms; **pNN50:** Percentage of NN50 intervals; **LF:** Low Frequency; **HF:** High Frequency; **LF-HF ratio:** Low Frequency-High Frequency ratio.

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