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ORIGINAL ARTICLE

Prevalence and Clinical Significance of Subclinical Hypothyroidism in Diabetic Peripheral Neuropathy

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ABSTRACT

Background and Objective: The diabetic Mellitus common and spiking complication is Diabetic peripheral neuropathy (DPN). It is frequently associated with thyroid dysfunction. The subclinical hypothyroidism prevalence and clinical outcomes have been investigated by various studies. The present study aims to determine the prevalence of subclinical hypothyroidism in diabetic peripheral neuropathy patients.

Methods: This cross-sectional study was carried out on 164 diabetic neuropathy patients attending the medicine department of Qazi Hussain Ahmad Medical Complex, Nowshera KPK during the study period from 2020 to 2021. Patients' demographic details, clinical history, and neurological examination were recorded. Normal free thyroxin value was set as a referential standard for subclinical hypothyroidism diagnosis among all the patients. Diabetic neuropathy patients' clinical manifestations were recorded as per neurological screening instrument. The clinical scoring system was utilized for DPN severity categorization into mild (6-8), moderate (9-11), and severe (>12). SPSS version 20 and a logistic regression model were used for data analysis.

Results: This study enrolled 164 diabetic peripheral neuropathy patients. Of the total 164, 69 (42.1%) were male and 95 (57.9%) were female. The overall mean age was 49.61±13.72 years. The prevalence of subclinical hypothyroidism was 32 [19.5%; 95% CI; 14.3%-23.7%]. The diabetic peripheral neuropathy patients with subclinical hypothyroidism had a higher prevalence of severity 86 [52.4%; 95%CI] compared to DNP patients without SCH 46 [28.04%; 95% CI] with a 3% level of significance. A higher HbA1c and HOMA-IR was found in patients with their respective values were (8.3±1.1 against 7.2±1.3) where p-value <0.001 and (3.5 ± 0.9 vs. 2.6 ± 0.8, p<0.001) respectively.

Conclusion: The diabetic peripheral neuropathy patients are susceptible to have frequent subclinical hypothyroidism independently associated with severity and complications of DPN. Thyroid function should be tested in DM patients and given to DM patients with SCH.

Keywords: Diabetes mellitus; Subclinical hypothyroidism; Diabetic peripheral neuropathy

INTRODUCTION

The diabetic Mellitus common and spiking complication is Diabetic peripheral neuropathy (DPN). It is frequently associated with thyroid dysfunction. The subclinical hypothyroidism prevalence and clinical outcomes have been investigated by various studies [1, 2]. The disease's enormous burden is due to long-term and devastating complications, as well as associated comorbidities [3]. Thyroid dysfunction is one of the most common morbidities associated with diabetes. Diabetes mellitus, conversely, is an impartially common thyroid dysfunction patient [4]. Many studies have been conducted to determine the subclinical hypothyroidism occurrence in diabetic patients [5, 6]. DPN can manifest as an acute or chronic condition that affects all marginal concerns segments to instigating root causes to the distal axon [7]. DPN is characterized clinically by paresthesias, numbness, and scorching agony that spreads crosswise feet and hands in a pattern of stocking-glove [8]. Pathogenic mechanisms proposed comprise of mitochondrial dysfunction [9] and dyslipidemia, hyperglycemia causing Schwann cell apoptosis [10], oxidative stress, insulin resistance, and the chronic inflammatory state associated with diabetes [11].

Numerous epidemiological research shows that diabetes mellitus patients have a higher overt hypothyroidism prevalence compared to the general population [12, 13]. However, the subclinical hypothyroidism (SCH) association with diabetes is debatable. SCH is asymptomatic mild hypothyroidism, but thyroid-stimulating hormone (TSH) mild elevations are observed with free thyroid hormone concentrations normal circulating [14]. Several studies reported that hypertension, abnormal homocysteine levels, and high cholesterol level is significantly associated with subclinical hypothyroidism and such patients are more risky and susceptible to developing cardiovascular events, metabolic syndrome, atherosclerosis, and mortality [15, 16]. Currently, subclinical hypothyroidism treatment and individual dysfunction screening persist and are debatable [17]. Despite significant advances in DPN management, the available treatment efficiency is lagging behind, and no drug for ailment-adapting subsists. This is due to the guidelines of existing treatment of not concerning specified pathogenic procedures. To make significant progress in this field, a comprehensive details are required. The current study sought to ascertain the SCH occurrence in DPN patients, as well as its association to disease severity.

MATERIALD AND METHODS

This cross-sectional study was carried out on 164 diabetic neuropathy patients attending the medicine department of Qazi Hussain Ahmad Medical Complex, Nowshera KPK during the study period from 2020 to 2021. Patients' demographic details, clinical history, and neurological

examination were recorded. Normal free thyroxin value was set as a referential standard for subclinical hypothyroidism diagnosis among all the patients. Diabetic neuropathy patients' clinical manifestations were recorded as per neurological screening instrument. The clinical scoring system was utilized for DPN severity categorization into mild (6-8), moderate (9-11), and severe (>12). The Hospital ethics committee approved the study and written informed consent was taken from each individual. DPN was diagnosed using conveyance of abnormal nerve or peroneal nerves) in conjunction with DPN symptoms and signs. The validated version of the Michigan Neuropathy Screening Instrument was used to document the DPN clinical manifestations. Thyroid disease patients or thyroid function treatment receivers were excluded. Based on Toronto Clinical Scoring System, DPN severity was classified as mild (6–8 points), moderate (9–11points), or severe (12+ points).

The patient's thorough history, neurological and clinical investigations were recorded. A complete blood count, insulin levels, and fasting and postprandial glucose in blood were all part of the laboratory work-up. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [18] was used for insulin resistance determination using the following formula;

HOMA-IR= fasting insulin (U/L) × fasting glucose (mg/dL)/405

HbA1c levels were used to assess glycemic control. Subclinical hypothyroidism was diagnosed in patients with an exceeding than normal TSH level whereas the thyroid functions normal range were TSH (0.27–4.5 μIU/mL) and FT4 (free thyroxine) (0.93–1.7 ng/dL). For data analysis, SPSS version 20 was used. Fisher's exact test or chi-square test were used to compare categorical data, while the t-test was used to compare numerical data. A logistic regression model was used for the severity identification of DPN with a 5% level of significance.

RESULTS

This study enrolled 164 diabetic peripheral neuropathy patients. Of the total 164, 69 (42.1%) were male and 95 (57.9%) were female. The overall mean age was 49.61±13.72 years. The prevalence of subclinical hypothyroidism was 32 [19.5%; 95% CI; 14.3%-23.7%]. The diabetic peripheral neuropathy patients with subclinical hypothyroidism had a higher severity 86 [52.4%; 95%CI] compared to DNP patients without SCH 46 [28.04%; 95% CI] with a 3% level of significance. A higher HbA1c and HOMA-IR was found in SCH patients with their respective values (8.3±1.1 against 7.2±1.3) where p-value <0.001 and (3.5 ± 0.9 vs. 2.6 ± 0.8, p<0.001) respectively. Figure 1 depicts the patient gender distribution. Table-1 shows a comparison of laboratory and clinical data from patients. Figures 2 show a comparison of glycemic control and insulin resistance in patients with and without SCH. The prevalence of mild, moderate, and severe diabetic peripheral neuropathy were 71 (43.3%), 34 (20.7%), and 59 (36%) respectively as shown in Figure-3. Patients' age [OR (95% CI): 1.04 (1.02–1.05), p=0.001], SCH [OR (95%CI): 7.4 (3.4–14.2), p=0.001], and HbA1c [OR (95% CI): 2.1 (1.4–2.6), p=0.001] were DPN severity independent predictors identified in logistic regression analysis as shown in Table 2.

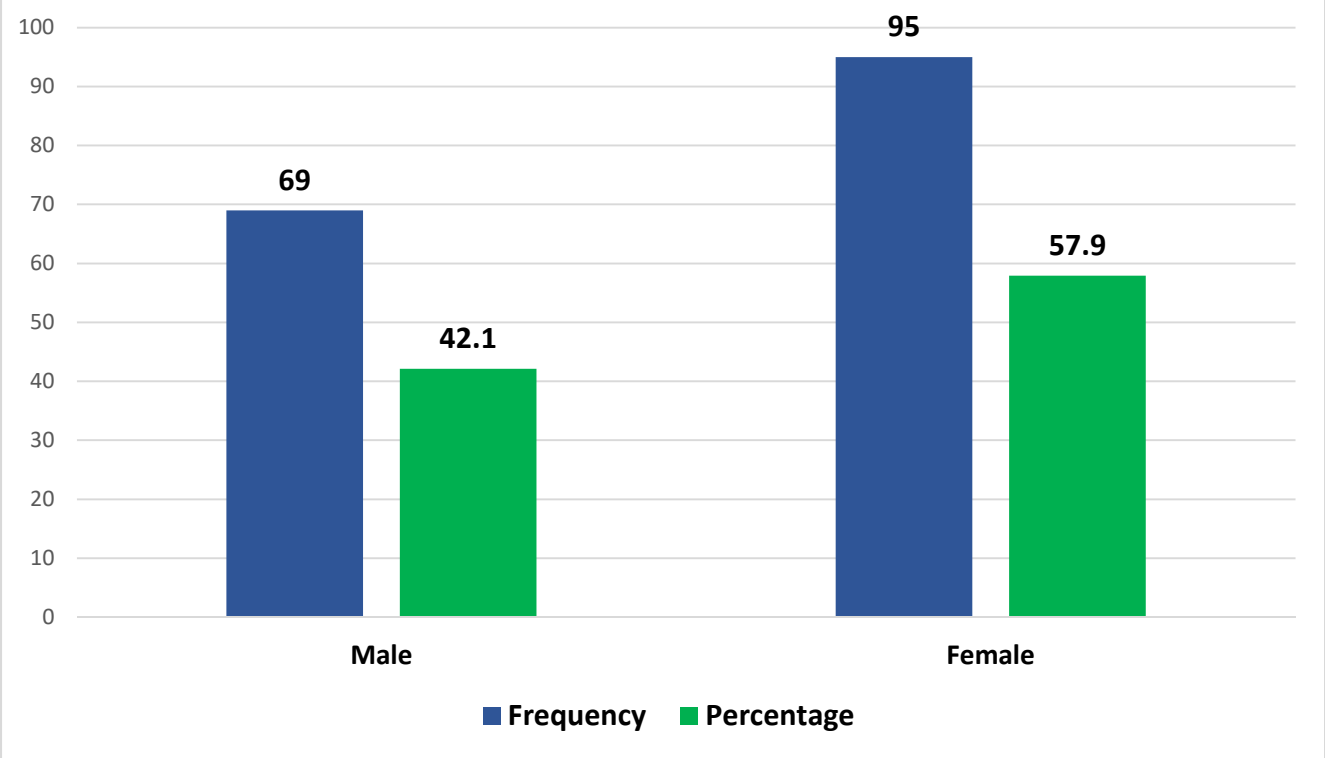

Figure-1 Gender distribution (n=164)

Table-1 Patient's Laboratory and Clinical Data (n=164)

Parameters	Patients (n=164)	Positive SCH, n=32	Negative SCH, n=132	P-value
Age ± SD (year)	49.61±13.72	51.43±14.32	53.3±14.92	0.67
Gender				
Male	69	14	55	0.51
Female	95	18	77	
Associated Morbidities				
Hypertension	116	17	99	0.19
Smoking	33	7	26	0.13
Stroke	7	3	4	0.40
Ischemic Heart Disease	8	5	3	0.89
DPN severity n (%)				
Severe	59 (36)	16	43	0.002
Moderate	34 (20.7)	5	29	
Mild	71 (43.3)	11	60	
Laboratory Results Mean± SD	225.3 ± 36.6	229.3 ± 32.6	221.3 ± 40.5	0.14
Cholesterol (mg/dL)	225.8 ± 84.9	235.2 ± 83.1	216.3 ± 86.6	0.58
Triglycerides (mg/dL)	42.5 ± 9.3	42.6 ± 8.8	42.4 ± 9.8	0.21
HDL (mg/dL)	130.7 ± 43.9	134.2 ± 41.7	127.2 ± 46.1	0.29
LDL (mg/dL)	7.8 ± 1.2	8.3 ± 1.1	7.3 ± 1.3	<0.001
HbA1c (%)	3.05 ± 0.9	3.5 ± 0.9	2.6 ± 0.8	<0.001
HOMA-IR				

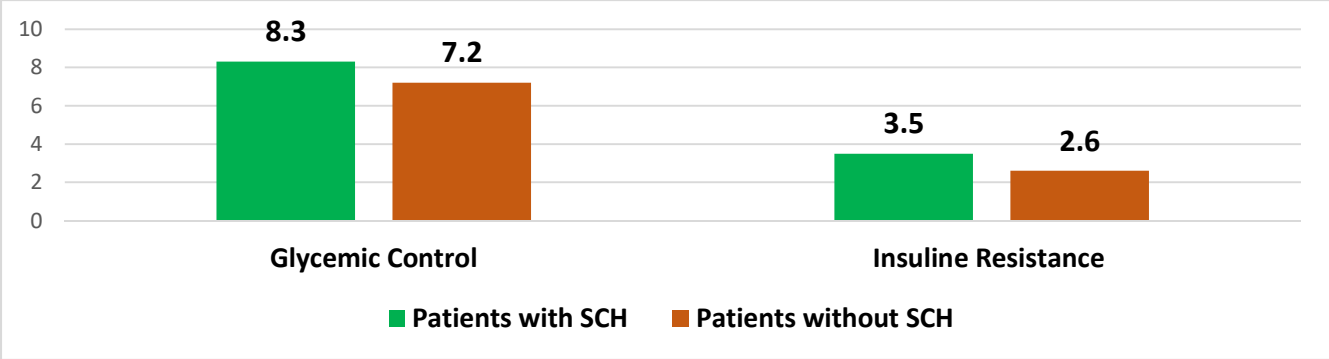

Figure-2 Glycemic control and insulin resistance among patients with and without SCH

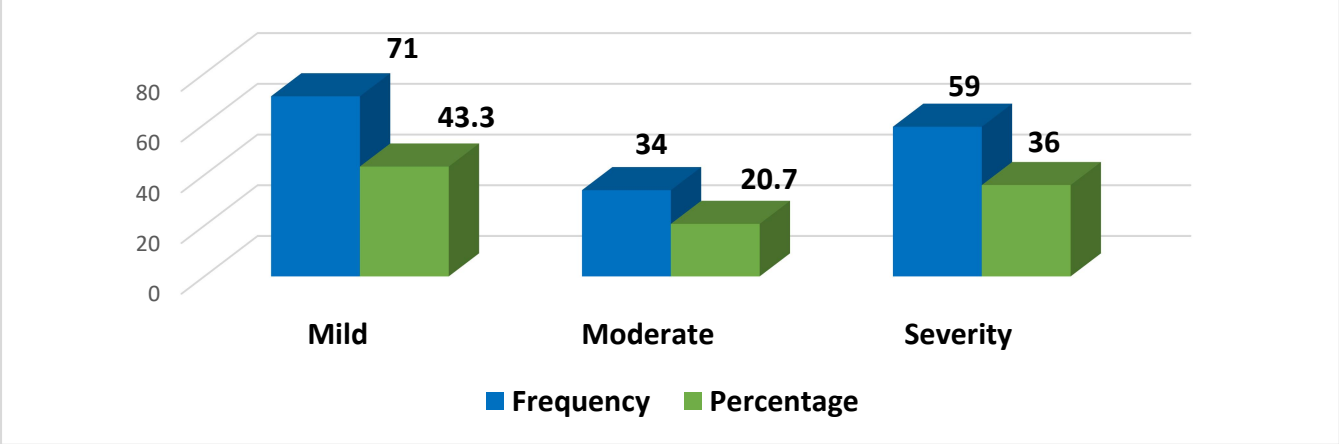

Figure-3 Prevalence of mild, moderate, and severe diabetic peripheral neuropathy

Table-2 Diabetic Peripheral Neuropathy severity predictors (Univariate vs. Multivariate analysis) among investigative patients (n=164)

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P-value	AOR	95%CI	P-value
Age	1.04	1.02-1.09	<0.001	1.04	1.02-1.09	<0.001
Gender	0.53	0.34-0.97	0.033	1.2	0.69-3.4	0.36
SCH	2.7	1.4-5.1	0.001	7.5	3.4-15.7	<0.001
HbA1c	1.9	1.3-2.3	<0.001	2.1	1.5-3.1	<0.001
HOMA-IR	0.81	0.59-1.1	0.069	_	_	_

DISCUSSION

The current study evaluated the incidence of 164 consecutive diabetic neuropathy patients. The incidence of subclinical hypothyroidism (SCH) was found in 32 patients (19.5%). SCH was identified earlier with numerous hitches of diabetes such as retinopathy and diabetic nephropathy [18, 19]. Previous research found 11.3% patients had SCH in the general population [20]. The prevalence of diabetic peripheral neuropathy with subclinical hypothyroidism patients in terms of severity was substantially higher than those without SCH in the present study. SCH was found to be an independent predictor of DPN severity in multivariate analysis, also found similar results in a Chinese-based study [21]. SCH's role in the DPN pathogenesis can be enlightened by a variety of mechanisms. Initially, it has been demonstrated that SCH increases oxidative stress [22, 23]. Secondly, SCH has been linked to a more pronounced inflammatory state [24]. The pro-inflammatory state is well-known to play a role in DPN pathogenesis [25, 26]. Another risk factor for diabetic peripheral neuropathy is dyslipidemia caused by SCH [27].

Furthermore, the current study found a relationship between glycemic poor control and SCH. These findings are buoyed with Cho et al [28] findings reported that poor glycemic control in diabetic patients are at developing SCH higher risk. Furthermore, HOMA-IR levels were substantially higher in subclinical hypothyroidism. A similar association has formerly been found in DM patients. Indeed, Kocatürk et al [29] discovered a substantial connection between insulin resistances and increased TSH in general population.

The prevalence of SCH in the general population is 19.5%, and our data suggest that the same prevalence is around 17.5% in the DM population [30]. As previously stated, factors such as age and gender may skew the results of these meta-analyses [31]. As a result, subgroup analyses were carried out. Gender difference, old age, and a clear geographic disparity were found to be associated with the prevalence of SCH in DM. In particular, there were 1.7 times more female SCH individuals in the DM population than male SCH individuals, and DM individuals over 60 years of age were also more likely to experience SCH-associated risks. These findings are consistent with the NHANES III study in the non-diabetic population [32].

Our findings suggest that the pathogenic mechanisms exacerbates by subclinical hypothyroidism associated with DPN, which are the result of metabolic imbalances caused by hyperglycemia. Screening diabetic patients as a whole for SCH may be beneficial in preventing or limiting serious neuropathic impediments. Indeed, both the Associations endorse that diabetic patients be screened for anomalies related to thyroid. Nevertheless, British guidelines [33] limit screening time, whereas American guidelines [34] endorse for elder age (>35 years) patients should have considered thyroid evaluation once after half decade. The results of present study are likely to support the American guidelines. Remarkably, the Thyroid Association of European proposes that if the onset of SCH is associated with worsening glycemic control, L-thyroxine may be tried [35].

CONCLUSION

The diabetic peripheral neuropathy patients are susceptible to have frequent subclinical hypothyroidism independently associated with severity and complications of DPN. Thyroid function should be tested in DM patients and given to DM patients with SCH.

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