Original Article

Study on Loss of Protection Sense in Type 2 Diabetes Mellitus with Special Reference to TSH Value within Normal Range

Sourav Kumar Bhakta[1], Saumik Datta[2], Arnab Roy[1], Partha Pratim Mukherjee[3]

Peripheral neuropathy is estimated to affect around half of people with diabetes. Thyroid dysfunction is found in 4-17% in Type- 2 Diabetes. T2DM with Hypothyroidism is more likely to have peripheral neuropathy. We planned this study to find correlation of Thyroid-stimulating Hormone (TSH) level (within normal range) with loss of protection sense (LOPS) in T2DM. It had been observed that those with TSH ≥3 mIU/ml had 5.47, 2.59, 2.96, 3.08, 10.25, 4.56, 2.51 times more risk of having abnormal VPT (VPT>25), absent ankle jerk, absent vibration sense , absent pin prick sense , abnormal 10-MFT, abnormal skin and musculoskeletal status of foot, respectively comparing to those with TSH <3 mIU/ml. Overall, those with TSH ≥3 mIU/ml were observed at 14.82 times more risk of having LOPS comparing to those with TSH <3mIU/ml .

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Key words **: Diabetic neuropathy, Hypothyroid, VPT, LOPS.**

Diabetes mellitus is a major health problem with rising prevalence globally. Diabetic peripheral neuropathy is the most common cause of neuropathy worldwide. Some Diabetic patients may present with spontaneous discomfort. But, neuropathic symptoms poorly correlate with sensory loss[1].

Prevalence of thyroid dysfunction in diabetes is higher than that of general population. Thyroid dysfunction is found in up to a third of patients with Type 1 Diabetes Mellitus (T1DM)[2] and 4-17% with Type 2 Diabetes Mellitus (T2DM)[3].

Peripheral neuropathy in hypothyroidism is correlated with segmental demyelination. It results from a basal metabolism disorder of Schwann cells[4]. T2DM with Sub Clinical Hypothyroidism is more likely to have Diabetic peripheral neuropathy and it is due to incipient axonal alteration presented in hypothyroidism[5].

But, association between TSH level within normal range and loss of protection sense in T2DM had not been comprehensively studied. So, we planned this study to find out whether there is any correlation of TSH level (within normal range) with loss of protection sense (LOPS) in type 2 Diabetes Mellitus.

Materials and Method

This cross sectional study had been conducted in Calcutta National Medical College and Hospital, Kolkata for a period of 1 year on 100 type 2 diabetic patients attending Endocrine OPD.

Exclusion Criteria :

- T1DM
- Ulcerated foot
- Gestational Diabetes Mellitus (GDM)

Editor's Comment :

- Result of Thyroid function test in every case of Type 2 Diabetes Mellitus has to be interpreted more carefully when TSH is at high normal range.
- A larger longitudinal prospective case control study may tell us whether thyroid hormone replacement to keep TSH value within 3 mu/L will be more effective to preserve protective sense in foot of persons living with Type 2 Diabetes Mellitus by avoiding additive effect of thyroid related neuropathy.

- HbA1c≥9%,
- HIV
- Serum TSH >5 mIU/L
- eGFR<30 ml/min/1.73m^2
- Malignancy
- Hypothyroid, Graves' disease, Multinodular goiter, Thyroiditis
- Sick patient
- H/o heavy metal exposure.

After taking careful history regarding duration of diabetes, addiction, neuropathic symptoms, past history of ulcer and other macro and microvascular complication, we focused in foot examination. Dermatological assessment was done for skin status; such as color, thickness, dryness, cracking, fungal infection between toes, ulceration, calluses/blistering. We also looked for any foot deformity like claw toes, prominent metatarsal heads, Charcot joint and muscle wasting.

Neurological assessment was done with 10-g monofilament, 128-Hz tuning fork. Pinprick sensation, ankle reflexes and Vibration Perception Thresholds (VPT) were assessed. Any abnormal test among these suggests LOPS.

Vibration Perception Threshold Test :

Biothesiometer gives a semiquantitative assessment of VPT. Stylus of the instrument was placed over six different places (First toe, 1st, 3rd, 5th metatarsal head, instep, and heel) on both feet with patient lying supine. Amplitude was increased until patient

Department of General Medicine, Calcutta National Medical College, Kolkata 700014

[1]MBBS, MD, Post Graduate Trainee

[2]MD, DM (Endocrinology), Associate Professor and Corresponding Author

[3]MD, Professor

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detected vibration. Resulting number is known as the VPT. The final value had been taken as per average of twelve readings. A VPT >25 V was regarded as abnormal.

Laboratory investigation : Serum TSH, free T4, T3 was estimated by chemiluminescent immunoassay.HbA1c was estimated using High Performance Liquid Chromatography (HPLC) system.

Statistical Analysis :

Categorical variables were compared across the groups using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate. Continuous were compared across the groups using Mann-Whitney U test. Associations between continuous variables were captured using Spearman's Rank Correlation Coefficient. Multivariate analysis had been done using Binary Logistic Regression Method. The statistical software SPSS version 20 had been used for the analysis.

Results

Different characters of study population had been described in Table 1.

Abdominal obesity (waist-hip ratio of more than 0.85 for females and 0.9 for males) was present in around 78% of patients. The mean HbA1c was 7.03 ± 1.3%, whereas 41% of persons had HbA1c value of >7%.The mean creatinine was 0.86 ±0.21 mg/dl. Average e GFR 90.62 ± 20 (ml/min/1.73 m²). 54% ,41% and 5% having STAGE 1, 2, 3 CKD, respectively .Nearly 46 % patients had microalbuminuria and 7% having macroalbuminuria .The mean LDL C was 93.33 ± 21.88 mg/dl and 86% persons had a serum LDL level above >70 mg/ dl.

Positive symptoms and negative symptoms were complained by 74% & 29% of patients, respectively. Foot care awareness was not present in 67%. History of ulcers present in 20% of patients. Abnormal skin status of foot was found in 68% of patients which included mostly cracking (44%) ,dry skin (35%), deformities (10%) callus (30%), fungal infection (5%). LOPS was found in 63% of group.

On examination, 58% had loss of sensation on 10 g SW monofilament testing .51% patients had abnormal VPT (>25). 36% had abnormal ankle reflexes and 33% of subjects had reduced/ absent vibration perception with 128 Hz tuning fork. 31% had absent pinprick sensation.

Mean VPT was 25.84± 11.60.It was higher (mean VPT = 32.27 ± 9.86) in LOPS group (n 63) comparing with those without LOPS (mean VPT=14.91±2.77) with p value < 0.001.

Age, Duration of diabetes, waist hip ratio, TSH, eGFR, LDL cholesterol, Urine ACR had significant association with LOPS by univariate analysis.Hypertension, addiction (alcohol /smoking) , BMI, waist circumference, FBS, PPBS, HbA1c were not significantly associated with LOPS using univariate analysis.

Those with TSH≥3(mIU/ml) were at 4.56 times more risk of having abnormal skin status (OR:4.56 ,CI:1.79-11.62) and 2.51 times more abnormal musculoskeletal status (OR:2.51 ,CI:1.04-6.03) comparing to those having TSH<3(mIU/ml) and both were statistically significant (p = 0.001 & p = 0.037 respectively).Though foot deformities were 2.67 times (OR:2.67, CI:0.65-10.97) more in patients having TSH≥3(mIU/ml), but it was not statistically significant.

Table 1 — *Distribution of variables of study population*

Variables	Mean ± SD or n (%)
Age (Years)	50.39 ± 8.17
Duration of T2 DM(Years)	6.92 ± 5.95
Gender :	
Male	48
Female	52
History of Hypertension	20
Family history of diabetes	68
Smoker	32
Alcoholic	22
SBP(mm of Hg)	130.92 ± 11.83
DBP (mm of Hg)	80.49 ± 7.97
BMI (kg/m²)	23.32 ± 2.82
Waist Circumference(cm)	88.02 ± 8.61
Waist Hip Ratio	0.94 ± 0.07
VPT	25.84 ± 11.60
FBS(mg/dl)	134.01 ±40.41
PPBS(mg/dl)	196.72 ± 63.79
HbA1c %	7.03 ±1.30
TSH (mIU/ml)	3.11 ± 1.81
e GFR (ml/min/1.73 m²)	90.62 ±20.19
LDL (mg/dl)	93.33 ±21.88
Urine ACR (mg/gram)	70.54 ± 93.87

Table 2 — *Multivariate logistic regression analysis for the association of factors for Loss of protective sense (LOPS)*

	p Value	Odds Ratio	95% C.I. for Odds Ratio	
			Lower	Upper
Age	0.155	1.124	0.957	1.320
Gender	0.959	0.941	0.093	9.525
Duration of Diabetes	0.429	1.118	0.848	1.473
Alcoholic	0.309	0.200	0.009	4.425
Smoker	0.737	0.595	0.029	12.250
INSULIN	0.162	0.082	0.002	2.730
Waist circumference	0.012	0.761	0.615	0.941
Waist Hip Ratio	0.005			
BMI	0.121	1.488	0.900	2.461
TSH	0.003	2.984	1.447	6.152
HbA1C	0.478	0.735	0.313	1.722
FBS	0.160	0.975	0.941	1.010
PPBS	0.468	1.008	0.987	1.029
eGFR	0.664	1.012	0.959	1.068
LDLC	0.157	1.035	0.987	1.085
Urine ACR	0.054	1.053	0.999	1.111
Constant	0.013	0.000		

Those with TSH≥3(mIU/ml) were at 14.82 times (OR:14.82, CI: 5.01-43.87) more risk of having LOPS comparing to those with TSH <3(mIU/ml) and this was statistically significant (p <0.001).

TSH had a significant positive correlation with VPT (P <0.001).

Multivariate logistic regression analysis had shown TSH, waist hip ratio, waist circumference as independent correlates of LOPS.

Discussion

The overall prevalence of LOPS was 63% in our study. This is similar to a study carried out by Kulkarni *et al*[6]. They observed 60% prevalence of diabetic neuropathy[6]. Reported prevalence of foot at risk from another center in north India was 66.9%[7] which is also similar to this study. A higher prevalence of LOPS in this study was also compounded with lack of awareness about foot care. 64.2% of patients having LOPS did not have foot care awareness.

Most abnormal test in this study was 10 -g MFT followed by abnormal VPT (>25) which was also similar to finding of Kishore S *et al*[8].

The use of VPT (cut-off of ≥24.5V) for the diagnosis of neuropathy has been well validated by clinical studies with a sensitivity and specificity of 80% and 98%, respectively[9].

In this study there is significant association of age, duration of diabetes, systolic blood pressure, waist-hip ratio, TSH, PPBS, Cr, eGFR, Urine ACR with abnormal VPT (VPT > 25),which is similar to study by Lakshmana N *et al*[10]. But, multivariate logistic regression analysis found that only TSH had a statistically significant relationship with high VPT(>25).

A significant correlation of Urine ACR with VPT supports the concept of coexistence of other microvascular complications like nephropathy along with neuropathy.

Table 3 — *Multivariate logistic regression analysis for the association of factors for VPT >25*

	p Value	Odds Ratio	95% CI for Odds Ratio	
			Lower	Upper
Age	0.051	1.124	0.999	1.264
Gender	0.638	0.667	0.124	3.594
Duration of Diabetes	0.065	1.197	0.989	1.449
Alcoholic	0.856	0.822	0.100	6.759
Smoker	0.654	1.530	0.238	9.859
INSULIN	0.054	0.113	0.012	1.039
Waist circumference	0.686	0.972	0.847	1.116
Waist Hip Ratio	0.134	27965.941	0.043	18168510895.124
BMI	0.966	1.008	0.691	1.472
TSH	0.009*	1.823	1.164	2.857
HbA1C	0.693	0.870	0.435	1.737
FBS	0.783	0.997	0.973	1.021
PPBS	0.180	0.988	0.972	1.005
eGFR	0.610	1.010	0.973	1.047
LDLC	0.554	0.991	0.963	1.021
Urine ACR	0.365	1.004	0.995	1.013
Constant	0.066	0.000		

This study showed that advanced age was significantly associated with LOPS and it was similar to the finding across India[11-14].

Longer duration of diabetes had been identified as a statistically significant risk factor and 1.18 times more likely to develop LOPS compared to shorter-duration . It was in accordance with many neuropathy prevalence studies[14,15].

Smoking is an important risk factor . We found that smokers are 1.79 times more at risk of having LOP. However, smoking and alcohol intake were not statistically significantly associated with LOPS in our study.

Those having BMI≥23 kg/m² were at 1.19 times more likely to develop LOPS compared to patients with BMI of <23 kg/m² but BMI and LOPS have no statistically significant association.

The waist-hip ratio had a positive association with LOPS on multivariate analysis, but BMI and LOPS had no statistically significant association. This again proves discordance between Obesity and BMI in the Indian population which is well known to us.

This present study did not show association of LOPS with HbA1c. This is supported in other studies[16,13]. Though, it was observed that the risk of neuropathy had an association with HbA1c in study by Kumar HK *et al*[14]. HbA1c of that[14] study was (8.7± 1.8) % which is higher than HbA1c (7.03 ±1.30) % of our study. This fact can explain the discordance.

This study found no association of LDL with LOPS on multivariate analysis. However, insulin taken for the treatment had a significant association with LOPS.

Table 4 — *Association of clinical variables of foot examination & LOPS with TSH*

Variables	(*n*=37) *n* (%)	OR	95% CI for Odds Ratio		p value
			Lower	Upper	
VPT>25					<0.001
TSH <3	16(31.3)	1			
TSH ≥3	35(68.7)	5.47	2.32	12.88	
Absent Ankle Jerk					0.025
TSH <3	13(36.1)	1			
TSH≥3	23(63.9)	2.59	1.11	6.01	
Absent Vibration sense					0.013
TSH <3	11(33.3)	1			
TSH ≥3	22(66.7)	2.96	1.24	7.09	
Absent pinprick test					0.012
TSH <3	10(32.3)	1			
TSH ≥3	21(67.7)	3.08	1.26	7.51	
Absence of 10-g MFT					<0.001
TSH <3	17(29.3)	1			
TSH ≥ 3	41(70.7)	10.25	3.94	26.65	
Presence of LOPS					<0.001
TSH <3	19(30.2)	1			
TSH ≥3	44(69.8)	14.82	5.01	43.87	

Among the LOPS group, 65% of patients had microalbuminuria. The prevalence of microalbuminuria was only 13.5% in those not having LOPS. However,multivariate analysis did not show any significant association.

TSH showed a significant association with VPT >25.The mean TSH of our study is 3.11 ± 1.81 mIU/ml .Those with higher TSH are at 1.82 times more risk of having VPT > 25 .

In this present study, there was a positive association of TSH with LOPS (coefficient of 1.093 in multivariate analysis) and those with higher TSH levels were at 2.98 times more risk for having LOPS (OR 2.98, CI: 1.44–6.15).

It had been observed that those with TSH≥3 mIU/ml had 5.47, 2.59, 2.96, 3.08, 10.25, 4.56, 2.51 times more risk of having abnormal VPT (VPT>25), absent ankle jerk, absent vibration sense, absent pin prick sense, abnormal MFT, abnormal skin and musculoskeletal status of foot, respectively comparing to those with TSH <3 mIU/ml.

Those with TSH≥3 mIU/ml were at statistically significant 14.82 times (OR:14.82, CI: 5.01-43.87) more risk of developing LOPS.

So, present study observed higher prevalence LOPS though TSH was within normal limit.

TSH had a significant positive correlation with VPT (p <0.001) which was similar to study by Pramanik *et al*[17]. They included overt hypothyroidism in their study along with subclinical hypothyroidism. We excluded even subclinical hypothyroid population and found a positive correlation between VPT >25 and TSH.

Limitations:

We have not considered Type 1 Diabetes Mellitus.

We have not considered secondary hypothyroid.

We have not considered Free T4 and T3 value for analysis and interpretation.

Conclusion

Loss of Protective Sense was detected in 63% of our study population. We observed that TSH was an independent predictor of LOPS. Patients having LOPS showed a higher TSH level, even when TSH value was within normal range. To our best knowledge, it is the first study to report correlation of TSH (within normal range) with diabetic foot at risk.

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Conflict of Interest : None

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