Association between thyroid dysfunction and diabetic peripheral neuropathy in Egyptian people with type 2 diabetes mellitus

By

Hadeer M. Nageeb¹, Hanan Gawish¹, Mohammed I. Abd El-Ghany¹

¹Department of Internal Medicine (Endo & Diabetes unit), Faculty of Medicine, Mansoura University, Mansoura, Egypt.

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- HbA1c

Abstract

Background: Type 2 diabetes (T2DM) and thyroid diseases are the two most common endocrine disorders encountered in clinical practice. Diabetes and thyroid dysfunction are shown to mutually influence each other. The peripheral nervous system is one of the various systems affected by diabetes and thyroid dysfunction. **Aim:** To assess the prevalence of thyroid dysfunction among subjects with T2DM complicated by Diabetic peripheral neuropathy (DPN) to discover the possible association of thyroid dysfunction to the development and severity of DPN. **Methods:** A cross-sectional study includes 160 participants with T2DM that were subdivided into 2 groups. Group A includes subjects with DPN. Group B includes subjects without DPN. Detailed clinical history was taken. Also, TSH, free T4, free T3, and HbA1c were measured. **Results:** The prevalence of thyroid dysfunction was observed in 25% of subjects with T2DM with hypothyroidism (67.5%) as the commonest thyroid disorder. Thyroid dysfunction was more prevalent in older females. There was a statistically significant association between thyroid status and DPN among studied cases with 12.3% of cases with DPN have overt hypothyroidism, 10.4% have subclinical hypothyroidism. Among cases with DPN, HbA1c level was statistically significantly higher among subclinical and overt hypothyroidism cases than cases with normal thyroid status. Subjects with TSH ≥ 2.4 uIU/ml have 2.4 times higher odds to exhibit neuropathy (COR = 2.423, 95% CI = 1.13 – 5.196, P = 0.023). **Conclusion:** Thyroid dysfunction mainly hypothyroidism, is more prevalent and positively correlates with DPN among T2DM subjects.

INTRODUCTION

Diabetes is a huge and rapidly growing health problem worldwide. In 2019, IDF estimated that the number of people with diabetes was 463 million and expected to be 578 million by 2030, and 700 million by 2045. Two-thirds of people with diabetes live in urban areas, and one in five people with diabetes is above 65 years [1].

T2DM is characterized by peripheral insulin resistance and pancreatic β -cell failure, leading to major comorbidity and mortality as a result of micro and macrovascular complications [2]. Globally, T2DM accounts for 87 to 91% of the diabetes burden and still increasing [3].

Diabetic peripheral neuropathy (DPN) is a common complication of long-standing diabetes that affects up to 50% of diabetic subjects [4]. Painful diabetic distal symmetrical polyneuropathy (DSPN) causes a huge burden on subjects' lives with increased rates of unemployment, mental health disorders, and physical comorbidities. Unfortunately, due to limited understanding of the mechanisms to painful DSPN, current treatments remain inadequate [5].

Thyroid dysfunction is associated with characteristic symptoms, signs, and functional alteration in many organs and systems. The peripheral nervous system is one of the various organ systems affected by thyroid dysfunction [6].

T2DM and thyroid diseases are the two most common endocrine disorders encountered in clinical practice. Diabetes and thyroid disorders are shown to mutually influence each other [7].

Several epidemiological studies showed a higher prevalence of overt hypothyroidism in the population with T2DM than in the general population. However, the relationship between

T2DM and subclinical hypothyroidism (SCH) is controversial [8].

SCH defined as high serum TSH but normal free T4 (FT4) level, is a common endocrine disease. The prevalence of SCH increased with age, about 4 to 10% in the adult population and 12.7% in diabetic subjects [9].

Because of these data, we aimed to assess the prevalence of thyroid dysfunction among subjects with T2DM complicated by DPN to discover the possible contribution or association of thyroid dysfunction to the development and severity of DPN among diabetic subjects.

Patients and methods:

Patients:

This Cross-Sectional, comparative study includes 160 participants with T2DM aged from 40 to 65 years. In all cases, both men and women were recruited from subjects attending diabetes and endocrinology outpatient clinic at Mansoura specialized medical hospital, Mansoura University, Egypt. The study was carried out over the period from January 2020 to January 2021. The agreement to participate in the study by informed written consent was approved by the local ethical committee at the Mansoura faculty of medicine. This research was approved by Institutional Review Board (IRB) Mansoura Faculty of Medicine, Mansoura University. The diabetic state was confirmed or excluded according to the revised American Diabetes Association criteria.

The following were excluded:

- 1) Subjects with organ failure (renal failure and liver failure).
- 2) Subjects with malignant disorders.

- 3) Subjects with connective tissue disease (e.g. Systemic Lupus Erythematosus and Vasculitis)
- 4) Subjects with other causes of neuropathy.
- 5) Subjects receiving neurotoxic drugs (e.g. Isoniazid)
- 6) Subjects refuse to participate in the study.

Grouping of the patients:

The 160 participants were classified into 2 groups:

- **Group A:** Subjects with DPN.
- **Group B:** Subjects without DPN.

Clinical and Anthropometric Measurements:

All participants were subjected to full medical history, anthropometric measurements as weight, height, body mass index (BMI), and complete clinical examination with specific reference to any micro or macrovascular complications.

All participants were evaluated regarding various microvascular complications such as diabetic retinopathy using fundus camera & retinal imaging (TRC-50DX Series). The quantitative urine albumin/creatinine ratio in the morning spot urine samples, eGFR, increased BUN, and creatinine was used for the standard diagnosis of diabetic nephropathy. Also, ECG was performed.

All participants were subjected to nervous system examination including, superficial sensation assessment (pain, temperature, and fine touch), deep sensation assessment (deep pressure using monofilament, vibration sense using tuning fork, sense of movement, position, and muscle sense, and deep reflexes as ankle jerk). DPN was diagnosed based on clinical assessment of vibration perception, temperature perception, pinprick sensation, and Achilles reflex.

Blood Sampling and Biochemical Measurements:

After overnight fasting (12h), venous blood samples (5 ml) were withdrawn from each subject via proper venipuncture technique under complete aseptic condition. A complete hemogram was performed by using an automatic blood counter (CBC Analyzer Sysmex XP300, Germany). HbA1c was measured by the ion-exchange chromatography method (Biosystem co, Spain). Plasma glucose was measured by the glucose oxidase method (Cobas Integra 400 plus, Germany). Total cholesterol (TC), and triglyceride (TG) levels were measured by spectrophotometric method (Human, Germany). Urine Albumin-to-Creatinine Ratio (UACR) in a spot urine sample was measured by Roche Cobas c311 Albumin (Turbidimetric).

Estimation of serum levels of TSH, free T3, and free T4 was done by (Cobas e411, Roche Diagnostics, Germany) which works by the electrochemiluminescence immunoassay technology method. TSH normal population range is 0.27- 4.2 uIU/ml, free T4 normal population range is 0.9 – 1.7 ng/dl, free T3 normal population range is 1.9 – 5.1 pg/ml.

Statistical analysis and data interpretation:

Data were fed to the computer and analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using numbers and percentages. Quantitative data were described using median (minimum and maximum) for non-parametric data and mean, the standard deviation for parametric data after testing normality using Kolmogorov-

Smirnov test. The significance of the obtained results was judged at the (0.05) level.

Data analysis:

Qualitative data:

- Chi-Square test for comparison of 2 or more groups
- Monte Carlo test as correction for Chi-Square test when more than 25% of cells have count less than 5 in tables ($>2 \times 2$).
- Fischer Exact test was used as a correction for the Chi-Square test when more than 25% of cells have to count less than 5 in 2×2 tables.

Quantitative data between groups:

Parametric tests:

- Student t-test was used to compare 2 independent groups.
- One Way ANOVA test was used to compare more than 2 independent groups with the Post Hoc Tukey test to detect pair-wise comparison.

Non Parametric tests:

- Mann-Whitney U test was used to compare 2 independent groups.
- Kruskal Wallis test was used to compare more than 2 independent groups with Mann Whitney U test to detect pair-wise comparison.

Binary stepwise logistic regression analysis was used for the prediction of independent variables of a binary outcome. Significant predictors in the univariate analysis were entered into the regression model using the forward Wald method/Enter. Adjusted odds ratios and their 95% confidence interval were calculated.

Results:

Demographic data of subjects:

Our 160 diabetic participants were aged 40-65 years old, with medians of age were 53.9 years. Most of them were females (66.2%), with medians of diabetic duration were 9 years. 82 subjects were taking insulin (51.2%), 69 subjects were taking oral anti-diabetic (43.1%), 9 subjects were taking combined therapy (5.6%).

As regard complications, 106 subjects having diabetic neuropathy (66.2%), 45 subjects having diabetic retinopathy (28.1%), 35 subjects having diabetic nephropathy (21.9%), 61 subjects were hypertensive (38.1%), and 29 subjects having Ischemic heart disease (18.1%).

Assessment of the thyroid status among the diabetic subjects:

As regard thyroid status, 120 subjects were euthyroid (75.0%), 14 subjects having overt hypothyroidism (8.8%), 13 subjects having subclinical hypothyroidism (8.1%), 4 subjects having overt hyperthyroidism (2.5%), and 9 subjects having subclinical hyperthyroidism (5.6%).

The flow chart in **Figure (1)** shows that abnormal thyroid function was observed in 25% of cases. Of these 40 cases, 27 (67.5%) have hypothyroidism, and 13 (32.5%) have hyperthyroidism. The Chi-square goodness of fit test shows that this differs significantly from the null hypothesis of equal proportions ($\chi^2 = 4.9$, $P = 0.027$).

Quantitative and qualitative characteristics of studied cases with different thyroid statuses:

Table (1) shows a statistically significantly higher mean age value among cases of overt hypothyroidism, subclinical

hypothyroidism, and hyperthyroidism than cases of normal thyroid status. It also shows a statistically significantly higher proportion of female cases in overt hypothyroidism and subclinical hypothyroidism cases than cases of normal thyroid status.

There was a statistically significantly higher proportion of diabetic neuropathy among cases of subclinical, overt hypothyroidism, and hyperthyroidism than cases of normal thyroid status. Also, there was a statistically significantly higher proportion of diabetic nephropathy and

diabetic retinopathy among cases of subclinical hypothyroidism than cases of normal thyroid status.

Also, this table showed a statistically significantly higher value of albumin/creatinine ratio and serum cholesterol levels among cases with overt hypothyroidism than cases with normal thyroid status. Serum cholesterol levels were statistically significantly lower among cases with hyperthyroidism than cases with normal thyroid status.

Figure (1). Assessment of the thyroid status among the diabetic subjects:

Association between neuropathy and thyroid status among studied cases:

Table (2) shows a statistically significant association between thyroid status and neuropathy among studied cases with 12.3% of cases with neuropathy have overt hypothyroidism, 10.4% have subclinical hypothyroidism, 7.5% have subclinical hyperthyroidism, and 3.8% have overt hyperthyroidism.

Quantitative and qualitative characteristics of studied cases with and without neuropathy:

Table (3) shows a statistically significant association between neuropathy and the following; older age, female sex, use of hypoglycemic drugs,

presence of hypertension, longer disease duration, and higher mean cholesterol level.

Quantitative and qualitative characteristics among normal and hypothyroid cases with and without neuropathy:

Among cases with neuropathy, **Table (4)** shows a statistically significantly higher proportion of nephropathy among cases with subclinical hypothyroidism than cases with normal thyroid status. HbA1c level was statistically significantly higher among subclinical and overt hypothyroidism cases than cases with normal thyroid status. Also, serum triglycerides and serum cholesterol levels were statistically significantly

higher among cases with hypothyroidism than cases with normal thyroid status. Among cases without neuropathy, there is a statistically significant association between thyroid status and hypertension ($p=0.002$).

Predictors of neuropathy among studied cases:

Table (5) shows that the following are predictors of neuropathy among studied cases; older age with every increase one year increases the risk of neuropathy by 1.25, use of

hypoglycemic drugs (Odds ratio= 1.25), presence of hypertension (odds ratio= 2.58), longer disease duration (odds ratio=3.25), and higher mean cholesterol level (odds ratio=4.2).

TSH as a predictor of neuropathy in those with normal thyroid status or hypothyroidism:

As shown in Table (6) and Figure (2), those participants with TSH ≥ 2.4 have 2.4 times higher odds to exhibit neuropathy (COR = 2.423, 95% CI = 1.13 – 5.196, $P = 0.023$).

Table (1): Quantitative and qualitative characteristics of studied cases with different thyroid statuses

Characteristic		Thyroid status					Test of significance
		Normal	Subclinical hypothyroidism	Subclinical hyperthyroidism	Hypothyroidism	Hyperthyroidism	
Age (years)		52.97 $\pm$ 10.77	50.69 $\pm$ 13.48	60.78 $\pm$ 8.03	56.14 $\pm$ 11.86	69.0 $\pm$ 5.23	F=3.47 P=0.01*
Sex	Male	46 (38.3%)	1 (7.7%)	5 (55.6%)	0 (0%)	2 (50%)	MC P=0.006*
	Female	74 (61.7%)	12 (92.3%)	4 (44.4%)	14 (100%)	2 (50%)	
DM duration (years)		9.5 (0.5-35.0)	7 (2.0-30.0)	10 (2.0-30.0)	8 (3.0-33.0)	17.5 (15.0-25.0)	KW P=0.224
Anti diabetic drugs	Oral	54 (45%)	4 (30.8%)	3 (33.3%)	8 (57.1%)	0 (0%)	MC P=0.284
	Insulin	57 (47.5%)	9 (69.2%)	6 (66.7%)	6 (42.9%)	4 (100%)	
	Combined	9 (7.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Coma		11 (9.2%)	3 (23.1%)	0 (0%)	1 (7.1%)	1 (25%)	MC P=0.321
Diabetic Nephrology		23 (19.2%)	7 (53.8%)	3 (33.3%)	1 (7.1%)	1 (25%)	MC P=0.029*
Diabetic Retinopathy		30 (25%)	5 (38.5%)	3 (33.3%)	3 (21.4%)	4 (100%)	MC P=0.018*
Diabetic Neuropathy		70 (58.3%)	11 (84.6%)	8 (88.9%)	13 (92.9%)	4 (100%)	MC P=0.008*
Hypertension		39 (32.5%)	9 (69.2%)	7 (77.8%)	3 (21.4%)	3 (75%)	MC P=0.002*
Ischemic Heart Disease		29 (24.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	MC P=0.019*
Creatinine		0.985 $\pm$ 0.420	1.48 $\pm$ 0.85	1.09 $\pm$ 0.81	0.892 $\pm$ 0.25	1.20 $\pm$ 0.35	F=3.56 P=0.008*
Total cholesterol (mg/dL)		192.12 $\pm$ 46.37	177.77 $\pm$ 51.31	172.77 $\pm$ 35.53	212.86 $\pm$ 35.19	146 $\pm$ 9.76	F=2.49 P=0.04*
Triglycerides (mg/dL)		142 (60-477)	142 (59-185)	132 (95-180)	173 (125-484)	102.5 (96-127)	KW P=0.064
HbA1c		8.86 $\pm$ 1.65	10.17 $\pm$ 2.81	9.07 $\pm$ 2.14	8.95 $\pm$ 2.04	8.9 $\pm$ 0.88	F=1.53 P=0.197
Albumin creatinine ratio (mg/g)		4.36 $\pm$ 1.42	3.31 $\pm$ 1.52	4.01 $\pm$ 1.35	4.74 $\pm$ 1.02	3.12 $\pm$ 0.79	F=2.84 P=0.026*

F:One Way ANOVA test , KW: Kruskal Wallis test , MC: Monte Carlo test *statistically significant if $p<0.05$ parameters described as mean $\pm$ SD or median (range)

Table (2): Assessment of thyroid status in subjects with positive and negative neuropathy

Thyroid status		Neuropathy		Monte Carlo test	Total
		-VE	+VE		
Normal	N	50	70	MC P=0.008*	120
	%	92.6%	66.0%		75.0%
Subclinical hypothyroidism	N	2	11		13
	%	3.7%	10.4%		8.1%
Subclinical hyperthyroidism	N	1	8		9
	%	1.9%	7.5%		5.6%
Hypothyroidism	N	1	13		14
	%	1.9%	12.3%		8.8%
Hyperthyroidism	N	0	4		4
	%	.0%	3.8%		2.5%

MC: Monte Carlo test *statistically significant if $p < 0.05$ **Table (3):** Quantitative and qualitative characteristics of studied cases with and without neuropathy

Characteristic		Negative Neuropathy	Positive Neuropathy	Test of significance
		N=54	N=106	
Age (years)		51.26 ± 10.38	55.24 ± 11.45	t=2.15 P=0.03*
Sex	Male	24 (44.4%)	30 (28.3%)	$\chi^2=4.17$ P=0.04*
	Female	30 (55.6%)	76 (71.7%)	
DM duration (years)		7 (2-25)	10 (0.5-35)	z=2.06 P=0.04*
Anti diabetic drugs	Oral	21 (38.9%)	48 (45.30)	$\chi^2=6.47$ P=0.039*
	Insulin	33 (61.1%)	49 (46.2%)	
	Combined	0 (0%)	9 (8.5%)	
Coma		6 (11.1%)	10 (9.4%)	$\chi^2=0.112$ P=0.738
Diabetic Nephropathy		10 (18.5%)	25 (23.6%)	$\chi^2=0.537$ P=0.464
Diabetic Retinopathy		14 (25.9%)	31 (29.2%)	$\chi^2=0.195$ P=0.659
Hypertension		5 (9.3%)	56 (52.8%)	$\chi^2=28.79$ P<0.001*
Ischemic Heart Disease		29 (53.7%)	0 (0%)	$\chi^2=59.53$ P<0.001*
Creatinine		1.05 ± 0.44	1.02 ± 0.52	t=0.389 P=0.698
Total cholesterol (mg/dL)		175.37 ± 42.93	198.25 ± 45.54	t=3.06 P=0.003*
Triglycerides (mg/dL)		142.43 ± 46.31	158.42 ± 76.34	t=1.41 P=0.160
HbA1c		8.78 ± 1.81	9.09 ± 1.84	t=1.01 P=0.313
Albumin creatinine ratio (mg/g)		4.11 (0.72-6.71)	4.45 (0.92-10.5)	z=0.928 P=0.354

 χ^2 =Chi-Square test t:Student t test *statistically significant if $p < 0.05$ Z:Mann Whitney U test

Table (4): Quantitative and qualitative characteristics among normal and hypothyroid cases with and without neuropathy

Characteristic		Negative Neuropathy			Test of significance	Positive Neuropathy			Test of significance
		Normal N=55	Hypothyroidism N=1	Subclinical hypothyroidism N=2		Normal N=70	Hypothyroidism N=13	Subclinical hypothyroidism N=11	
Age (years)		51.34±10.38	45.0±0.0	45.0±9.89	F=0.529 P=0.593	54.13±10.96	57.0±11.89	51.73±14.16	F=0.642 P=0.528
Sex	Male	22 (44%)	0 (0%)	1 (50%)	MC	24 (34.3%)	0 (0%)	0 (0%)	MC
	Female	28 (56%)	1 (100%)	1 (50%)	P=0.667	46 (65.7%)	13 (100%)	11 (100%)	P=0.004*
DM duration (years)		6.5 (2.0-25.0)	9.0 (9.0-9.0)	5.5 (4.0-7.0)	KW P=0.762	10 (0.5-35)	8 (3-33)	9 (2-30)	KW P=0.873
Anti diabetic drugs	Oral	18 (36%)	1 (100%)	2 (100%)	MC	36 (51.4%)	7 (53.8%)	2 (18.2%)	MC
	Inulin	32 (64%)	0 (0%)	0 (0%)	P=0.089	25 (35.7%)	6 (46.2%)	9 (81.8%)	P=0.037*
	combined	0 (0%)	0 (0%)	0 (0%)		9 (12.9%)	0 (0%)	0 (0%)	
Coma		6 (12%)	0(0%)	0(0%)	MC P=0.816	5 (7.1%)	1 (7.7%)	3 (27.3%)	MC P=0.105
Diabetic Nephropathy		9 (18%)	0 (0%)	0 (0%)	MC P=0.722	14 (20%)	1 (7.7%)	7 (63.6%)	MC P=0.002*
Diabetic Retinopathy		13(26%)	0 (0%)	0 (0%)	MC P=0.596	17 (24.3%)	3 (23.1%)	5 (45.5%)	MC P=0.320
Hypertension		3 (6%)	1(50%)	1(100)	MC P=0.002*	36 (51.4%)	8 (72.7%)	6 (75%)	MC P=0.067
Ischemic Heart Disease		29 (58%)	0 (0%)	0 (0%)	MC P=0.171	0 (0%)	0 (0%)	0 (0%)	P=1.0
Creatinine		0.95 (0.6-2.0)	0.9 (0.9-0.9)	0.8 (0.7-0.9)	KW P=0.545	0.9(0.4-4.0)	0.8(0.7-1.7)	1.3(0.9-4.0)	KW P=0.001*
Total cholesterol (mg/dL)		173.40±39.85	236±0	221±94.7	F=2.291 P=0.111	205.49±46.32	211.08±35.9	169.91±42.65	F=3.32 P=0.04*
Triglycerides (mg/dL)		141.82±47.66	125±0	151±31.1	F=0.101 P=0.905	162.0±75.69	202.69±107.28	122.0±39.65	F=3.24 P=0.04*
HbA1c		8.83±1.86	8.2±0	8.3±1.13	F=0.131 P=0.878	8.88±1.49	9.0±2.1	10.51±2.92	F=3.92 P=0.023*
Albumin creatinine ratio (mg/g)		0.75±0.50	0	0		0.667±0.49	0	0.833±0.41	F=4.94 P=0.019*

MC: Monte Carlo test , F:One Way ANOVA test , KW: Kruskal Wallis test

*statistically significant if p<0.05

Table (5): Predictors of neuropathy among studied cases.

Predictors		β	P-value	Odds ratio	95.0% C.I.for odds ratio	
					Lower	Upper
TSH		.097	.179	1.102	.956	1.269
free T3		-.440	.105	.644	.379	1.096
free T4		.619	.347	1.857	.511	6.749
Age (years)		0.460	0.02*	1.25	1.08	7.24
Sex	Male (r)					
	Female	1.214	0.07	2.45	0.89	4.58
	Oral	1.42	0.02*	1.25	1.14	2.58
	Insulin	r	0.89	undefined		
Anti diabetic drugs	Combined					
HTN		0.54	0.03*	2.58	1.24	5.87
DM duration (years)		0.45	0.02*	3.25	1.09	4.87
Total cholesterol (mg/dL)		0.78	0.01*	4.2	1.21	8.9
Constant		.891	.437	2.438		

Table (6): TSH as a predictor of neuropathy in those with normal or hypothyroidism

		Variables in the Equation					95% C.I.for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	
Step 1 ^a	TSH at cutoff 2.4(1)	.885	.389	5.167	1	.023	2.423	Lower
	Constant	.294	.206	2.027	1	.155	1.341	Upper

a. Variable(s) entered on step 1: TSH at cutoff 2.4.

Figure (2): TSH as a predictor of neuropathy in those with normal or hypothyroidism

Discussion:

T2DM and thyroid diseases are the two most common endocrine disorders encountered in clinical practice. Diabetes and thyroid disorders are shown to mutually influence each other [7].

The present study is a Cross-Sectional study with an analytic component that is carried

out on 160 subjects suffering from T2DM to assess the prevalence of thyroid dysfunction among subjects with T2DM complicated by Diabetic peripheral neuropathy (DPN) to discover the possible contribution or association of thyroid dysfunction to the development and severity of neuropathy in diabetic subjects.

In our current study, the prevalence of thyroid dysfunction was observed in 25% of subjects with T2DM with hypothyroidism (67.5%) as the commonest thyroid disorder. Thyroid dysfunction was more prevalent in females with a higher mean age value. Significantly higher proportions of diabetic nephropathy and diabetic retinopathy were observed among cases of subclinical hypothyroidism.

Also, significantly higher values of albumin/creatinine ratio and serum cholesterol levels were observed among cases with hypothyroidism than cases with normal thyroid status. HbA1c level was higher among cases with thyroid dysfunction than cases with normal thyroid status but wasn't statistically significant.

These results came in agreement with **Ozair et al.** who reported that the prevalence of thyroid dysfunction was observed in 28% of T2DM subjects, with subclinical hypothyroidism (18.8%) as the commonest thyroid disorder. Thyroid dysfunction was more prevalent in females, with the presence of dyslipidemia, retinopathy, poor glycemic state ($\text{HbA1c} \geq 7$), and longer duration of diabetes as significant contributing factors associated [10].

Similar results were obtained by **Jali et al.** who noted that the prevalence of thyroid dysfunction among subjects with T2DM was found in 16.2%. The gender-specific prevalence was higher in females (25%) compared to males (10.1%). The age-specific prevalence was higher in the age group ≥ 50 yrs. (19%) compared to other age groups. Higher prevalence was demonstrated among subjects with poor glycaemic control (27.9%). Subjects with long-standing T2DM had

an increased risk for thyroid dysfunction (19.8%) [11].

In the same context, **Radaideh et al.** reported that thyroid dysfunction was found to be more in subjects with T2DM (16%) with subclinical hypothyroidism and hypothyroidism were the most common thyroid dysfunction in both cases and controls. Thyroid dysfunction was more common among females with old age [12].

On the contrary, although **Mehalingam et al.** reported that the prevalence of thyroid dysfunction is 17.5% in subjects with T2DM with hypothyroidism was seen in 13.9%, while hyperthyroidism was observed in 3.6% and thyroid dysfunction was more common among females than males. But, he reported that no correlation was seen between thyroid dysfunction and diabetic complications in the studied subjects [13]. Similarly, **Khassawneh et al.** reported no significant associations between thyroid disorders and complications or duration of diabetes ($p > 0.050$) [14].

In our current study, there is a statistically significant association between thyroid status and diabetic neuropathy among studied cases with 12.3% of cases with diabetic neuropathy have overt hypothyroidism, 10.4% have subclinical hypothyroidism, 7.5% have subclinical hyperthyroidism, and 3.8% have overt hyperthyroidism. Also, there is a statistically significant association between DPN and the following; older age, female sex, presence of hypertension, longer disease duration, and higher mean cholesterol level.

Such results agreed with **Zhao et al.** who reported that serum TSH levels were significantly higher in DPN and signs of DPN compared with

non-DPN T2DM subjects (both $P < 0.01$). The prevalence of DPN and signs of DPN in SCH subjects was higher than that in euthyroid subjects (both $P < 0.01$) [4].

A study done by **Nishi** showed that diabetic complications were more prevalent in subjects with both T2DM and subclinical hypothyroidism than those with T2DM and normal thyroid function. The odds ratio for diabetic peripheral neuropathy was 1.87 (95% CI 1.06–3.28). Also, a higher incidence of diabetic complications has been reported in subclinical hypothyroidism [15].

Pramanik et al. in their study stated that one in four people living with diabetes was suffering from thyroid dysfunction. A trend toward higher diabetic complications (neuropathy and nephropathy) was associated with rising TSH. SCH might affect the development of diabetic complications with an overall odds ratio of 1.87 (95% CI: 1.06, 3.28) for diabetic peripheral neuropathy [16].

Zhu & Yang in their study reported that serum-free triiodothyronine level is associated with nerve conduction in diabetes. Low free triiodothyronine level may be a potential risk for diabetic peripheral neuropathy [17].

In contrary to these results, **Mohamed & Elsayed** stated that no significant difference in the prevalence of diabetic neuropathy ($p = 0.420$) among SCH group than the euthyroid group. while SCH group had a higher prevalence of dyslipidemia ($p = 0.017$), diabetic nephropathy ($p = 0.003$) diabetic retinopathy ($p = 0.004$), and IHD ($p = 0.011$) than the euthyroid group [18].

In our current study, among cases with DPN, HbA1c level was statistically significantly

higher among subclinical and overt hypothyroidism cases than cases with normal thyroid status.

This was in agreement with **Kandasamy et al.** who reported that HbA1c values among hypothyroid subjects were higher when compared to that of euthyroid subjects [19]. Also, **Liu et al.** stated that poor lipid and glycemic control was observed among T2DM subjects with SCH and were prominent among subjects with TSH > 10 μ IU/ml. In addition, a significant positive correlation between serum TSH and FPG, TC, LDL-C, and HbA1c was observed among T2DM subjects with SCH [20].

In contrast to these results, **Sharma et al.** reported that TSH level wasn't found to be significantly associated with HbA1c [21].

As regards quantitative and qualitative characteristics among normal and hypothyroid cases with and without neuropathy, our current study revealed that there was a statistically significantly higher proportion of nephropathy among cases with subclinical hypothyroidism than those with neuropathy cases with normal thyroid status. Also, serum triglycerides and serum cholesterol levels were statistically significantly higher among cases with hypothyroidism than cases with normal thyroid status.

Such results agreed with **Khan et al.** who stated that non-HDL-C, LDL-C, and UACR increased from euthyroid subjects to overt hypothyroidism group. However, these changes were more subtle in the subclinical hypothyroid subjects than in cases with overt hypothyroidism [22]. Also, **Zhao et al.** reported that in subjects with diabetic nephropathy, TSH was positively correlated with SCr and UACR, and the

correlations between FT3 with SCr and UACR were negative [23].

Another study done by **Jiffri** showed low thyroid function was positively associated with lipid dysregulation in subjects with T2DM [24]. Also, **Wolide et al.** reported that hypothyroid subjects with T2DM had higher lipid levels than euthyroid subjects with T2DM. TSH level has a positive significant correlation with all lipid profile parameters except HDL-C [25].

On the contrary, **Nair et al.** documented that HbA1c, abdominal obesity, poor hypertension control, lipid parameters, microalbuminuria, and renal dysfunction showed no difference among subjects with hypothyroidism when compared with euthyroid subjects [26].

Regarding Predictors of neuropathy among studied cases, our current study revealed that older age with every increase of one year increases the risk of neuropathy by 1.25, use of hypoglycemic drugs (Odds ratio= 1.25), presence of hypertension (odds ratio= 2.58), longer disease duration (odds ratio=3.25), and higher mean cholesterol level (odds ratio=4.2).

Regarding TSH level as a predictor of neuropathy in those with normal thyroid status or hypothyroidism, the present study revealed that those participants with $TSH \geq 2.4$ have 2.4 times higher odds to exhibit neuropathy ($COR = 2.423$, $95\% CI = 1.13 - 5.196$, $P = 0.023$).

These results came in agreement with **Zhao et al.** who reported that TSH level was significantly and independently associated with DPN in subjects with T2DM. The optimal cutoff point of TSH to indicate DPN was 3.045 mIU/L in men and 2.94 mIU/L in women. High serum TSH

level may be a potential risk factor for DPN in the Chinese population with T2DM [4].

Conclusion:

The prevalence of thyroid dysfunction was observed in 25% of T2DM subjects with hypothyroidism (67.5%) as the commonest thyroid disorder. Thyroid dysfunction was more prevalent in older females. There was a statistically significant association between thyroid status and DPN among studied cases, with 12.3% of cases with DPN have overt hypothyroidism, 10.4% have subclinical hypothyroidism. Among cases with DPN, HbA1c level was statistically significantly higher among subclinical and overt hypothyroidism cases than cases with normal thyroid status. Subjects with $TSH \geq 2.4$ uIU/ml have 2.4 times higher odds to exhibit neuropathy ($COR = 2.423$, $95\% CI = 1.13 - 5.196$, $P = 0.023$).

Abbreviations:

T2DM: type 2 diabetes mellitus; **DPN:** Diabetic peripheral neuropathy; **IDF:** International Diabetes Federation; **HbA1c:** glycosylated hemoglobin; **TC:** total cholesterol; **TG:** triglyceride; **HDL-C:** high-density lipoprotein cholesterol; **LDL-C:** low-density lipoprotein cholesterol; **IHD:** ischemic heart disease; **eGFR:** estimated glomerular filtration rate; **UACR:** Urine Albumin-to-Creatinine Ratio; **AUC:** area under curve; **OR:** odds ratios; **COR:** crude odds ratios; **CI:** confidence interval; **ROC:** Receiver Operating Characteristic.

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