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ORIGINAL ARTICLE

Prevalence of Hypothyroidism in Diabetic Foot Ulcer Patients

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ABSTRACT

Introduction: Diabetes foot ulcers (DFUs) is a severe complication of diabetes mellitus, and it can be affected by a large number of metabolic and endocrine factors. Hypothyroidism which has been most of the time ignored could be a factor in pathogenesis and seriousness of DFUs.

Objective: To establish the incidence of hypothyroidism among diabetic foot ulcer patients and evaluate its relationships with the severity and nature of ulcers.

Materials and Methods: It was a cross-sectional study, which was carried out in the Endocrinology Ward of Hayatabad Medical Complex, Peshawar, in the range of December, 2022 to May, 2023. Among 150 patients with diabetic foot ulcers (DFUs), 100 percent of them were tested on their level of thyroid hormones and their ulcers were classified using the wagner classification system. The SPSS was used to analyse the data.

Results: The present study revealed that twenty-eight percent of the patients who had DFU had Hypothyroidism. There was a significant association between hypothyroidism and higher Wagner grades, female gender as well as greater duration of diabetes ($p<0.05$).

Conclusion: Routine thyroid screening in DFU patients may aid early detection and improve clinical outcomes.

Keywords: Diabetic foot ulcer, hypothyroidism, Wagner grade, thyroid dysfunction, prevalence, diabetes mellitus.

INTRODUCTION

Diabetic foot ulcers (DFUs) are one of the most dangerous disorders of diabetes mellitus, which leads to high levels of morbidity, mortality, and expenses connected with diabetes mellitus care in the global community. They are linked to the interaction of multiple interrelated metabolic disturbances, neuropathy, vascular deficiency, and immunological dysfunctions, rendering wound healing difficult[1]. Microvascular and macrovascular complications expose diabetic patients to high risks of getting foot ulcers due to the creation of an ideal environment that favours the formation and maintenance of foot ulcers. However, taking into account the last years, there has been an increasing volume of literature examining the metabolic and endocrine factors that also add to the risk of DFUs, of which thyroid dysfunction, especially hypothyroidism, has gained scrutiny as it affects systemic metabolism and wound healing. Overt and subclinical hypothyroidism may adversely affect peripheral circulation, immune responses, glucose-lipid metabolism, and lipid profiles, which are essential in the pathogenesis and treatment of DFUs. The concentration of free triiodothyronine (fT3) and the fT3/fT4 ratio have a good predictive value for assessing diabetic foot ulcer patients' mortality, demonstrating the importance of thyroid tests in this situation[2].

Moreover, there is another issue linked with thyroid hormone disorders, i.e., neurovascular complications that are characteristic of diabetes and reflect the reason for DFU development. For example, neuropathy may significantly increase the risk of foot injury and ulcer complications, especially in diseased and thyroid malfunctioning patients with diabetes[3]. This has proved that subclinical hypothyroidism may be a potential risk factor in diabetic polyneuropathy, which has a central impact on the occurrence of DFU. This result gives a sign that this affiliation is a possible potentiation of thyroid hormone deficiency with diabetic neuropathy, which worsens foot outcomes[4]. Severity of DFUs is also caused by other systemic agents alongside hard hormonal agents, including anemia. DFU patients who exhibit anemia are likely to heal with delay, are at risk of infection, and are likely to be admitted to hospitals[5]. The pathogenesis of anemia can be triggered by dysfunction of the thyroid gland itself, which, in its turn, might aggravate the clinical manifestations of diabetic patients with foot ulcers.

The next component of the multifactorial pathogenesis of DFUs is linked to deficiencies in micronutrients. The thyroid hormones are very important in maintaining the metabolism and absorption of various micronutrients, which are vital in causing tissue integrity and immune integrity. A meta-analysis revealed that changes in the micronutrient status are frequent factors associated with DFUs, which may be related to an underlying abnormal thyroid gland[6]. These results in type 2 diabetic patients without euthyroidism used on the peripheral neuropathy also support the theory that the thyroid hormone can be causing DFU pathogenesis as well[7]. Glycemic control is a hallmark of diabetes care, and inefficient glucose control during perioperative periods has been linked to inferior outcomes when it comes to DFU cases. Dysfunction of the thyroid may have a strong influence on the sensitivity to insulin and glucose metabolism, which in turn may jeopardize the attempts to control glycemic levels in a sufficient way in the course of the treatment[8].

In addition, dysmetabolic patients are much more at risk of developing DFUs, both those with aberrant thyroid parameters and those without. They are also common in hypothyroidism and include lipid abnormalities, high levels of inflammatory markers, and insulin resistance among other profiles[9]. DFU recurrence is also important despite the healing of the initial wound. The causes of recurrence comprise inadequate vascular supply, infection, and hampered metabolic control, most of which have been shown to depend on the levels of thyroid hormone[10]. The process of wound healing, in general, represents a multifactorial process that is affected by age, blood supply, infection, and the endocrine system. Hypothyroidism has been found to retard the healing of wounds because of reduced cell proliferation, angiogenesis, and collagen formation that can significantly impair the results of DFU patients[11]. Other recent investigations of large groups have demonstrated connections between anemia and diabetic lower extremity ulcers, potentially indicating that blood disorders related disorders that usually occur in hypothyroid patients are a contributory aspect concerning DFU development and advancement[12].

Furthermore, the rate of diabetic peripheral neuropathy and foot ulceration is different in different regions, but the underlying endocrine diseases, including hypothyroidism, are underdiagnosed antecedents of these complications[13]. There is thus an urgent need to screen thyroid functional abnormalities in diabetic patients, and specifically, foot ulcers. Thyroid hormones also affect renal activities, and alterations in thyroid characteristics have been connected with chronic kidney disease indicators in type 2 diabetic individuals. Dysfunction of the kidneys is a known risk factor of poor DFU outcome, indicating an alternative route through which thyroid dysfunction can lead to complications of DFU[14]. Moreover, patients with hypothyroidism are more susceptible to infections,

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possess poor thermoregulation, and suffer from skin integrity, all of which may exacerbate foot ulcerations and impede the recovery[15].

Another severe complication of diabetes, known as Charcot neuroarthropathy, closely exhibits similar pathogenic pathways to DFUs, as it involves neuropathy or vascular dysfunctions, among others. Thyroid hormones play a role in the metabolism of bone and neuromuscular development, implying that there could be an overlap effect in the patient between both conditions[16]. Also, hypothyroidism has been identified to be more common in some genetic syndromes, such as Klinefelter syndrome, which possesses a higher risk of metabolic syndrome and diabetes, and hence adds to the threat of foot complications[17]. The triglyceride-glucose index biomarker is one of the sensitive indicators of macrovascular occurrence in DFU patients. Hypothyroidism frequently has deranged metabolic parameters, with these pointers once again indicating that thyroid dysfunction has the possibility of causing poor outcomes of DFU[18]. Although the importance of thyroid hormones in maintaining metabolic homeostasis is well defined, no sufficient correction of overt hypothyroidism is carried out in the general population. The use of a population-based study has indicated that many people with hypothyroidism are untreated or under-treated, which highlights the threat of such inattention in the case of the diabetic population presenting with foot ulcers[19].

Objective: To estimate the incidence of hypothyroidism among diabetic foot ulcer patients and investigate whether this thyroid dysfunction can influence the level or development of diabetic foot ulcer complications.

MATERIALS AND METHODS

Study Design: Cross-sectional Observational study.

Study Setting: The study was carried out in the Endocrinology Ward of Hayatabad Medical Complex, Peshawar.

Study Duration: The data were collected over a period of six months, from December, 2022 to May, 2023.

Inclusion Criteria: The study included male and female patients between the ages of 30 and 80 years who were diagnosed with type 2 diabetes mellitus and had active diabetic foot ulcers. Informed consent was obtained from all participants, and ulceration of the lower extremities was confirmed in all participants by a consultant endocrinologist.

Exclusion Criteria: Patients with known thyroid disorders, on treatment, people with type 1 diabetes mellitus, people with foot ulcers that originate due to non-diabetic factors (e.g., traumatic/venous ulcers), pregnant women, patients with chronic renal failure, or patients with malignancy were not included in the study.

Methods: The participants included 150 patients with diabetic foot ulcers who were included in the study using non-probability consecutive sampling. The history of each patient was taken, after gaining informed consent, and that covered the age, gender, duration of diabetes, any medication used, and any previous thyroid condition. All patients were clinically examined in detail, and the severity of a foot ulcer was classified according to the Wagner classification system. Blood was taken to assess thyroid function tests, such as serum TSH, free T3, and free T4. Hypothyroidism was defined in patients as increased values of TSH and low levels of free T3/T4 within the laboratory parameters. Laboratory tests were undertaken in the central laboratory of the hospital using standardized assays. SPSS version 25 was used to analyze the data. Frequencies and percentages were adapted with the use of descriptive statistics, and associations between hypothyroidism and demographic or clinical variables were checked using chi-square tests, where the p-value of less than 0.05 was considered statistically significant.

The sample size for estimating prevalence in a cross-sectional study is typically calculated using the following formula:

$n = Z^2.p.(1-P)/E^2$

Z = 1.96 $ (95% confidence level)

P = 0.28 $ (expected prevalence, from study's 28%)

E= margin of error

N= 100.1.5= 150

RESULTS

This study involved a total of 150 diabetic foot ulcer patients. The average age of the patients was 57.4 ± 9.8 years, with a male predominance (n = 96, 64%) compared to females (n = 54, 36%). The median years of diabetes of the study group were 10.6 ± 4.3 years. According to the thyroid function tests, it was found that 42 patients had hypothyroidism, with this condition representing 28 % of diabetic foot ulcer patients.

Table 1 presents the demographic and clinical characteristics of the study population.

Table 1: Demographic and Clinical Characteristics of Study Participants (n = 150)

Variable	Value
Mean Age (years)	57.4 ± 9.8
Gender (Male/Female)	96 (64%) / 54 (36%)
Duration of Diabetes (years)	10.6 ± 4.3
Hypothyroidism Present	42 (28%)
Wagner Grade ≥ 3 Ulcer	63 (42%)
Hypertension	78 (52%)
Smoking History	45 (30%)

Among the 42 hypothyroid patients, 71.4% had ulcers graded as Wagner ≥ 3, indicating a more severe presentation. In contrast, only 31.4% of euthyroid patients had ulcers of the same severity, showing a significant association between hypothyroidism and higher-grade ulceration ($p < 0.01$).

Table 2 shows the association between thyroid status and Wagner grade severity.

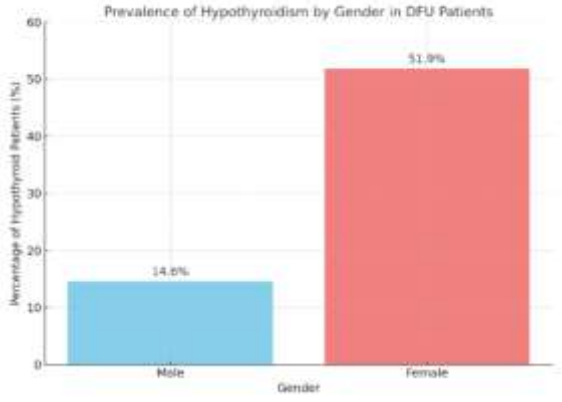
Table 2: Association of Thyroid Status with Wagner Ulcer Grade Severity

Thyroid Status	Wagner Grade < 3	Wagner Grade ≥ 3	Total	p-value
Hypothyroid	12 (28.6%)	30 (71.4%)	42	<0.01
Euthyroid	75 (69.4%)	33 (30.6%)	108	

A gender-wise distribution of hypothyroidism showed that 59.5% of female DFU patients had hypothyroidism, compared to 14.6% of male DFU patients. This difference was statistically significant ($p < 0.001$), suggesting a higher predisposition in females with diabetic foot ulcers.

Table 3: Gender-wise Distribution of Hypothyroidism in DFU Patients

Gender	Total Patients	Hypothyroid Patients	Prevalence (%)	p-value
Male	96	14	14.6%	
Female	54	28	51.9%	<0.001



Graph 1: Prevalence of Hypothyroidism by Gender

Furthermore, patients with hypothyroidism had a higher mean duration of diabetes (12.4 ± 3.8 years) compared to euthyroid patients (9.9 ± 4.2 years), with the difference being statistically significant ($p < 0.05$). This suggests a possible correlation between long-standing diabetes and the development of thyroid dysfunction.

The findings indicate that there is a strong relationship between hypothyroidism and prolongation of diabetic foot ulcers, gender, and years of diabetes. The findings indicate a need to perform routine thyroid function tests, especially on patients with long-lasting diabetes and foot issues that are complicated and severe, and female patients.

DISCUSSION

The study was a quest to ascertain the prevalence of hypothyroidism among DFUs patients and to evaluate the relationship of the disease with the grade of ulcers and clinical presentation. The results show that 28 percent of the patients with DFU had hypothyroidism, and the malfunctioning of the thyroid was found to be strongly connected to ulcer, and even worse, Wagner grade, the female gender, and a long period of diabetes. These findings are consistent and supported by the fact that more and more evidence is accumulating, indicating that there may indeed be a major role of thyroid dysfunction, and especially hypothyroidism, as a hitherto under-recognized factor that adds to the complexity and severity of DFUs. This evaluation showed that the rate of hypothyroidism was rather impressive. A comparative analysis of the metabolic disturbances in diabetic patients with and without foot ulcers revealed serious metabolic dysfunctions, specifically lipid profiles and glycemic control, both of which were found in people with hypothyroidism[1]. This is because, in findings, hypothyroidism coexists with diabetic complications such as DFUs.

Moreover, Hong et al. showed that reduced fT3 concentration and decreased fT3/fT4 ratio were linked to higher mortality in DFU patients, which prompted the conclusion that impaired thyroid function possesses prognostic significance in this patient group[2]. Thyroid dysfunction has also been associated with neuropathy, which is a well-defined risk factor for DFUs. According to Fan et al., neurovascular complications also contribute to the increase in risk of foot ulceration in diabetics to a great extent[3]. Distal symmetric polyneuropathy in patients with type 2 diabetes has been suggested to be linked to subclinical hypothyroidism, which supports the idea that even such thyroid hormone deficits may worsen neurological impairments and expose patients to traumatic injury and foot ulceration[4]. The results of this study indicate that assessment of thyroid health in diabetic patients with neuropathy can be used to give important information that can be used to intervene early. Hypothyroid patients had a higher prevalence of patients with Wagner grade ulcers equal to or greater than three in the study. This finding can be supported by previous studies regarding systemic factors that intensify the severity of the ulcer.

For instance, anemia that may serve both as its etiology and result of hypothyroidism has been reported to have notable effects on the severe DFU among hospitalized patients[5]. In addition, Kurian et al. conducted a meta-analysis and outlined the importance of micronutrient deficiencies in the development of DFU, many of which are thyroid hormone-regulated, further suggesting the presence of the underlying association between the issue of hypothyroidism and delayed wound healing[6]. Remarkably, changes in thyroid hormone profile in peripheral neuropathy have been recorded in even the euthyroid diabetic patients observed by He et al.[7]. This finding implies that thyroid hormones non-dependently of overt thyroid disease directly impact on peripheral nerve functioning, and this finding could be relevant in explaining why even patients with subclinical hypothyroidism remain at a greater risk of developing the sequelae of DFUs. Moreover, another leading factor in DFU outcomes is poor perioperative glycemic control, which is, in most cases, harder to control in patients with an accompanying thyroid disorder as a result of insulin resistance[8].

Inflammation and insulin resistance (with dysmetabolism in diabetes) are common phenomena in hypothyroid patients with chronic diseases, as demonstrated in the retrospective studies forecasting the risks of DFUs[9]. It is also worth mentioning the correlation between the DFU recurrence and thyroid dysfunction. Hu et al. discovered that metabolic disorders and infections of poor wound healing responses are some of the primary contributors to ulcer recurrence[10], which is a process that has been shown to be affected by thyroid hormones. Additionally, other issues like impaired angiogenesis, lower collagen production, and slow cellular proliferation, which are characteristic of hypothyroidism, may greatly inhibit the healing of the ulcers and promote the recurrence of ulcers. The significant role of thyroid function in tissue repair is also supported by a finding of Lee et al., who revealed that unfavorable DFU wound healing outcomes were related to an underlying endocrine and vascular pathology[11]. One noticeable finding in research work was a high rate of gender variance in the prevalence of hypothyroidism, in that female patients were found to be disproportionately prevalent in this disease.

This result correlates with the results of a retrospective study that indicated that anemia, a frequent problem of hypothyroid patients, was more common in women and had an associated progression in the development of DFU[12]. Regional studies have also been conducted on gender-specific prevalence of diabetic complications, neuropathy, and ulceration, indicating that females might be at a greater risk in comparison to males due to the difference in hormonal and metabolic levels[13]. Furthermore, early manifestations of chronic kidney disease have been attributed to hypothyroidism, indicating that, unlike other normal studies, even euthyroid patients show substantial changes in the thyroid parameters[14]. Considering the fact that renal impairment is the complicating factor in the management of DFU and enhances morbidity, thyroid dysfunction can indirectly worsen the situation. Systemic diseases like hypothyroidism have also been identified as risk factors for amputation in DFU patients, as seen in a meta-analysis on Chinese diabetic patients[15].

Adding to the clinical complexity is Charcot neuroarthropathy, which is a debilitating but rare disorder caused by an overlapping etiological pathway with DFUs like neuropathy and poor metabolic regulation. Wukich et al. stressed that there was a necessity to change the paradigm in identifying and treating such complications, most of which are dependent on thyroid dysfunction[16]. Additionally, some of the genetic disorders related to hypothyroidism, e.g., Klinefelter syndrome, predispose a person to metabolic syndrome and diabetes, which are indirect causes of higher predisposition to foot ulcers[17]. The other interesting discovery is that of the metabolic markers such as the triglyceride-glucose index and the extent of major adverse cardiovascular events in DFU patients as found by Wei et al.[18]. These markers tend to be aberrant in patients with hypothyroidism and this fact lends credence to the notion that thyroid dysfunction can lead to systemic vascular complications in diabetes. Finally, the poor management of overt thyroid disorder is to be mentioned, with Nielsen et al. reporting that a large number of patients continue being untreated or undertreated, additionally exposing them to a risk of complications, including DFUs[19].

CONCLUSION

This research indicates a high incidence of hypothyroidism (28%) in subjects with diabetic foot ulcers, and there exists a close relationship between thyroid dysfunction and worse ulcer severity, gender(female), and duration of diabetic disease. A high-grade ulcer and extended history of diabetes occurred more often in patients with hypothyroidism, which only proves a point about the importance of thyroid activity in wound healing and progression. The results indicate that hypothyroidism can worsen the diabetic complications of the metabolic and vascular events, thereby

creating and intensifying the foot ulcers. As hypothyroidism was underdiagnosed and undertreated, the screening of thyroid function may be proposed on a routine basis in all diabetic patients with foot ulcers, especially in women and those with long-standing diabetes. Prompt detection and treatment of thyroid dysfunction can boost ulcer healing, prevent ulcer relapse, and improve overall patient outcomes. The inclusion of thyroid screening as an element of diabetic foot care might provide an effective and affordable measure in multidisciplinary diabetic practice.

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