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Diabetology

INVESTIGATING THE ASSOCIATION BETWEEN HYPOTHYROIDISM AND MICROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS: A MULTIFACETED APPROACH WITH CLINICAL IMPLICATIONS

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ABSTRACT **Introduction:** Type 2 Diabetes Mellitus is marked by hyperglycemia which is chronic in origin, and affects 90% of diabetes cases globally. Concurrently, hypothyroidism, affecting 6-20% of T2DM patients, poses an additional challenge due to its impact on metabolism. Despite growing evidence, the underlying mechanisms connecting hypothyroidism to diabetic microvascular complications remain unclear, necessitating further investigation. **Methods:** This is a cross-sectional study which explored the link between hypothyroidism with microvascular complications of Type 2 Diabetes Mellitus in 250 patients. Microvascular complications were identified using standardized criteria. Descriptive statistics summarized patient characteristics. Correlation coefficients assessed thyroid markers and complications association. Odds ratios gauged hypothyroidism's impact on complications. **Results:** Comparative analysis revealed no significant differences in age, gender, diabetes duration, or HbA1c levels between hypothyroid and non-hypothyroid groups. However, hypothyroid T2DM patients exhibited significantly higher prevalences of retinopathy (13.8%), nephropathy (19.04%), and neuropathy (25%) compared to non-hypothyroid counterparts. Analysis of correlation identified positive correlations among TSH levels and retinopathy ($r=0.23$, p-value < 0.05) and neuropathy ($r=0.31$, p value<0.02), while free T4 levels correlated negatively with nephropathy ($r=-0.19$, p-value <0.05). **Conclusion:** The study contributes valuable insights into the potential correlation between hypothyroidism and diabetic microvascular complications in T2DM patients. Further investigations are warranted to elucidate underlying pathways and establish causation.

KEYWORDS : T2DM, Retinopathy, Nephropathy, Neuropathy, Hyperglycaemia, Hypothyroid

INTRODUCTION

Diabetes mellitus (DM) is a chronic disorder of metabolism identified by hyperglycemia, which results from either impaired secretion of insulin, resistance to the action of insulin, or both (Henson et al., 2023). Type 2 diabetes mellitus contributes to approximately 90% of all Diabetes Mellitus cases. Using a model based on data from 1990 to 2017, statistical forecasting indicated that worldwide diabetes prevalence could rise to 7079 per 100,000 by 2030 and 7862 by 2040 (Khan et al., 2020).

Complications which are microvascular in origin, including nephropathy, retinopathy, and neuropathy, are the leading cause of morbidity as well as mortality in T2DM patients. These complications arise from chronic hyperglycemia and can lead to irreversible damage to the eyes, kidneys, and nerves (Chawla et al., 2016).

Hypothyroidism, a condition characterized by insufficient thyroid hormone production, is a prevalent comorbidity in T2DM patients, affecting up to 6-20% of this population (Kalra et al., 2021). The thyroid gland is pivotal for the regulation of metabolism, furthermore, its dysfunction can alter glycemic regulation and heighten the likelihood of microvascular complications (Biondi et al., 2019).

The association between hypothyroidism along with microvascular complications of Type 2 Diabetes Mellitus has been the subject of considerable research, with conflicting results reported. While some studies demonstrated a positive correlation between hypothyroidism and the development of microvascular complications,(Lin et al., 2022) others have found no significant association.(Vemula et al., 2023)

These inconsistencies in the existing literature highlight the need for further investigation into this critical relationship. A comprehensive understanding of the correlation between hypothyroidism and microvascular complications is essential for developing effective management strategies and improving patient outcomes in T2DM.

Despite the growing evidence linking hypothyroidism to diabetic microvascular complications, the underlying mechanisms remain incompletely understood.

With this background, the present study aimed to fill gaps in understanding the link association between hypothyroidism along microvascular complications in Type 2 Diabetes Mellitus patients. By analyzing a large cohort of T2DM patients, the study seeks to:

1. Evaluate the prevalence of hypothyroidism among Type 2 Diabetes Mellitus patients.
2. Assess the correlation between hypothyroidism and onset of microvascular complications (nephropathy, retinopathy and neuropathy).
3. Identify possible factors that may increase the likelihood of microvascular complications in patients with hypothyroid and Type 2 Diabetes Mellitus.
4. Provide evidence to support the development of clinical guidelines for hypothyroidism management in Type 2 Diabetes Mellitus patients to reduce the risk of microvascular complications.

METHODOLOGY

For investigation of the correlation between hypothyroidism and diabetic microvascular complications in patients with Type 2 Diabetes Mellitus, this study used an analytical cross-sectional design. The study examined data collected from 250 known cases of T2DM patients attending the outpatient department of General Medicine, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly according to inclusion-exclusion criteria for the sample selection.

Adult patients (≥18 years) diagnosed with T2DM and with at least 3 years were involved in the study. Patients with a history of autoimmune thyroid disorders, thyroid surgery, or any other condition potentially affecting thyroid function were excluded.

Data collection was focused on demographic characteristics, HBA_1C, thyroid function tests such as free T4, free T3 and Serum TSH), and the presence of microvascular complications (retinopathy, nephropathy, and neuropathy).

Hypothyroidism was defined based on TSH levels above the upper maximum reference limit and free T4 or free T3 levels below the lower minimum reference limit. Thyroid function test results were obtained from the earliest available record within the study period.(Chaker et al., 2017)

The normal reference limit:
- TSH (Thyroid-stimulating hormone): 0.4–4.5 mIU/L.
- Free T4: 0.8–1.5 ng/dL.
- Total T3: 1.1–3 nmol/L.

If a patient's TSH level is above the upper reference limit, and their free T4 or free T3 level is below the lower reference limit, then they are considered to have hypothyroidism.

The microvascular complications of diabetes were determined based on standardized diagnostic criteria.
- Retinopathy: Retinal examination by an ophthalmologist or documented diagnosis of diabetic retinopathy.
- Nephropathy: Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 or Microalbuminuria (urine albumin-to-creatinine ratio ≥30 mg/g).(Qi et al., 2017)
- Neuropathy: Clinical assessment of neuropathy, including monofilament testing and vibration perception threshold testing (Yang et al., 2018).

To summarize the characteristics of patients and the prevalence of microvascular complications descriptive statistics were employed in both hypothyroid and non-hypothyroid groups. The use of correlation coefficients was done to assess the strength and direction of association among thyroid function markers and microvascular complications. 95% confidence intervals (CIs) and Odds ratios (ORs) were analyzed to approximate the risk of developing microvascular complications in hypothyroid patients in comparison to non-hypothyroid patients. P-value <0.05 was used for statistical significance.

The study protocol followed the ethical guidelines and principles, including assurance of patient's confidentiality and acquiring informed consent from participants. The Institutional Review Board (IRB) approved the study before data collection commenced.

RESULT

A total of 250 T2DM patients were included in the study. The average age of patients was 62 years, and 54% were female. Among study participants, 84 (33.6%) had hypothyroidism (Table 1).

TABLE – 1 Patient Characteristics among Hypothyroid and Non-Hypothyroid Groups

Characteristic	Hypothyroid Group (n=84)	Non-Hypothyroid Group (n=166)	p-value
Age (years)	62.4 ± 7.3	61.6 ± 7.1	0.405
Gender (% female)	54.8%	53.0%	>0.05
Duration of diabetes (years)	10.2 ± 5.1	9.8 ± 4.9	0.548
HbA1c (%)	7.5 ± 1.2	7.4 ± 1.3	0.556

The mean age of patients in the hypothyroid group was 62.4 years, while the average age of patients in the non-hypothyroid group was 61.6 years. This age difference was not statistically significant (p-value = 0.534) (Table 1).

Female patients' percentage in the hypothyroid group was 54.8%, while the percentage of female patients in the non-hypothyroid group was 53.0%. This difference in gender distribution was also not statistically significant (p-value > 0.05).

The average duration of diabetes in the hypothyroid group was 10.2 years, while the average duration of diabetes in the non-hypothyroid group was 9.8 years. This difference in the duration of diabetes was not statistically significant (p-value = 0.612).

The average HbA1c level in the hypothyroid group was 7.5%, while the average HbA1c level in the non-hypothyroid group was 7.4%. This difference in HbA1c levels was not statistically significant (p-value = 0.431).

TABLE – 2 Prevalence of Diabetic Microvascular Complications in T2DM Patients with and without Hypothyroidism

Microvascular Complication	Hypothyroid Patients	Microvascular Complication	Hypothyroid Patients
Retinopathy (n=20)	11 (13.09%)	9 (5.4)%	0.034*
Nephropathy (n=21)	16 (19.04%)	15 (9.03%)	0.023*
Neuropathy (n=46)	21 (25%)	23 (13.8%)	0.036*

Prevalence of retinopathy was significantly higher in patients with hypothyroidism (13.8%) than in patients without hypothyroidism (5.4%), with a p-value of 0.034 revealing a statistically significant association among hypothyroidism and retinopathy in T2DM patients. The prevalence of nephropathy was also significantly higher in patients of hypothyroidism (19.04%) as compared to patients with non-hypothyroid status(9.03%), with a p-value of 0.023 means there is a very strong statistically significant association between hypothyroidism and nephropathy in T2DM patients.

The prevalence of neuropathy was highest among all three microvascular complications, and it was also significantly higher in patients with hypothyroidism (25%) in comparison to patients without hypothyroidism (13.8%), with a p-value of < 0.036. This suggests a powerful statistically significant association between hypothyroidism and neuropathy in T2DM patients (Table 3).

TABLE – 3 Correlation between Thyroid Function Markers and Microvascular Complications

Thyroid Function Marker	Correlated Microvascular Complication	Correlation Coefficient	p-value
TSH	Retinopathy	0.23	0.04
TSH	Neuropathy	0.31	0.02
Free T4	Nephropathy	0.19	0.05

Table 3 further demonstrates the correlation between thyroid function markers and microvascular complications. Correlation analysis found a significant positive correlation between levels of TSH and the presence of retinopathy (r=0.23, p value<0.05) and neuropathy (r=0.31, p value<0.02). A significant negative correlation was also found between levels of free T4 and the presence of nephropathy (r=-0.19, p<0.05).

Elevated levels of TSH were associated with a higher risk of retinopathy as well as neuropathy, while decreased free T4 levels were associated with a higher risk of nephropathy. These findings suggest that hypothyroidism may be an independent contributing factor to the development of microvascular complications in T2DM patients (Table 4).

TABLE – 4 Association between Hypothyroidism and Diabetic Microvascular Complications

Microvascular Complication	Odds Ratio	95% Confidence Interval	p-value
Retinopathy	2.3	1.4-3.7	<0.01
Nephropathy	1.8	1.1-2.8	<0.05
Neuropathy	2.4	1.5-3.9	<0.001

Hypothyroidism remained an independent risk factor for retinopathy (OR-2.3, 95% CI =1.4-3.7, p value<0.01), nephropathy (OR -1.8, 95% CI= 1.1-2.8, p value <0.05), and neuropathy (OR -2.4, 95% CI =1.5-3.9, p value <0.001).

DISCUSSION

The study involved 250 patients with Type 2 Diabetes Mellitus (T2DM), with a mean age of 62 years and a gender distribution of 54% females. The observed prevalence of hypothyroidism among T2DM patients in the present study, at 33.6%, is greater than the prevalence reported in similar research which was 24.8% and might be due to the comparatively older population in the study (Talwalkar et al., 2019).

The lack of statistically significant differences in mean age, gender distribution, diabetes duration, and levels of HbA1c between the hypothyroid and non-hypothyroid groups in the current study aligns with Sharma et al. study findings (Sharma et al., 2020). While some studies have reported similar non-significant differences, others have found associations between hypothyroidism and certain demographics like in cases with Type 2 Diabetes Mellitus patients of age >65 years with OR of 4.2 and clear difference among males and females (OR, 4.82 vs 2.60) and clinical parameters like HBA1c.(Biondi et al., 2019) The variations in findings could be attributed to the heterogeneity of study populations and methodologies across different investigations.

The study findings reveal a notable increase in the prevalence of complications of microvascular origin such as retinopathy, nephropathy, and neuropathy—among Type 2 Diabetes Mellitus (T2DM) patients with hypothyroidism. Specifically, the prevalence of retinopathy was markedly higher in patients with hypothyroidism (13.8%) compared to patients without hypothyroidism(5.4%). This

aligns with existing literature by Wu et al. where Random-effects meta-analysis indicated a significant association with diabetic retinopathy and hypothyroidism (odds ratio = 2.13, 95% confidence interval = 1.41 – 3.23, p < 0.001). (Wu et al., 2015) Likewise, the study identified a higher prevalence of nephropathy in the hypothyroid group (19.04%) in contrast to the non-hypothyroid group (9.03%). This finding resonates with previous research by Bajaj et al. that has suggested a link between hypothyroidism and an increased risk of nephropathy in T2DM patients where they reported out of a total of 41 DKD patients 14 (34.14%) patients were diagnosed with hypothyroid. (Bajaj et al., 2016)

Similarly, Meena et al. reported Prevalence of Nephropathy was also significantly higher (p=0.011) in Hypothyroid group (60%) as compared to the Euthyroid group.(38.75%). (Krishan et al., 2021)

Furthermore, the study highlighted neuropathy as the most prevalent among the three microvascular complications, with hypothyroid patients exhibiting a rate of 25% compared to 13.8% in non-hypothyroid patients. This aligns with certain studies that have explored the relationship between thyroid dysfunction and neuropathy, emphasizing a potential connection between hypothyroidism and an elevated risk of neuropathy in T2DM patients (Gupta et al., 2016).

The correlation analysis conducted in this study explored the intricate relationship between thyroid function markers and Type 2 Diabetes Mellitus patients having microvascular complications. The findings revealed positive correlations between Thyroid Stimulating Hormone levels and the presence of retinopathy (r=0.23, p value <0.05) and also with neuropathy (r=0.31, p<0.02). The positive associations align with Zhao et al. study finding which emphasises the potential link between elevated TSH levels and an increased risk of retinopathy and neuropathy where Spearman's correlation analysis revealed a positive association between serum TSH levels and DPN (r=0.172, P value <0.01) (Zhao et al., 2016).

Conversely, a significant negative correlation was observed between levels of free thyroxine (free T4) and the presence of nephropathy (r=-0.19, p value<0.05). Lower levels of free T4 have been linked with an elevated risk of renal complications in diabetes in some studies. This negative correlation is consistent with Shrivastava et al. research indicating a potential protective effect of adequate free T4 levels against the development of nephropathy in diabetic individuals and no significant correlation with TSH was found (r = 0.206, P = 0.114). (Srivastava et al., 2018)

While these correlations align with existing literature in specific aspects, it is important to recognize the inherent heterogeneity in study populations and methodologies across the field. The variability in findings may be influenced by factors such as the definition of complications, sample sizes, and participant demographics. Nonetheless, this study contributes valuable insights by reinforcing associations between thyroid function markers and microvascular complications in T2DM patients.

The study also conducted risk factor analysis, revealing that hypothyroidism remained independent risk factor for nephropathy (OR- 1.8, 95% CI -1.1-2.8, p<0.05), retinopathy (OR- 2.3, 95% CI -1.4-3.7, p<0.01), and neuropathy (OR- 2.4, 95% CI -1.5-3.9, p<0.001).

Comparison of existing research suggests consistency in findings, emphasizing the potential link between hypothyroidism and higher risk in Type 2 Diabetes Mellitus patients experiencing microvascular complications. These results underscore the importance of thyroid function assessment in the comprehensive clinical care of individuals with T2DM.

The findings of this study align with those of many other studies that have examined the association of hypothyroidism with T2DM patients having microvascular complications. A cross-sectional study by Chen et al. found that there was a significant association of hypothyroidism with a higher risk of retinopathy (odds ratio [OR] -1.15 [95% CI, 0.59-2.26) and nephropathy (OR -3.15 [95% CI,1.48-6.69) in T2DM patients (Chen et al., 2007). Binodi et al. study found that hypothyroidism emerged as independent contributing factor for nephropathy in patients with Type 2 Diabetes Mellitus, even after adjustment of potential confounding factors like age, sex, duration of diabetes, and glycemic control (Biondi et al., 2019).

These findings indicate that hypothyroidism is a major risk factor for the development of microvascular complications in T2DM patients. The exact mechanisms by which hypothyroidism increases the risk of microvascular complications are not fully understood, but it is thought that several factors may be involved.

Hypothyroidism can impair glycemic control by decreasing insulin sensitivity and increasing hepatic glucose production (Sharma et al., 2022). Hypothyroidism can lead to endothelial dysfunction, which is a hallmark of microvascular complications (Sara et al., 2015) Hypothyroidism can increase levels of inflammatory markers, which may contribute to the development of microvascular complications (Mancini et al., 2016).

CONCLUSION

Hypothyroidism is a significant risk factor for all three of the diabetic microvascular complications that were studied. This information is important for clinicians who are managing T2DM patients, as it suggests that early diagnosis and treatment of hypothyroidism may help to reduce the risk of developing these complications. All T2DM patients should be screened for hypothyroidism at least annually. Treatment of hypothyroidism should promptly be sought to reduce the risk of developing diabetic microvascular complications.

REFERENCES

[1] Bajaj, S., Purwar, N., Gupta, A., Gupta, P., & Srivastava, A. (2016). Prevalence of hypothyroidism in diabetic kidney disease and effect of thyroid hormone replacement on estimate glomerular filtration rate. *Indian Journal of Endocrinology and Metabolism*, *20*(6), 795.

[2] Biondi, B., Kahaly, G. J., & Robertson, R. P. (2019). Thyroid Dysfunction and Diabetes Mellitus: Two Closely Associated Disorders. *Endocrine Reviews*, *40*(3), 789.

[3] Chaker, L., Bianco, A. C., Jonklaas, J., & Peeters, R. P. (2017). Hypothyroidism. *Lancet (London, England)*, *390*(10101), 1550.

[4] Chawla, A., Chawla, R., & Jaggi, S. (2016). Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian Journal of Endocrinology and Metabolism*, *20*(4), 546.

[5] Chen, H. S., Wu, T. E. J., Jap, T. S., Lu, R. A., Wang, M. L., Chen, R. L., & Lin, H. D. (2007). Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in Type 2 diabetic patients. *Diabetic Medicine : A Journal of the British Diabetic Association*, *24*(12), 1336–1344.

[6] Sharma, A., Virmani, T., Sharma, A., Chhabra, V., Kumar, G., Pathak, K., & Alhalmi, A. (2022). Potential effect of DPP-4 inhibitors towards hepatic diseases and associated glucose intolerance. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 1845-1864.

[7] Gupta, N., Arora, M., Sharma, R., & Arora, K. (2016). Peripheral and Central Nervous System Involvement in Recently Diagnosed Cases of Hypothyroidism: An Electrophysiological Study. *Annals of Medical and Health Sciences Research*, *6*(5), 261.

[8] Henson, J., Anyiam, O., & Vishnubala, D. (2023). Type 2 Diabetes. *Exercise Management for Referred Medical Conditions*, 223–252.

[9] Kalra, S., Aggarwal, S., & Khandelwal, D. (2021). Thyroid dysfunction and dysmetabolic syndrome: The need for enhanced thyrovigilance strategies. *International Journal of Endocrinology*, *2021*.

[10] Khan, M. A. B., Hashim, M. J., King, J. K., Govender, R. D., Mustafa, H., & Kaabi, J. Al. (2020). Epidemiology of Type 2 Diabetes – Global Burden of Disease and Forecasted Trends. *Journal of Epidemiology and Global Health*, *10*(1), 107.

[11] Krishan, D., Meena, K., Sharma, P., Srivastava, S., Uma, D., & Meena, K. (2021). ASSOCIATION OF HYPOTHYROIDISM WITH MICROVASCULAR COMPLICATIONS AMONG PATIENTS OF TYPE-2 DIABETES MELLITUS. *International Journal of Medical and Biomedical Studies*, *5*(12), 55–58.

[12] Lin, J., Xiang, X., Qin, Y., Gui, J., & Wan, Q. (2022). Correlation of thyroid-related hormones with vascular complications in type 2 diabetes patients with euthyroid. *Frontiers in Endocrinology*, *13*, 1037969.

[13] Mancini, A., Di Segni, C., Raimondo, S., Olivieri, G., Silvestrini, A., Meucci, E., & Currò, D. (2016). Thyroid Hormones, Oxidative Stress, and Inflammation. *Mediators of Inflammation*, *2016*.

[14] Qi, C., Mao, X., Zhang, Z., & Wu, H. (2017). Classification and Differential Diagnosis of Diabetic Nephropathy. *Journal of Diabetes Research*, *2017*.

[15] Sara, J. D., Zhang, M., Gharib, H., Lerman, L. O., & Lerman, A. (2015). Hypothyroidism Is Associated With Coronary Endothelial Dysfunction in Women. *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease*, *4*(8), e002225.

[16] Sharma, P., Sinha, R., Prasad, A., & Mitra, J. K. (2020). Lack of Association between Poor Glycemic Control in T2DM and Subclinical Hypothyroidism. *Journal of Thyroid Research*, *2020*.

[17] Srivastava, S., Rajput, J., Shrivastava, M., Chandra, R., Gupta, M., & Sharma, R. (2018). Correlation of Thyroid Hormone Profile with Biochemical Markers of Renal Function in Patients with Undialyzed Chronic Kidney Disease. *Indian Journal of Endocrinology and Metabolism*, *22*(3), 316.

[18] Talwalkar, P., Deshmukh, V., & Bhole, M. (2019). Prevalence of hypothyroidism in patients with type 2 diabetes mellitus and hypertension in India: a cross-sectional observational study. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, *12*, 369.

[19] Thyroid Test: Types, Why do you need, Normal range and results . (n.d.). Retrieved November 24, 2023, from https://www.metropolisindia.com/blog/health-test/is-fasting-required-for-thyroid-test-and-other-questions-answered

[20] Vemula, S. L., Aramadaka, S., Mannam, R., Narayanan, R. S., Bansal, A., Yanamaladoddi, V. R., & Sarvepalli, S. S. (2023). The Impact of Hypothyroidism on Diabetes Mellitus and Its Complications: A Comprehensive Review. *Cureus*, *15*(6).

[21] Wu, J., Yue, S., Geng, J., Liu, L., Teng, W., Liu, L., & Chen, L. (2015). Relationship between Diabetic Retinopathy and Subclinical Hypothyroidism: a meta-analysis. *Scientific Reports*, *5*.

[22] Yang, Z., Zhang, Y., Chen, R., Huang, Y., Ji, L., Sun, F., Hong, T., & Zhan, S. (2018).

Simple tests to screen for diabetic peripheral neuropathy. *The Cochrane Database of Systematic Reviews*, *2018*(7).

[23] Zhao, W., Zeng, H., Zhang, X., Liu, F., Pan, J., Zhao, J., Zhao, J., Li, L., Bao, Y., Liu, F., & Jia, W. (2016). A high thyroid stimulating hormone level is associated with diabetic peripheral neuropathy in type 2 diabetes patients. *Diabetes Research and Clinical Practice*, *115*, 122–129.