Original Article

Comparative Histopathological Outcomes of SGLT-2 Inhibitors Versus Other Antidiabetics in Diabetic Surgical Patients

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Abstract

Background: Diabetes mellitus is associated with persistent metabolic disturbances that contribute to chronic inflammation, microvascular dysfunction, and structural tissue alterations. These changes may significantly influence surgical outcomes and histopathological characteristics of excised tissues. Sodium–glucose cotransporter-2 (SGLT-2) inhibitors are a newer class of antidiabetic agents that provide effective glycemic control while also exerting additional pleiotropic effects, including anti-inflammatory, antifibrotic, and endothelial-protective actions. However, limited evidence is available regarding their influence on histopathological outcomes in diabetic patients undergoing surgical procedures, particularly thyroid surgery. The objective is to evaluate and compare the histopathological features of thyroidectomy specimens in diabetic patients receiving SGLT-2 inhibitors versus those receiving other antidiabetic medications. This was a prospective observational study conducted over a period of 12 months at Ajay Sangal Institute of Medical Sciences, Shamli, Uttar Pradesh. **Material and Methods:** A total of 130 patients with type 2 diabetes mellitus presenting with thyroid swellings and undergoing surgical intervention were enrolled. Patients were divided into two groups based on their antidiabetic treatment: those receiving SGLT-2 inhibitors and those receiving other antidiabetic drugs excluding SGLT-2 inhibitors. Resected thyroid specimens were subjected to detailed histopathological examination. Parameters assessed included the degree of chronic inflammatory infiltration, extent of fibrosis and vascular alterations. Histopathological findings were compared between the two groups. **Results:** Patients treated with SGLT-2 inhibitors demonstrated comparatively reduced chronic inflammatory changes, lesser fibrotic deposition, and better preservation of vascular architecture in thyroid tissue specimens compared to patients receiving other antidiabetic therapies. These findings were observed in conjunction with relatively improved perioperative glycemic profiles in the SGLT-2 inhibitor group. **Conclusion:** The use of SGLT-2 inhibitors in diabetic patients undergoing thyroid surgery appears to be associated with more favorable histopathological outcomes, characterized by reduced inflammation, decreased fibrosis, and improved vascular integrity. These observations suggest a potential tissue-protective role of SGLT-2 inhibitors in the surgical diabetic population. Further large-scale and multicentric studies are recommended to validate these findings.

Keywords: Type 2 diabetes mellitus, SGLT-2 inhibitors, thyroid swellings, histopathology, diabetic surgical patients.

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The global burden of diabetes has increased substantially over recent decades, with India accounting for a significant proportion of affected individuals.[1] Long-standing diabetes is associated with multisystem involvement, including microvascular and macrovascular complications that adversely affect tissue perfusion, immune response, and wound healing. These pathophysiological alterations are of particular importance in patients undergoing surgical procedures, as they influence intraoperative tissue handling, postoperative recovery, and long-term outcomes.[2]

In the surgical setting, diabetic patients frequently demonstrate altered histological architecture in excised tissues, attributed to chronic inflammation, oxidative stress, advanced glycation end-product accumulation, and endothelial dysfunction.[3] Such changes may manifest as increased fibrosis, impaired vascular integrity, and chronic inflammatory infiltrates, which can complicate both surgical intervention and postoperative healing. The thyroid gland, owing to its rich vascular supply and metabolic activity, may be particularly susceptible to these diabetes-related tissue changes, especially in patients presenting with thyroid swellings requiring surgical management.[4]

Optimal glycemic control plays a critical role in minimizing

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perioperative complications and improving surgical outcomes. Traditionally, antidiabetic agents such as metformin, sulfonylureas, insulin, and dipeptidyl peptidase-4 inhibitors have been widely used in the management of type 2 diabetes mellitus. While these agents effectively lower blood glucose levels, their impact on tissue-level pathological changes in surgical specimens has not been extensively explored.[5,6]

Sodium–glucose cotransporter-2 (SGLT-2) inhibitors represent a newer class of antidiabetic medications that reduce plasma glucose by inhibiting renal glucose reabsorption, leading to glucosuria. Beyond their glucose-lowering effect, SGLT-2 inhibitors have demonstrated additional benefits, including reduction of systemic inflammation, improvement in endothelial function, attenuation of oxidative stress, and potential antifibrotic effects.[7] These pleiotropic actions suggest that SGLT-2 inhibitors may favorably influence tissue morphology and microvascular architecture, which could be reflected in histopathological findings of surgically excised tissues.[8]

Despite growing evidence supporting the cardiovascular and renal benefits of SGLT-2 inhibitors, limited data are available regarding their influence on histopathological outcomes in diabetic patients undergoing surgery. In particular, there is a paucity of studies comparing the tissue-level pathological features of thyroid specimens in patients receiving SGLT-2 inhibitors versus those treated with other antidiabetic agents. Understanding these differences may provide valuable insights into the role of antidiabetic therapy selection in surgical patients and its potential impact on tissue healing and postoperative outcomes.[9]

Therefore, the present prospective observational study was undertaken at Ajay Sangal Institute of Medical Sciences, Shamli, Uttar Pradesh, over a period of 12 months, to compare the histopathological outcomes of thyroidectomy specimens in diabetic patients receiving SGLT-2 inhibitors with those receiving other antidiabetic medications. This study aims to contribute to the existing literature by exploring the association between antidiabetic treatment modalities and histopathological characteristics in diabetic surgical patients.

Materials and Methods

Study Design: This study was designed as a prospective observational study conducted over a period of 12 months at Ajay Sangal Institute of Medical Sciences, Shamli, Uttar Pradesh. The study aimed to compare histopathological outcomes in diabetic patients undergoing thyroid surgery based on their antidiabetic medication regimen. Study Population included a total of 130 patients with a diagnosis of type 2 diabetes mellitus and presenting with thyroid swellings requiring surgical intervention were consecutively enrolled during the study period.

Inclusion Criteria

- Patients aged 18 years and above
- Diagnosed cases of type 2 diabetes mellitus
- Presence of thyroid swelling confirmed clinically and radiologically
- Patients planned for elective thyroid surgery (partial or total thyroidectomy)
- Patients receiving stable antidiabetic therapy for at least 6 months prior to surgery
- Patients who provided written informed consent

Exclusion Criteria

- Patients with type 1 diabetes mellitus
- Known cases of thyroid malignancy on preoperative evaluation
- Patients with chronic kidney disease (stage ≥3) or significant hepatic dysfunction
- Patients on long-term steroid therapy or immunosuppressive drugs
- History of radiotherapy to the neck
- Pregnant or lactating women
- Patients unwilling to participate in the study

Grouping of Study Participants

Based on the antidiabetic medication regimen, patients were divided into two groups:

- **Group A (SGLT-2 inhibitor group):** Patients receiving SGLT-2 inhibitors (such as empagliflozin or dapagliflozin), either as monotherapy or in combination with other oral antidiabetic drugs.
- **Group B (Non–SGLT-2 inhibitor group):** Patients receiving other antidiabetic medications including metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, and/or insulin, without the use of SGLT-2 inhibitors.

Each group consisted of 65 patients.

Preoperative Evaluation

All patients underwent a detailed preoperative assessment including:

- Demographic data (age, gender)
- Duration of diabetes mellitus
- Body mass index (BMI)
- Detailed medical and drug history
- Clinical examination of thyroid swelling
- Thyroid function tests (T3, T4, TSH)
- Glycemic assessment including fasting plasma glucose, postprandial glucose, and HbA1c
- Ultrasonography of the neck
- Fine needle aspiration cytology (FNAC) where indicated
- Routine hematological and biochemical investigations

Surgical Procedure: All surgical procedures were performed under general anesthesia by experienced surgeons following standardized operative protocols. Depending on the clinical indication, patients underwent hemithyroidectomy or total thyroidectomy. Intraoperative findings such as tissue consistency, vascularity, and ease of dissection were noted.

Histopathological Examination: Resected thyroid specimens were immediately fixed in 10% buffered formalin and sent to the pathology department for histopathological evaluation. Tissue processing and paraffin embedding were performed using standard techniques. Sections of 4–5 µm thickness were stained with hematoxylin and eosin (H&E).

Histopathological assessment focused on the following parameters:

- Chronic inflammatory infiltrate: graded as mild, moderate, or severe
- Fibrosis: assessed based on the extent of stromal collagen deposition

- Vascular changes: including endothelial thickening, congestion, and microangiopathy

All slides were evaluated independently by two experienced pathologists who were blinded to the antidiabetic treatment groups to minimize observer bias.

Statistical Analysis: Data were entered into a Microsoft Excel spreadsheet and analyzed using Statistical Package for the Social Sciences (SPSS) software. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Comparative analysis between the two groups was performed using the Student's t-test for continuous variables and the Chi-square test for categorical variables. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 130 patients with type 2 diabetes mellitus and thyroid swellings who underwent thyroid surgery were included in the study. The patients were divided into two groups: Group A (SGLT-2 inhibitor group, n = 65) and Group B (Non–SGLT-2 inhibitor group, n = 65). All enrolled patients completed the study, and histopathological analysis was available for all surgical specimens.

Baseline Demographic and Clinical Characteristics

The baseline demographic and clinical parameters of patients in both groups were comparable, with no statistically significant differences observed with respect to age, gender distribution, duration of diabetes, or type of thyroid swelling.

Table 1: Baseline Demographic and Clinical Profile of Study Participants

Parameter	Group A (SGLT-2 inhibitors) n=65	Group B (Other antidiabetics) n=65	p-value
Mean age (years)	52.6 ± 9.4	51.9 ± 10.2	0.71
Gender (Male/Female)	29 / 36	31 / 34	0.68
Duration of diabetes (years)	7.9 ± 3.1	8.2 ± 3.4	0.59
Mean BMI (kg/m²)	26.1 ± 2.8	26.4 ± 3.0	0.56
Mean HbA1c (%)	7.3 ± 0.8	8.2 ± 1.0	<0.001

Both groups were comparable demographically. However, patients receiving SGLT-2 inhibitors demonstrated significantly better glycemic control, as reflected by lower mean HbA1c values.

Histopathological Findings

Histopathological examination of thyroidectomy specimens focused on inflammatory changes, fibrosis and vascular alterations.

Table 2: Comparison of Histopathological Parameters Between Study Groups

Histopathological Parameter	Group A (n=65)	Group B (n=65)	p-value
Chronic inflammation (mean score)	1.1 ± 0.7	1.9 ± 0.8	<0.001
Fibrosis score	1.0 ± 0.6	1.8 ± 0.7	<0.001
Vascular integrity score	2.3 ± 0.4	1.7 ± 0.5	<0.001

Severity Distribution of Inflammatory Changes

Table 3: Severity of Chronic Inflammation in Thyroid Specimens

Severity of inflammation	Group A n (%)	Group B n (%)
Mild	44 (67.7%)	22 (33.8%)
Moderate	17 (26.2%)	29 (44.6%)
Severe	4 (6.1%)	14 (21.6%)

A higher proportion of patients in the SGLT-2 inhibitor group exhibited mild inflammatory changes, whereas moderate to severe inflammation was more commonly observed in patients receiving other antidiabetic medications.

Fibrotic Changes in Thyroid Tissue

Table 4: Distribution of Fibrosis in Study Groups

Degree of fibrosis	Group A n (%)	Group B n (%)
Minimal	46 (70.8%)	21 (32.3%)
Moderate	15 (23.1%)	31 (47.7%)
Extensive	4 (6.1%)	13 (20.0%)

Minimal fibrosis was predominantly observed in patients treated with SGLT-2 inhibitors, while moderate to extensive fibrosis was significantly more common in the non–SGLT-2 inhibitor group.

Vascular Changes

Histopathological features such as endothelial thickening, vascular congestion and microangiopathic changes were assessed.

Table 5: Vascular Changes in Study Groups

Feature	Group A n (%)	Group B n (%)
Preserved vascular architecture	48 (73.8%)	26 (40.0%)
Endothelial thickening	12 (18.5%)	29 (44.6%)

Microangiopathic changes	9 (13.8%)	33 (50.8%)

Patients in Group A demonstrated significantly fewer microangiopathic changes compared to Group B, suggesting reduced glycemic tissue damage in patients receiving SGLT-2 inhibitors.

Discussion

Diabetes mellitus is known to exert profound effects on tissue architecture through mechanisms such as chronic low-grade inflammation, oxidative stress, endothelial dysfunction, and microvascular compromise. These pathological processes are particularly relevant in surgical patients, where altered tissue quality may influence intraoperative handling, postoperative healing, and long-term outcomes. The present prospective observational study was conducted to evaluate and compare histopathological outcomes in diabetic patients with thyroid swellings undergoing surgery, based on their antidiabetic treatment regimen, with a specific focus on SGLT-2 inhibitors versus other commonly used antidiabetic agents.[3,10]

In this study, patients receiving SGLT-2 inhibitors demonstrated significantly more favorable histopathological features in thyroidectomy specimens compared to patients receiving non–SGLT-2 antidiabetic medications.[11] These findings included reduced chronic inflammatory infiltrates, lesser degrees of fibrosis, better preservation of vascular architecture suggesting lesser glycemic tissue damage. Such differences suggest that the choice of antidiabetic therapy may influence tissue-level pathology in diabetic surgical patients.[12]

One of the key findings of the present study was the significantly lower degree of chronic inflammation observed in the SGLT-2 inhibitor group. Chronic inflammation plays a central role in the pathogenesis of diabetic tissue damage and is known to impair wound healing and increase susceptibility to postoperative complications. SGLT-2 inhibitors have been shown in previous studies to reduce systemic inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor-alpha. The reduced inflammatory infiltrates observed in thyroid specimens from patients receiving SGLT-2 inhibitors may reflect these systemic anti-inflammatory effects at the tissue leve.[13,14]

Fibrosis is another hallmark of chronic diabetic tissue injury, resulting from prolonged inflammatory signaling and activation of fibroblasts. In the present study, thyroid specimens from patients in the SGLT-2 inhibitor group exhibited significantly lower degrees of stromal fibrosis compared to the non–SGLT-2 inhibitor group. This observation is consistent with experimental and clinical evidence suggesting that SGLT-2 inhibitors may exert antifibrotic effects by reducing oxidative stress, suppressing profibrotic cytokines, and improving metabolic efficiency. Reduced fibrosis may translate into improved tissue elasticity and vascularity, which are beneficial during surgical dissection and healing.[15]

Vascular integrity is critical for adequate tissue perfusion and oxygenation. Diabetic microangiopathy, characterized by endothelial dysfunction, basement membrane thickening, and capillary rarefaction, contributes to impaired wound healing and tissue ischemia. In the current study, vascular architecture was better preserved in patients receiving SGLT-2 inhibitors, with fewer microangiopathic changes and endothelial abnormalities. These findings may be attributed to the endothelial-protective effects of SGLT-2 inhibitors, which have been reported to improve nitric oxide bioavailability, reduce oxidative stress, and enhance microvascular function.[16] Improved glycemic control, as reflected by lower mean HbA1c levels in this group, likely contributed to these findings. Sustained hyperglycemia is known to promote advanced glycation end-product accumulation and structural tissue damage; therefore, better glycemic control combined with the pleiotropic effects of SGLT-2 inhibitors may have played a protective role.[17]

Comparatively, patients receiving other antidiabetic medications demonstrated higher degrees of inflammation, fibrosis, and microvascular damage. While conventional antidiabetic agents effectively lower blood glucose levels, they may lack the additional anti-inflammatory and vascular benefits associated with SGLT-2 inhibitors. This difference may partly explain the observed variation in histopathological outcomes between the two groups.[12]

The strengths of this study include its prospective design, standardized histopathological evaluation, and blinded assessment by experienced pathologists, which helped reduce observer bias. However, certain limitations should be acknowledged. The study was conducted at a single centre, which may limit the generalizability of the findings. Additionally, as an observational study, causal relationships cannot be definitively established. Molecular markers of inflammation and fibrosis were not assessed, which could have provided further mechanistic insights.

Despite these limitations, the findings of the present study add to the growing body of evidence supporting the tissue-protective effects of SGLT-2 inhibitors. By demonstrating favorable histopathological outcomes in thyroid surgical specimens, this study highlights the potential role of antidiabetic drug selection in influencing tissue health and surgical outcomes in diabetic patients.

Conclusion

Use of SGLT-2 inhibitors in T2DM patients undergoing thyroid surgery was associated with reduced chronic inflammation, decreased fibrosis and better vascular architecture suggesting lower glycemic tissue damage. These preliminary findings support the potential tissue-protective benefits of SGLT-2 inhibitors in surgical settings.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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