



Study Effects Of Metformin On Thyroid Functions In Patients Of Type 2 Diabetes Mellitus

Dr. Sachin A. Bangar^{1*}, Dr. Sanket Arun Pawar², Dr. Ajinkya Deshmukh³, Dr. Rahul Talekar⁴, Dr. Om Hada⁵

^{1*}HOU (Associate Professor) at Department of Medicine, MGM Medical College, Aurangabad, Maharashtra, India.

²PG Student at Department of Medicine, MGM Medical College, Aurangabad, Maharashtra, India.

³Assistant Professor at Department of Medicine, MGM Medical College, Aurangabad, Maharashtra, India.

⁴PG Student at Department of Medicine, MGM Medical College, Aurangabad, Maharashtra, India.

⁵PG Student at Department of Medicine, MGM Medical College, Aurangabad, Maharashtra, India.

***Corresponding Author:** Dr. Sachin A. Bangar

*Email: [mailto: sachin.bangar1@gmail.com](mailto:mailto:sachin.bangar1@gmail.com)

Abstract

Background: Metformin, the most widely used oral hypoglycemic agent, remains the cornerstone of Type 2 Diabetes Mellitus (T2DM) management. Recent evidence suggests that metformin may influence thyroid function by reducing serum Thyroid-Stimulating Hormone (TSH) levels in diabetic patients. This study aimed to compare the effects of metformin-based and non-metformin-based therapies on thyroid function in patients with T2DM.

Methodology: A case-control observational study was conducted at a tertiary care center after obtaining approval from the Institutional Ethics Committee. A total of 140 adults with T2DM aged above 18 years were enrolled. Group 1 included patients on metformin therapy for more than six months, while Group 2 included patients on other antidiabetic medications without metformin. Patients with known thyroid disorders, those on thyroid-affecting drugs, pregnant women, and individuals with major systemic illnesses were excluded. Thyroid profile parameters—TSH, Free Triiodothyronine (FT3), and Free Thyroxine (FT4)—were measured using the Vitros 5600 analyzer at baseline, 3 months, and 6 months. Statistical analysis was performed to compare thyroid function changes between the two groups.

Results: The mean age of participants was 56.08 ± 14.59 years. In the metformin group, FT3 and FT4 levels showed a mild, non-significant increase, while TSH levels demonstrated a significant decline from 2.86 ± 2.43 μ IU/mL to 1.41 ± 0.94 μ IU/mL ($p < 0.0001$), indicating a suppressive effect of metformin on TSH secretion. The non-metformin group exhibited non-significant changes in FT3 and FT4 and a non-significant reduction in TSH from 6.93 ± 24.77 μ IU/mL to 2.97 ± 2.67 μ IU/mL ($p = 0.1866$).

Conclusion: Metformin therapy significantly reduces serum TSH levels in patients with Type 2 Diabetes Mellitus without affecting FT3 and FT4 concentrations. These findings highlight the importance of regular thyroid function monitoring in diabetic patients receiving metformin, particularly those with pre-existing thyroid disorders. Further research with larger sample sizes and

longer follow-up periods is warranted to elucidate the mechanisms underlying metformin's influence on thyroid regulation.

Keywords: Type 2 Diabetes Mellitus, Metformin, Thyroid-Stimulating Hormone, Free Triiodothyronine, Free Thyroxine.

INTRODUCTION

Diabetes mellitus and thyroid disorders are among the most common endocrine diseases worldwide, posing major public health concerns due to their chronic nature and serious complications. [1] The incidence of type 2 diabetes mellitus (T2DM) is driven by genetic and epigenetic factors, and its global burden is projected to reach 643 million by 2030 and 783 million by 2045. [2, 3] A strong association exists between T2DM and hypothyroidism, with studies reporting thyroid dysfunction in 10–15% of diabetic patients.[4]

Diabetes and thyroid disorders are closely interrelated through shared endocrine pathways. Even slight variations in thyroid hormone levels can influence the development of T2DM, particularly in prediabetic individuals. Both hyperthyroidism and hypothyroidism may induce insulin resistance, with subclinical hypothyroidism linked to altered **GLUT2** gene expression [5, 6].

Metformin is the first-line hypoglycemic agent used in the management of T2DM and has been used clinically for more than half a century. Its primary mechanisms include reducing hepatic glucose production (gluconeogenesis), decreasing intestinal glucose absorption, and improving insulin resistance by enhancing peripheral glucose uptake and increasing insulin sensitivity [7,8]. Metformin is generally considered a safe medication with minimal side effects and no significant drug interactions. Beyond its glucose-lowering properties, metformin exhibits a wide range of pleiotropic effects, including anti-inflammatory, cardioprotective, and anticancer activities. Early clinical studies by **Vigersky et al.**, [9] were among the first to identify a potential association between metformin and changes in thyroid-stimulating hormone (TSH) levels in hypothyroid patients receiving levothyroxine (LT4) therapy. Similarly, a retrospective study by **Condorelli et al.**,[4] demonstrated a significant reduction in serum TSH concentrations following metformin administration in diabetic patients.

Subsequent research has reported variable effects of metformin on thyroid function parameters, particularly TSH, free thyroxine (FT4), and free triiodothyronine (FT3) levels, in individuals with T2DM. [1] While most studies indicate a decline in TSH levels after metformin treatment, FT4 and FT3 levels generally remain unchanged, suggesting that metformin may influence the pituitary regulation of TSH secretion rather than directly altering thyroid hormone synthesis or release. [10]

Several mechanisms have been proposed to explain this effect. Metformin may alter TSH receptor sensitivity by modifying the number and affinity of thyroid hormone receptors, enhancing pituitary responsiveness to circulating hormones.[11] The drug can cross the blood–brain barrier and accumulate in the pituitary, where it inhibits hypothalamic AMPK activity. Despite activating it in peripheral tissues—leading to an enhanced feedback effect of thyroid hormones on the pituitary gland and consequent suppression of TSH secretion [11, 12]. However, findings remain inconsistent. **Patil et al.**,[13] reported increased TSH levels without changes in FT3 or FT4, whereas **Haroon S.M. et al.**, [14] observed a significant TSH reduction in hypothyroid (2.33 ± 0.70 , $p < 0.001$) but not euthyroid (3.87 ± 0.40 , $p = 0.206$) patients after six months of metformin therapy, with stable FT4 levels in both groups.

Given these inconsistencies, understanding metformin's effect on thyroid function is crucial due to the frequent coexistence of diabetes and thyroid disorders. Exploring these effects may provide valuable insights into metformin's broader endocrine actions and aid in optimizing treatment strategies. Hence, this study aims to evaluate metformin's impact on thyroid function in patients with type 2 diabetes mellitus to identify significant hormonal changes and support clinical decisions.

METHODOLOGY

This case-control observational study was conducted in the Department of General Medicine at a tertiary care center after obtaining approval from the Institutional Ethics Committee. A total of 140 adults with type 2 diabetes mellitus (T2DM) aged above 18 years, with metformin therapy for at least

six months, either as monotherapy or in combination with other antidiabetic agents. Those patients with known thyroid disorder, those on antithyroid or thyroid-affecting drugs (e.g., amiodarone), pregnant women, individuals with recent acute illness, pituitary disorders, malignancy, polycystic ovary syndrome, chronic kidney or liver disease, or a history of thyroid-related procedures.

Participants were divided into two groups:

- Group 1 (Cases): T2DM patients receiving metformin therapy (>6 months).
- Group 2 (Controls): T2DM patients on other antidiabetic medications without metformin.

Clinical data, including age, sex, duration of diabetes, BMI, waist-to-hip ratio, and treatment details, were recorded. Laboratory investigations thyroid profile was performed.

Thyroid function (TSH, FT3, FT4) was assessed using the Vitros 5600 automated analyzer. Two milliliters of fasting venous blood were collected, and thyroid parameters were measured at baseline, 3 months, and 6 months. Statistical analysis compared baseline and 6-month thyroid function values to evaluate the effect of metformin therapy.

RESULTS

Table 1: Gender distribution of patients with type 2 diabetes mellitus.

Gender	No of cases	Percentage
Male	69	49.29%
Female	71	50.71%

Table 1: The total of 140 patients with type 2 diabetes mellitus. Among them, 69 were males (49.29%) and 71 were females (50.71%). This showed that the female patients slightly outnumbered the male patients in the study population.

Table 1: Baseline physical characteristics of patients with type 2 diabetes mellitus.

Parameters	Min-Max	Mean $\pm$ SD
Age(years)	24.00-87.00	56.08 $\pm$ 14.59
Weight(kg)	46.00-88.00	64.81 $\pm$ 9.12
Height(cm)	147.0-183.0	165.1 $\pm$ 9.63
BMI (kg/m ²)	18.60-35.90	23.80 $\pm$ 3.05

Mean age of patients 56.08 years and Patients with type 2 diabetes have a minimum age of 24 and a maximum age of 87. Patients with type 2 diabetes have an average weight of 64.81 kg and an average height of 165.1 cm. Patients' average BMI is 23.80 kg/m² (Table 2).

Table 3: Effect of metformin on thyroid function (FT3, FT4, and TSH) in patients with type 2 diabetes mellitus.

Thyroid Function	Min-Max	Mean $\pm$ SD	P value for Pair t test
FT3			
0 months	1.44 -7.12	3.93 $\pm$ 1.30	0.1179
6 months	2.23 -6.35	4.24 $\pm$ 1.03	
FT4			
0 months	0.63-2.52	1.42 $\pm$ 0.32	0.3944
6 months	1.05-2.23	1.46 $\pm$ 0.29	
TSH			

0 months	0.34-19.4	2.86 $\pm$ 2.43	<0.0001
6 months	0.10-4.77	1.41 $\pm$ 0.94	

Table 3 shows, After, 6 months of metformin therapy, mean FT3 and FT4 levels showed a mild, non-significant rise, whereas mean TSH levels significantly decreased ($p < 0.001$), indicating a beneficial effect of metformin on thyroid function in type 2 diabetes patients.

Table 4: Effect of non-metformin-based treatment on thyroid function (FT3, FT4, and TSH) in patients with type 2 diabetes mellitus.

Thyroid function	Min-Max	Mean $\pm$ SD	P value for Pair t test
FT3			
0 months	0.85-5.03	3.37 $\pm$ 0.89	0.5987
6 months	1.33-6.00	3.45 $\pm$ 1.09	
Thyroid function FT4			
0 months	0.07-2.24	1.42 $\pm$ 0.39	0.072
6 months	0.73-4.18	1.56 $\pm$ 0.55	
Thyroid function TSH			
0 months	0.34-19.4	6.93 $\pm$ 24.77	0.1866
6 months	0.10-4.77	2.97 $\pm$ 2.67	

In table 4 shows that, After, 6 months of non-metformin-based treatment in patients with type 2 diabetes, mean FT3 and FT4 levels showed mild, non-significant increases (FT3: 3.37 $\pm$ 0.89 to 3.45 $\pm$ 1.09 pg/ml, $p = 0.599$; FT4: 1.42 $\pm$ 0.39 to 1.56 $\pm$ 0.55 ng/dl, $p = 0.072$). In contrast, TSH levels decreased significantly from 6.93 $\pm$ 24.77 to 2.97 $\pm$ 2.67 μ IU/ml ($p > 0.01$).

DISCUSSION

Metformin, a biguanide derivative, is a first-line oral hypoglycemic agent widely used for the management of Type 2 Diabetes Mellitus (T2DM). Beyond its well-established glucose-lowering effects, metformin exhibits multiple metabolic actions across various tissues through mechanisms involving the hypothalamic-pituitary-thyroid (HPT) axis. It has been shown to influence thyroid function by reducing serum thyroid-stimulating hormone (TSH) levels without significantly altering free triiodothyronine (FT3) and free thyroxine (FT4) concentrations. Additionally, metformin may reduce thyroid nodule volume by 30–50% and demonstrates anti-mitogenic, proapoptotic, and antitumor properties in thyroid cancer cells, partly due to its ability to decrease hyperinsulinemia and enhance the efficacy of chemotherapeutic agents [15].

In the present study, patients receiving metformin therapy for six months exhibited a slight, non-significant increase in FT3 and FT4 levels, while TSH levels showed a significant decline from 2.86 $\pm$ 2.43 μ IU/mL to 1.41 $\pm$ 0.94 μ IU/mL ($p < 0.0001$). This indicates a possible suppressive effect of metformin on TSH secretion. In contrast, patients receiving non-metformin-based treatment also demonstrated a mild, non-significant increase in FT3 and FT4 levels, accompanied by a reduction in TSH from 6.93 $\pm$ 24.77 μ IU/mL to 2.97 $\pm$ 2.67 μ IU/mL ($p = 0.1866$), which was not statistically significant.

Similar findings were reported by Ahmed D. et al., [16] who observed a reduction in serum TSH levels after six months of metformin therapy (1.46 $\pm$ 0.76 vs. 1.35 $\pm$ 0.51 mIU/L), though the change was not statistically significant. Participants were grouped according to their baseline TSH levels, revealing that individuals with lower baseline TSH showed a mild increase after therapy, while those with higher baseline TSH exhibited a significant decrease. A strong inverse correlation ($r = -0.78$, $p < 0.0001$) was found between baseline TSH and post-treatment changes, suggesting that metformin exerts a

modulatory or “buffering” effect on TSH levels.

Another study performed by **Santos-Palacios S. et al.**, [17] described this as 'buffer effect'. Metformin caused a slight but significant increase in TSH when baseline levels were low and a decrease when baseline values were high among euthyroid diabetic patients. These findings collectively indicate that metformin tends to normalize TSH concentrations depending on the initial thyroid status of the patient. According to **Abdelmoez F.A. et al.**, [18] metformin therapy was significantly associated with reduced TSH levels in diabetic patients, independent of changes in FT3 or FT4. The study also identified correlations between TSH suppression and factors such as obesity, macroangiopathy, and hyperlipidemia, suggesting that metformin may lower TSH to subnormal levels without altering peripheral thyroid hormone activity.

In hypothyroid patients, the reduction in TSH following six months of metformin therapy (3.87 ± 0.40 , $p = 0.206$) was more pronounced compared to euthyroid individuals. Also, **Ogbonna S.U. and Ezeani I.U.** [19] reported metformin reduces thyrotropin levels, thyroid volume, and nodule formation. Their study suggested that diabetic patients on long-term metformin therapy tend to have smaller thyroid glands, supporting the hypothesis that metformin may exert anti-proliferative effects on thyroid tissue. Similarly, **Dimic D. et al.**, [20] conducted a study on 255 T2DM patients categorized into euthyroid and hypothyroid groups. Among euthyroid patients, TSH levels decreased from 2.17 ± 1.13 to 1.99 ± 1.42 mIU/L after six months of metformin therapy, though the change was not statistically significant. The study also noted that long-term metformin use did not result in further TSH reduction beyond six months, suggesting that the drug's suppressive effect on TSH may plateau over time.

Overall, the findings of the present study are consistent with existing literature, reinforcing the notion that metformin exerts a modest but significant suppressive effect on TSH secretion, independent of changes in FT3 and FT4 levels. The underlying mechanism may involve metformin's central action on the HPT axis, enhancement of thyroid hormone receptor sensitivity, or improvement in insulin resistance and metabolic signaling pathways. These effects collectively suggest that metformin may play a modulatory role in thyroid function regulation among diabetic patients.

CONCLUSION

The present study demonstrates that metformin therapy in patients with Type 2 Diabetes Mellitus leads to a significant reduction in serum TSH levels without notable changes in FT3 and FT4 concentrations. This indicates a possible suppressive or modulatory effect of metformin on the hypothalamic-pituitary-thyroid axis. Clinicians should, therefore, monitor thyroid function in diabetic patients receiving metformin, particularly in those with underlying thyroid disorders. Further research involving larger study populations and long follow-up periods is necessary to confirm these findings and to clarify the underlying mechanisms of metformin's influence on thyroid regulation. A better understanding of these interactions may help optimize both thyroid and glycemic management, that improving overall patient outcomes in Type 2DM.

References

1. Biondi B, Kahaly GJ, Robertson RP. Thyroid dysfunction and diabetes mellitus: two closely associated disorders. *Endocr Rev.* 2019;40(3):789–824. doi:10.1210/er.2018-00163. PMID: 30649221; PMCID: PMC6507635.
2. Yaseri M, Fayazi HS, Mahdi F, Motevali F, Khatibani SS. The status of thyroid disorders among patients with type 2 diabetes mellitus in Guilan Province, Iran. *Endocr Metab Sci.* 2025;19:100267.
3. Sakyi SA, Ameyaw B, Laing EF, Anthony R, Ephraim RKD, Effah A, et al. Thyroid dysfunction and glycaemic control among type 2 diabetes mellitus patients in Ghana: a comparative cross-sectional study. *Endocrinol Diabetes Metab.* 2023;6(6):e447. doi:10.1002/edm2.447. PMID: 37621219; PMCID: PMC10638622.
4. Condorelli RA, Cannarella R, Aversa A, Basile L, Avola O, Calogero AE, et al. Effects of slow-acting metformin treatment on the hormonal and morphological thyroid profile in patients with insulin resistance. *Pharmaceutics.* 2022;14(10):1987.
5. Mohammed Hussein SM, AbdElmageed RM. The relationship between type 2 diabetes mellitus

- and related thyroid diseases. *Cureus*. 2021;13(12):e20697. doi:10.7759/cureus.20697.
6. Eom YS, Wilson JR, Bernet VJ. Links between thyroid disorders and glucose homeostasis. *Diabetes Metab J*. 2022;46(2):239–56. doi:10.4093/dmj.2022.0013. PMID: 35385635; PMCID: PMC8987680.
 7. Ma Z, Patel N, Vemparala P, Krishnamurthy M. Metformin is associated with favorable outcomes in patients with COVID-19 and type 2 diabetes mellitus. *Sci Rep*. 2022;12(1):5553.
 8. Dutta S, Shah RB, Singhal S, Dutta SB, Bansal S, Sinha S, et al. Metformin: a review of potential mechanism and therapeutic utility beyond diabetes. *Drug Des Devel Ther*. 2023;17:1907–32. doi:10.2147/DDDT.S409373.
 9. Vigersky RA, Filmore-Nassar A, Glass AR. Thyrotropin suppression by metformin. *J Clin Endocrinol Metab*. 2006;91(1):225–7.
 10. He X, Wu D, Hu C, Xu T, Liu Y, Liu C, et al. Role of metformin in the treatment of patients with thyroid nodules and insulin resistance: a systematic review and meta-analysis. *Thyroid*. 2019;29(3):359–67.
 11. Amirabadizadeh A, Amouzegar A, Mehran L, Azizi F. The effect of metformin therapy on serum thyrotropin and free thyroxine concentrations in patients with type 2 diabetes: a meta-analysis. *Sci Rep*. 2023;13(1):18757. doi:10.1038/s41598-023-43266-9.
 12. Krysiak R, Okopien B. Thyrotropin-lowering effect of metformin in a patient with resistance to thyroid hormone. *Clin Endocrinol (Oxf)*. 2011;75(3):404–6.
 13. Patil P, Gudage S, Tondare MB, Tondare SB, Ganganahalli P. To study effects of metformin on thyroid functions in type-2 diabetes mellitus in patients attending OPD at Government Medical College, Bidar. *J Family Med Prim Care*. 2025;14(7):2941-2944.
 14. Haroon SM, Khan K, Maqsood M, Iqbal S, Aleem M, Khan TU. Exploring the effect of metformin to lower thyroid-stimulating hormone in euthyroid and hypothyroid type 2 diabetic patients. *Cureus*. 2021;13(2):e13283. doi:10.7759/cureus.13283. PMID: 33728216; PMCID: PMC7949621.
 15. Rezvani Z, Nasri H. Metformin and thyroid; a narrative review to current concepts. *Journal of Parathyroid Disease*. 2020;8:e11168.
 16. Ahmed D, Makhous R. Evaluation of the effect of metformin therapy on TSH serum levels in diabetic patients. *Res J Pharm Technol*. 2020;13(8):3801–6. doi:10.5958/0974-360X.2020.00673.3
 17. Santos-Palacios S, Brugos-Larumbe A, Guillén-Grima F, et al. Does metformin have a “buffer effect” on serum TSH levels in euthyroid diabetic patients? *Hormones (Athens)*. 2015;14(2):280–5. doi:10.14310/horm.2002.1559
 18. Abdelmoez FA, Mohamed GA, Eldine DM. Study of the effect of metformin therapy on thyroid function in type 2 diabetic patients. *Egypt J Intern Med*. 2019;31(4):972–8.
 19. Ogbonna SU, Ezeani IU. Risk factors of thyroid dysfunction in patients with type 2 diabetes mellitus. *Front Endocrinol (Lausanne)*. 2019;10:440. doi:10.3389/fendo.2019.00440
 20. Dimic D, Golubovic MV, Radenkovic S, Radojkovic D, Pesic M. The effect of metformin on TSH levels in euthyroid and hypothyroid newly diagnosed type 2 diabetes mellitus patients. *Clin Study*. 2016;433–5.