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ORIGINAL RESEARCH

Prevalence and Clinical Significance of Subclinical Hypothyroidism in Diabetic Peripheral Neuropathy

Mahmoud A Allam[1]
Youssef A Nassar[1]
Hosameldeen S Shabana[1]
Sadek Mostafa[1]
Farag Khalil[1]
Hendawy Zidan[1]
Mohammed Abo-Ghebsha[2]
Amir Abdelghaffar[3]
Ahmed Essmat[3]
Essam Elmahdi[4]

[1]Department of Internal Medicine, Faculty of Medicine, Al-Azhar University, Cairo, Egypt; [2]Department of Clinical Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt; [3]Department of Neurology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt; [4]Department of Internal Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt

Background and Aim: Diabetic peripheral neuropathy (DPN) is one of the most common and disabling complications of DM. Many studies documented the prevalence of clinical and subclinical hypothyroidism (SCH) in diabetic patients but not in the particular group of patients with DPN. The present study aimed to determine the prevalence of SCH in DPN patients and to evaluate its association with severity of DPN.

Patients and Methods: The present cross-sectional study was conducted on 300 consecutive patients with DPN. The clinical manifestations of DPN were documented according to the validated Arabic version of the Michigan Neuropathy Screening Instrument. Severity of DPN was categorized into mild (6–8 points), moderate (9–11 points) or severe (12+ points) according to the Toronto Clinical Scoring System. All patients were submitted to careful history-taking and full clinical and neurological examination. Patients were diagnosed with SCH if they had TSH level above the upper limit of the normal reference range in association with normal free thyroxine (FT4) level.

Results: SCH was prevalent in 53 patients (17.7%, 95% CI: 13.5%–22.5%). Patients with SCH had significantly higher frequency of severe DPN (52.8% versus 28.3%, p=0.003). It was also shown that patients with SCH had significantly higher HbA1c (8.4 ± 1.0 versus 7.3 ± 1.2%, p<0.001) and HOMA-IR (3.7 ± 0.8 versus 2.7 ± 0.9, p<0.001) when compared with patients without SCH. Logistic regression analysis identified patients' age [OR (95% CI): 1.06 (1.03–1.08), p<0.001], HbA1c [OR (95% CI): 2.2 (1.7–2.9), p<0.001] and SCH [OR (95% CI): 7.7 (3.6–15.5), p<0.001] as independent predictors of DPN severity.

Conclusion: The present study showed that SCH is highly prevalent in DPN patients and is independently related to its severity.

Keywords: diabetes mellitus, diabetic peripheral neuropathy, subclinical hypothyroidism, thyroid hormones, thyroid dysfunction

Introduction

Diabetes mellitus (DM) is one of the most significant global health epidemics, with nearly 1 in 11 adults worldwide having DM, mostly of type 2. The huge burden of the disease is related to long-term and devastating complications and the wide range of associated comorbidities.[1] Among these morbidities, thyroid dysfunction is frequently reported in association with DM. On the other hand, DM is fairly common in patients with thyroid dysfunction.[2] Many studies documented the prevalence of clinical and subclinical hypothyroidism (SCH) in diabetic patients[3–6] and its relation to diabetic nephropathy.[7,8]

Diabetic peripheral neuropathy (DPN) is one of the most common and disabling complications of DM. DPN can present in acute or chronic forms affecting all

Correspondence: Mahmoud A Allam
Department of Internal Medicine, Faculty of Medicine, Al-Azhar University, Cairo, 11884, Egypt
Tel +20222602687
Fax +20224020184
Email dr.mahmoudallam75@gmail.com

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segments of peripheral nerves from the originating root to the distal axon.[9] Clinically, DPN is manifested by numbness, paresthesias and burning pain that proximally progresses across feet and hand in a stocking-glove distribution.[10]

The pathogenesis of DPN is quite complex. Suggested pathogenic mechanisms include mitochondrial dysfunction[11] and Schwann cells apoptosis[12] induced by hyperglycemia, dyslipidemia, insulin resistance, oxidative stress and the chronic inflammatory state related to DM.[13]

In spite of the marked progress achieved in management of DPN, the efficacy of available treatment options is far from optimal, and no disease-modifying drug exists. This is largely attributed to the fact that current treatment recommendations do not address the specific underlying pathogenic mechanisms. Thorough understanding of these mechanisms is essential for making significant progress in this field.[14,15]

The present study aimed to determine the prevalence of SCH in diabetic patients with DPN and to discover its relation to the clinical severity of the disease.

Methodology

The present cross-sectional study was conducted at the outpatient diabetes unit, Al-Azhar University Hospitals during the period from January 2019 through February 2020. The study protocol was approved by the ethical committee of Al-Azhar University Faculty of Medicine, and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki on clinical research involving human subjects.

The study included 300 consecutive patients with DPN. Diagnosis of DPN was established on the basis of nerve conduction studies (abnormal nerve conduction velocity of the sural or peroneal nerves) together with symptoms and signs of DPN. The clinical manifestations of DPN were documented according to the validated Arabic version of the Michigan Neuropathy Screening Instrument. The instrument includes a 15-item yes/no questionnaire in addition to physical examination.[16,17] Patients were excluded if they had known thyroid disease or were receiving treatment that can modify thyroid function.

Severity of DPN was categorized into mild (6–8 points), moderate (9–11 points) or severe (12+ points) according to the Toronto Clinical Scoring System (TCSS). TCSS is a validated peripheral neuropathy grading system that combines neurological symptoms scores, reflexes scores and sensory test scores.[18]

All patients had careful history-taking as well as full clinical and neurological examination. Laboratory work-up included complete blood count, fasting and postprandial blood glucose and fasting insulin levels. Insulin resistance was calculated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) using the equation: HOMA-IR=fasting insulin (U/L) × fasting glucose (mg/dL)/405. Glycemic control was assessed using HbA1c levels. Patients were diagnosed with SCH if they had a TSH level above the upper limit of the normal reference range in association with normal free thyroxine (FT4) level. The normal reference ranges of thyroid functions were: 0.27–4.5 μIU/mL for TSH and 0.93–1.7 ng/dL for FT4.

Data obtained from the present study were expressed as number and percent or mean and standard deviation (SD). Prevalence was expressed as proportion and 95% CI. Categorical data were compared using Fisher's exact test or chi-square test, while numerical data were compared using *t*-test. Logistic regression analysis was used to identify predictors of DPN severity. *P* value less than 0.05 was considered statistically significant. All statistical operations were processed using SPSS 25 (IBM, USA).

Results

Throughout the study period, there were 329 patients who fulfilled the clinical criteria of DPN. However, 29 patients were excluded. They comprised patients with other thyroid diseases (n=12) or those receiving medications that can affect thyroid functions (eg amiodarone, carbamazepine, etc.) (n=17). Finally, the study included 300 patients with DPN. There were 127 males (42.3%) and 173 females (57.7%) with an age of 52.9 ± 12.0 years. SCH was prevalent in 53 patients (17.7%, 95% CI: 13.5%–22.5%). Comparison between patients with SCH and patients without revealed that patients with SCH had significantly higher frequency of severe DPN (52.8% versus 28.3%, p=0.003) (Figure 1). It was also shown that patients with SCH had significantly higher HbA1c (8.4 ± 1.0 versus 7.3 ± 1.2%, p<0.001; Figure 2) and HOMA-IR (3.7 ± 0.8 versus 2.7 ± 0.9, p<0.001; Figure 3) when compared with patients without SCH (Table 1).

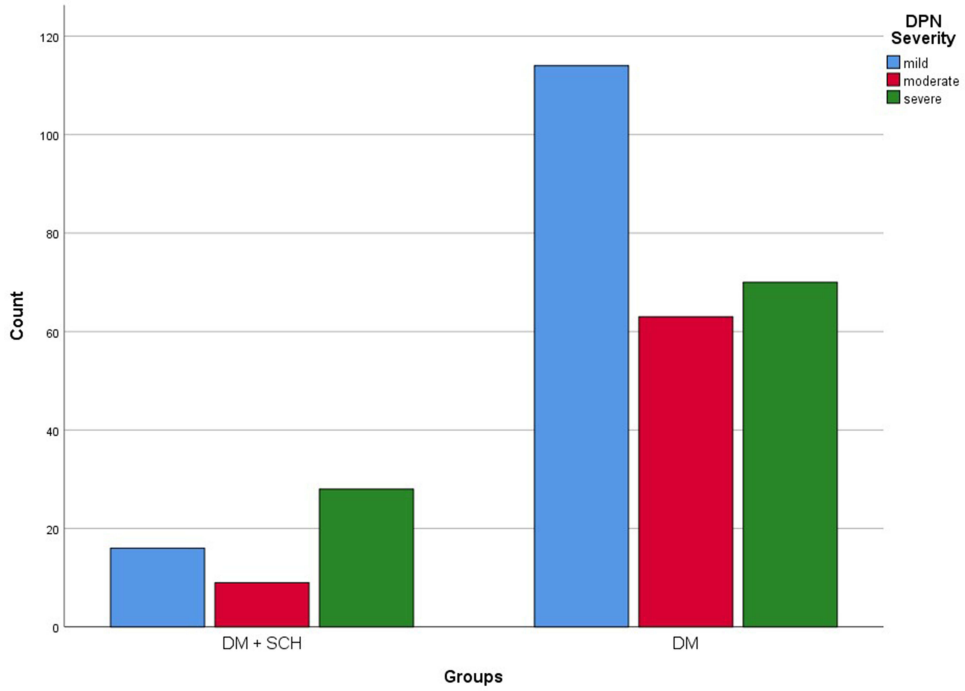

Figure 1 DPN severity in patients with and without SCH.

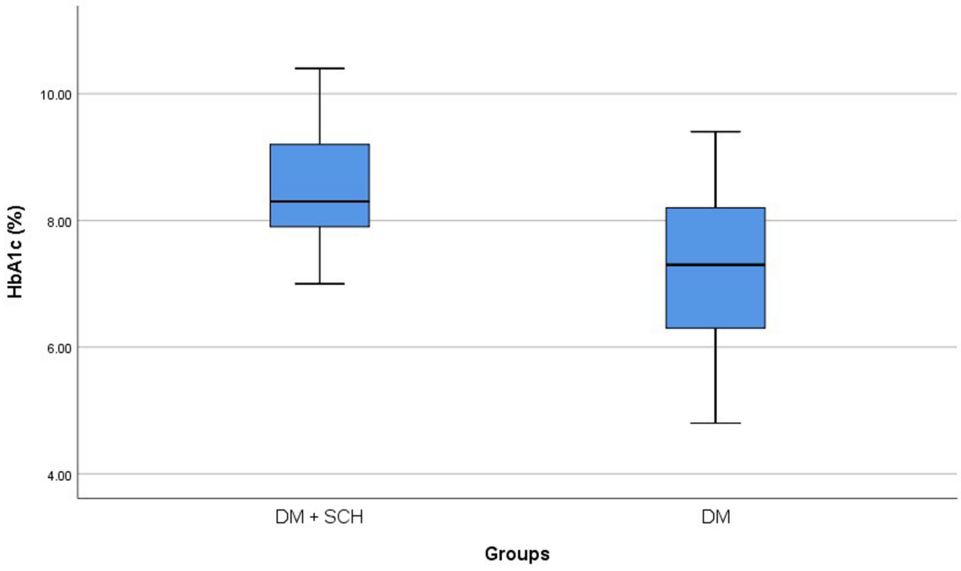

Figure 2 Glycemic control in patients with and without SCH.

According to DPN severity, patients were classified into those with severe DPN (n=98) and non-severe (mild/moderate) DPN (n=202). Logistic regression analysis identified patients' age [OR (95% CI): 1.06 (1.03–1.08), p<0.001], HbA1c [OR (95% CI): 2.2 (1.7–2.9), p<0.001] and SCH [OR (95% CI): 7.7 (3.6–15.5), p<0.001] as independent predictors of DPN severity (Table 2).

Discussion

The present study assessed the prevalence of SCH in 300 consecutive patients with DPN. The study found that 53 patients (17.7%) had SCH. The prevalence of SCH was previously determined in patients with various diabetic complications including diabetic nephropathy[8,19] and retinopathy.[20–22] In the general

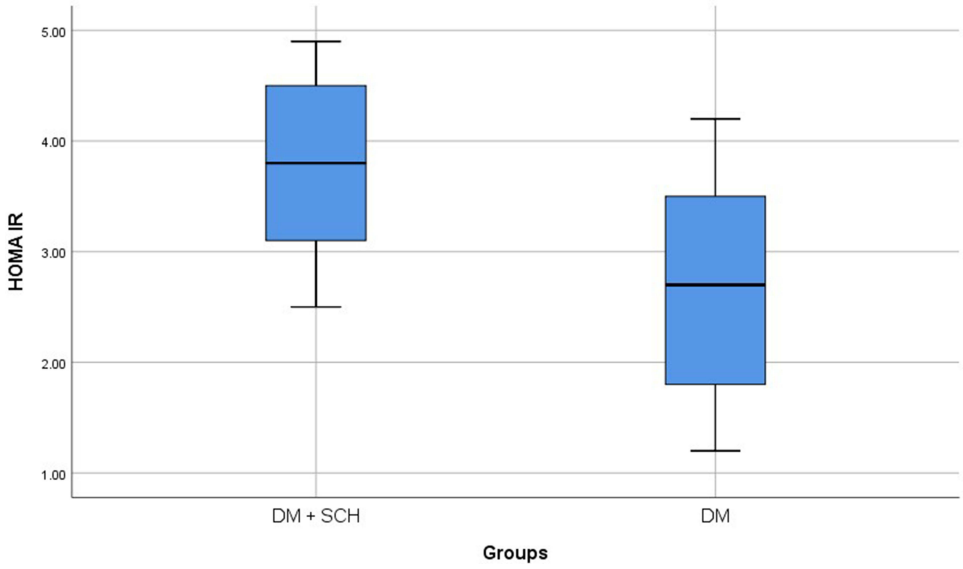

Figure 3 Insulin resistance in patients with and without SCH.

population, one study reported SCH in 11.3% of the included subjects.[23]

In our study, patients with SCH had significantly higher frequency of cases with severe DPN when compared with patients without SCH. Multivariate analysis confirmed SCH as an independent predictor of DPN severity. The relation between SCH and DPN was previously reported in a Chinese cohort.[24]

The contribution of SCH to the pathogenesis of DPN can be explained by multiple mechanisms. First, SCH has been shown to increase oxidative stress.[25,26] Augmented oxidative stress in turn is a well-known mechanism involved in the development of DPN as evidenced by experimental and clinical studies.[27–29]

Second, SCH has also been found to be associated with pronounced inflammatory state.[30–33] The role of proinflammatory state in the pathogenesis of DPN is well-documented.[34,35]

A third mechanism that may interrelate SCH and DPN is dyslipidemia which was found to be associated with SCH[36,37] and is considered as a risk factor for DPN.[38–40]

In addition, the current study recognized an association between SCH and poor glycemic control. These results are supported by the conclusions of Cho et al[41] who noted that diabetic patients with poor glycemic control have higher risk for development of SCH.

Moreover, we found that patients with SCH had significantly higher HOMA-IR levels. Such a relationship was previously reported in other diabetic patients.[20] In fact, even in the general population, Kocatürk et al[42] found a significant association between insulin resistance, impaired β-cell function and increased TSH levels.

Our study suggests that SCH aggravates the pathogenic mechanisms related to DM and DPN that are consequences of the metabolic derangements induced by insulin resistance and hyperglycemia. It may be beneficial to screen all diabetic patients for SCH to prevent or limit significant neuropathic complications. In fact, the British and American Associations recommend screening of diabetic patients for thyroid abnormalities. However, the British recommendations restrict screening to the time of diagnosis[43] while American guidelines[44] recommend that patients older than 35 years should have thyroid assessments every 5 years. Probably, our findings are supportive of the American recommendations. Interestingly, the European Thyroid Association suggests that L-thyroxine may be tried if onset of SCH was associated with worsening of glycemic control.[45]

In conclusion, the present study showed that SCH is prevalent in DPN patients and suggests that SCH is independently related to its severity. These conclusions are limited by the cross-sectional study design. Longitudinal follow-up of patients would better determine onset and deterioration of SCH and its clinical impact. In addition, adding a control diabetic group without DPN would add to the study value. This may be more conclusive regarding the association between

Table 1 Comparison Between Patients with SCH and Patients Without Regarding the Clinical and Laboratory Data

	All Patients *N*=300	SCH +ve *n*=53	SCH –ve *n*=247	*P* value
Age (years) mean ± SD	52.9 ± 12.0	52.3 ± 11.7	53.0 ± 12.1	0.69
Male/female *n*	127/173	20/33	107/140	0.46
BMI (kg/m^2) mean ± SD	33.0 ± 4.2	33.8 ± 3.9	32.8 ± 4.3	0.12
Duration of DM (years) mean ± SD	9.4 ± 8.7	10.6 ± 9.8	9.2 ± 8.5	0.26
Associated comorbidities *n* (%)				
Smoking	64 (21.3)	15 (28.3)	49 (19.8)	0.17
Hypertension	213 (71.0)	34 (64.2)	179 (72.5)	0.23
IHD	39 (13.0)	7 (13.2)	32 (13.0)	0.96
Stroke	25 (8.3)	6 (11.3)	19 (7.7)	0.39
Severity of DPN *n* (%)				
Mild	130 (43.3)	16 (30.2)	114 (46.2)	0.003
Moderate	72 (24.0)	9 (17.0)	63 (25.5)	
Severe	98 (32.7)	28 (52.8)	70 (28.3)	
Laboratory findings mean ± SD				
FBS (mg/dL)	133.8 ± 21.2	136.8 ± 14.9	131.6 ± 21.7	0.097
PPBS (mg/dL)	189.9 ± 41.5	193.2 ± 49.2	189.2 ± 39.7	0.53
Hb (g/dL)	11.6 ± 2.0	11.3 ± 1.1	11.7 ± 2.1	0.083
TLC (×10^3/mL)	7.8 ± 1.9	8.1 ± 1.6	7.7 ± 2.0	0.14
Platelets (×10^3/mL)	265.4 ± 72.8	282.0 ± 87.4	261.8 ± 69.0	0.12
Cholesterol (mg/dL)	222.3 ± 41.5	230.3 ± 34.6	220.6 ± 42.8	0.13
Triglycerides (mg/dL)	218.2 ± 88.0	233.5 ± 84.2	217.1 ± 88.9	0.63
HDL (mg/dL)	43.7 ± 10.1	41.9 ± 9.4	44.1 ± 10.2	0.15
LDL (mg/dL)	129.7 ± 44.8	135.3 ± 41.8	128.6 ± 45.5	0.32
HbA1c (%)	7.5 ± 1.2	8.4 ± 1.0	7.3 ± 1.2	<0.001
HOMA-IR	2.8 ± 1.0	3.7 ± 0.8	2.7 ± 0.9	<0.001

Abbreviations: BMI, body mass index; FBS, fasting blood glucose; FT3, free triiodothyronine; FT4, free thyroxine; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; PPBS, post-prandial blood sugar; SCH +ve, patients with subclinical hypothyroidism; SCH –ve, patients without subclinical hypothyroidism.

Table 2 Predictors of Severe DPN in the Studied Patients

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.06	1.03–1.08	<0.001	1.06	1.03–1.08	<0.001
Sex	0.58	0.35–0.96	0.035	1.3	0.73–2.3	0.37
HbA1c	1.8	1.4–2.2	<0.001	2.2	1.7–2.9	<0.001
HOMA-IR	0.79	0.61–1.02	0.071	–	–	–
SCH	2.8	1.5–5.2	0.001	7.7	3.6–15.5	<0.001

DPN development and SCH. Longitudinal studies with a larger sample size are recommended to allow generalization of our conclusions.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure

The authors declare no conflicts of interest, financial or otherwise, in this work.

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