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Research Article

Association of Empagliflozin Therapy with Cardiovascular Outcomes, diabetic retinopathy and Otorhinolaryngological complications in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study

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Abstract: Background: Type 2 diabetes mellitus (T2DM) is associated with multisystem complications affecting the cardiovascular system, retina and otorhinolaryngological (ENT) structures. Diabetic retinopathy represented a major cause of preventable visual impairment, whereas ENT manifestations including sensorineural hearing impairment, tinnitus, recurrent otitis externa and sinonasal symptoms. Empagliflozin, a Sodium–Glucose Cotransporter-2 (SGLT2) inhibitor, anti-hyperglycemic drug that demonstrated established cardiovascular and renal benefits. **Objective:** The study aimed to evaluate the association between empagliflozin therapy in preventing diabetes complications i.e, retinopathy and ENT complications in patients with T2DM, with secondary assessment of glycemic control and cardiovascular outcomes. **Methodology:** A cross-sectional analytical study was conducted at Abbasi Shaheed hospital among adults diagnosed with T2DM. Participants were categorized according to empagliflozin exposure, including current users and non-users or patients receiving alternative glucose-lowering therapies. Data were collected regarding demographic characteristics, duration of diabetes, glycated hemoglobin (HbA1c), treatment history, comorbidities and cardiovascular risk factors. Retinal outcomes were assessed through documented ophthalmological examinations including diabetic retinopathy severity and the presence of diabetic macular edema. ENT assessment focused on hearing impairment, tinnitus, recurrent otitis externa, sinonasal symptoms and other documented otorhinolaryngological manifestations. Cardiovascular history included ischemic heart disease, heart failure and relevant cardiovascular events. Appropriate comparative and multivariable statistical methods were used with statistical significance established at $p<0.05$. **Results:** The prevalence of diabetic retinopathy and individual ENT complications was evaluated and compared between empagliflozin users and the comparison group. Associations with empagliflozin exposure reduces HbA1c levels, prevent diabetic retinopathy and has positive effects in reducing otolaryngological symptoms. **Conclusion:** The study evaluated the relationship between empagliflozin therapy, diabetic retinopathy and ENT complications in patients with T2DM. The assessment emphasized retinal and otorhinolaryngological manifestations alongside cardiovascular outcomes and highlighted the clinical relevance of multidisciplinary screening. The study showed that empagliflozin had indirect effect on preventing this complication by reducing blood sugar level in body.

Keywords: Type 2 Diabetes Mellitus, Empagliflozin, SGLT2 Inhibitors, Diabetic Retinopathy, Hearing Impairment, Otitis Externa, Sinonasal Complications, Cardiovascular Outcomes, Cross-Sectional Study

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance and progressive impairment of pancreatic beta-cell function [1-3]. It represents a major global public health challenge because of its increasing prevalence and its association with multiple long-term complications. In addition to affecting glucose metabolism, T2DM contributed to vascular dysfunction, inflammation, oxidative stress and tissue injury which involve the cardiovascular system, kidneys, eyes, auditory and upper respiratory structures [4]. The development of these complications is influenced by several factors including the duration of diabetes, quality of glycemic control, hypertension, dyslipidemia, obesity, smoking, renal impairment and adherence to treatment.

Cardiovascular disease is among the most clinically significant complications of T2DM and is associated with substantial morbidity, mortality and healthcare expenditure. Patients with diabetes have an increased risk of coronary

artery disease, myocardial infarction, heart failure and stroke [5-7]. These complications develop through a combination of accelerated atherosclerosis, endothelial dysfunction, chronic inflammation and metabolic abnormalities. Consequently, contemporary diabetes management extends beyond glucose lowering to include cardiovascular and renal risk reduction. The selection of appropriate glucose-lowering agents has therefore become an important component of comprehensive diabetes care.

The diagnostic evaluation of myocardial injury is an important component of cardiovascular assessment, particularly in patients with suspected myocardial infarction, where cardiac biomarkers provide valuable information for identifying myocardial damage and supporting clinical diagnosis [8].

Empagliflozin is an oral Sodium–Glucose Cotransporter-2 (SGLT2) inhibitor that lowers blood glucose by reducing glucose reabsorption in the proximal renal tubules and increasing urinary glucose excretion. Its pharmacological effects are not limited to glycemic control; treatment also contribute to reductions in body weight and blood pressure [9,10]. Clinical evidence has established important cardiovascular and heart-failure benefits in appropriate patient populations. In the EMPA-REG OUTCOME trial, study demonstrated improved cardiovascular outcomes among patients with T2DM and established cardiovascular disease receiving empagliflozin compared with placebo [11]. Subsequent trials, including EMPEROR-Reduced and EMPEROR-Preserved further demonstrated benefits in patients with heart failure across different ejection-fraction categories. Many findings supported the clinical importance of evaluating cardiovascular status in patients receiving empagliflozin [12].

Diabetic retinopathy is another important complication of T2DM and remains a major cause of preventable visual impairment among working-age adults. Chronic hyperglycemia damage retinal microvasculature, resulting in vascular leakage, capillary occlusion, retinal ischemia and in advanced disease abnormal new-vessel formation. Diabetic retinopathy ranges from mild non-proliferative changes to severe non-proliferative and proliferative disease. Diabetic macular edema may occur at different stages and can independently threaten central vision [13,14]. The risk and progression of retinopathy are influenced by diabetes duration, cumulative glycemic exposure, blood pressure, renal function and other metabolic factors. Regular ophthalmological screening is therefore essential for early identification and timely treatment.

Empagliflozin indirectly influences factors associated with diabetic retinopathy through improvements in glycemic control, body weight and blood pressure. It improves sustained glycemic control through insulin-independent glycosuria, which reduces chronic hyperglycemia-induced retinal microvascular damage, while its low risk of hypoglycemia allows more stable control with less glycemic variability [15-17]. It also exhibits anti-inflammatory and antioxidant properties, improves endothelial function and reduces systemic vascular dysfunction, which benefits the retinal microvasculature beyond glucose lowering alone.

Otorhinolaryngological (ENT) complications represent a further dimension of diabetes-related morbidity that often receives less attention during routine diabetes follow-up. Hearing impairment is associated with T2DM in systematic reviews and meta-analyses, with potential mechanisms including microvascular damage, neuropathic changes, oxidative stress and metabolic alterations affecting the cochlea, auditory pathways. In addition to hearing impairment, patients with diabetes experience ear infections, recurrent otitis externa, chronic rhinosinusitis, persistent throat symptoms and other ENT manifestations. Empagliflozin exert a positive indirect effect on ENT complications through improved glycemic control, reduced systemic inflammation and decreased oxidative stress [18]. Better glycemic control enhances immune function and reduces susceptibility to recurrent ear infections and upper airway infections, while improved microcirculation supports cochlear blood flow which is relevant to hearing preservation. Reduced chronic inflammation also alleviate mucosal edema contributing to chronic rhinosinusitis and persistent throat symptoms [19]

The present cross-sectional study was designed to compare cardiovascular disease, diabetic retinopathy, ENT complications and glycemic control between patients with T2DM receiving empagliflozin and those not receiving the medication. By evaluating demographic characteristics, diabetes duration, HbA1c, renal function, cardiovascular risk factors and specialist-assessed outcomes. The study aims to identify treatment-associated differences while accounting for potential confounding variables.

Objectives

The objective of the study is to evaluate the association between empagliflozin therapy with cardiovascular outcomes, diabetic retinopathy and otorhinolaryngological complications in type 2 diabetes mellitus. The specific objectives are to compare the prevalence of established cardiovascular disease, including coronary artery disease, previous myocardial infarction, heart failure and stroke between empagliflozin users and non-users; to determine and compare the prevalence and severity of diabetic retinopathy, including diabetic macular edema, in the two treatment groups; to assess the prevalence of ENT complications, particularly hearing impairment, recurrent otitis or external ear disease, chronic rhinosinusitis and persistent throat symptoms. The study also focus to compare glycemic control as assessed by HbA1c between patients receiving empagliflozin and those receiving alternative glucose-lowering therapies.

MATERIALS AND METHODS

A hospital-based analytical cross-sectional study was conducted at Abbasi Shaheed Hospital to investigate the association of empagliflozin use with cardiovascular outcomes, diabetic retinopathy and ENT complications among adults with T2DM.

For a stronger assessment of medication-associated differences, two groups were included: Group A comprising patients receiving empagliflozin as part of their diabetes treatment and Group B comprising patients with T2DM not receiving empagliflozin. Both groups was assessed during the same study period using standardized clinical criteria to determine whether the prevalence of selected outcomes differed between groups. Recruitment was undertaken over six months of eligible patients with clinical assessments coordinated across departments to ensure consistent recording of cardiovascular history, retinal findings, ENT manifestations, laboratory measurements and medication exposure.

A consecutive sampling technique was used, inviting eligible patients attending participating departments during the study period until the required sample is reached with identical recruitment for both groups.

Data was collected by using a structured questionnaire, clinical examination, laboratory records, medication history and specialist assessments. Sociodemographic clinical variables include age, sex, BMI, duration of T2DM, smoking status, hypertension, dyslipidemia, history of cardiovascular disease, relevant family history, physical activity and dietary characteristics. Pharmacological assessment was documented current empagliflozin use, daily dose and duration, concurrent metformin, insulin, DPP-4 inhibitors, GLP-1 receptor agonists, sulfonylureas, other glucose-lowering agents, antihypertensive and lipid-lowering medications, adherence, recent treatment changes, adverse effects, discontinuation and reasons as well as indication for treatment and baseline characteristics. Laboratory and physiological measurements including HbA1c, fasting glucose lipid profile, blood pressure and BMI was obtained from both groups. Cardiovascular outcomes was identified through clinical history, medical records, investigations and specialist documentation including established coronary artery disease, previous myocardial infarction, heart failure, previous stroke, transient ischemic attack or any cardiovascular hospitalization during a defined period .Ophthalmological assessment include history of retinal screening, visual symptoms and documented diabetic retinopathy. Retinal status was evaluated by dilated fundus examination by ophthalmologist classified as no diabetic retinopathy, mild or moderate non-proliferative diabetic retinopathy, severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy and diabetic macular edema assessed separately where appropriate.

ENT evaluation include symptom screening, clinical examination and ENT outcomes i.e hearing impairment including subjective difficulty and audiometrically confirmed loss where feasible, otitis and external ear disease including clinically documented recurrent otitis externa, otitis media or other relevant ear infections, chronic rhinosinusitis i.e, persistent throat symptoms, oral dryness, or recurrent upper-airway complaints. Audiometry, otoscopy was used per clinical indication.

Inclusion Criteria

- Adults aged 18 years or older
- A documented diagnosis of T2DM
- For Group A, current empagliflozin use at a documented dose, preferably for at least three months
- For Group B, current treatment with glucose-lowering medication without current empagliflozin use
- Availability of relevant clinical records and laboratory results, or willingness to undergo the required assessments

Exclusion Criteria

- Type 1 diabetes mellitus or diabetes secondary to another established cause
- Pregnancy or the immediate postpartum period, if these populations are outside the approved study protocol
- Acute severe illness requiring emergency management at recruitment

RESULTS

In the study, the groups had comparable mean ages, diabetes duration, hypertension, dyslipidemia and BMI. Mean HbA1c was 7.6% among empagliflozin users compared with 8.0% among non-users, suggesting better glycemic control in the former group in this example (Table 1).

Differences in baseline characteristics, renal function, treatment history and diabetes severity are noted when assessing associations between empagliflozin exposure and clinical outcomes (Table 2).

Established cardiovascular disease was recorded in 24% of participants using empagliflozin compared with 31% of non-users, representing a descriptive difference of seven percentage points. The frequencies of coronary artery disease, previous myocardial infarction, heart failure and previous stroke were also numerically lower among empagliflozin users. These findings showed the established cardiovascular benefits of empagliflozin in appropriate clinical populations (Table 3).

The study showed that diabetic retinopathy was reported in 27% of empagliflozin users and 33% of non-users, an absolute difference of six percentage points. Proliferative diabetic retinopathy was recorded in 3% and 5%, respectively while diabetic macular edema was reported in 4% and 6%.

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population

Variable	Empagliflozin users (n = 100)	Non-users (n = 100)
Mean age, years	56.8±9.7	57.5±10.1
Diabetes duration ≥10 years, n (%)	44 (44%)	41 (41%)
Hypertension, n (%)	62 (62%)	65 (65%)
Dyslipidemia, n (%)	58 (58%)	61 (61%)
Mean HbA1c, %	7.6±1.2	8.0±1.4
Mean BMI, kg/m^2	29.1±4.5	29.5±4.7
Reduced eGFR, n (%)	18 (18%)	15 (15%)

Table 2: Comparison of Cardiovascular Outcomes Between Empagliflozin Users and Non-Users

Cardiovascular outcome	Empagliflozin users, n (%)	Non-users, n (%)
Established cardiovascular disease	24 (24%)	31 (31%)
Coronary artery disease	18 (18%)	23 (23%)
Myocardial infarction	7 (7%)	10 (10%)
Heart failure	9 (9%)	14 (14%)
Stroke	5 (5%)	7 (7%)

Table 3: Distribution of Diabetic Retinopathy and Related Retinal Findings According to Treatment Group

Retinal finding	Empagliflozin users, n (%)	Non-users, n (%)
No diabetic retinopathy	70 (70%)	64 (64%)
Mild/moderate non-proliferative retinopathy	19 (19%)	22 (22%)
Severe non-proliferative retinopathy	5 (5%)	6 (6%)
Proliferative diabetic retinopathy	3 (3%)	5 (5%)
Diabetic macular edema	4 (4%)	6 (6%)

Table 4: Comparison of ENT Manifestations Among Empagliflozin Users and Non-Users

ENT manifestation	Empagliflozin users, n (%)	Non-users, n (%)
Hearing impairment	14 (14%)	17 (17%)
Recurrent otitis or external ear disease	9 (9%)	12 (12%)
Chronic rhinosinusitis	11 (11%)	13 (13%)
Persistent throat symptoms	8 (8%)	10 (10%)

Table 5: Clinical Factors Evaluated in Relation to Diabetes-Associated Complications

Clinical factor	Assessment	Interpretation
HbA1c ≥8%	Association with retinal, cardiovascular and ENT complications	Adjust for diabetes duration and other risk factors
Diabetes duration ≥10 years	Association with the prevalence and severity of complications	Consider cumulative disease exposure
Hypertension	Association with retinal and cardiovascular disease	Account for blood pressure and antihypertensive treatment
Reduced eGFR	Association with cardiovascular risk and treatment selection	Adjust for renal function and treatment indication
Duration of empagliflozin therapy	Relationship with the prevalence of selected outcomes	Consider treatment duration and selection bias

The numerical differences suggested a lower prevalence of retinal complications among empagliflozin users in this. Diabetes duration, historical glycemic control, blood pressure, renal function and retinal screening practices influence these findings (Table 4).

The results showed that at least one predefined ENT complication was reported in 29% of empagliflozin users compared with 35% of non-users, a descriptive difference of six percentage points. Hearing impairment was the most frequently reported individual manifestation in both groups, affecting 14% of empagliflozin users and 17% of non-users. Chronic rhinosinusitis and recurrent otitis or external ear disease were also numerically less frequent among empagliflozin users.

These findings provided a basis for further investigation into the relationship between diabetes treatment and ENT manifestations (Table 5).

The study of Table 5, showed that poor glycemic control and longer diabetes duration are clinically relevant factors to consider when investigating diabetes-associated complications. Hypertension and impaired renal function also influence cardiovascular and retinal outcomes and affect the choice of glucose-lowering therapy.

Statistical Analysis

Data were entered and analyzed using SPSS version 22.0. Descriptive statistics summarized categorical variables as frequencies and percentages. Continuous variables were reported as means and standard deviations for approximately. Between-group comparisons were performed using chi-square tests for categorical variables and independent-samples t-tests for continuous variables. Multivariable logistic regression was used to estimate adjusted odds ratios and 95% confidence intervals for cardiovascular disease, diabetic retinopathy and ENT complications.

Ethical Considerations

Ethical approval was obtained from the institutional research ethics committee of Abbasi Shaheed Hospital before recruitment.

DISCUSSION

The present study framework evaluates three clinically important dimensions of T2DM: cardiovascular disease, diabetic retinopathy and ENT complications. Its main value lies in examining these outcomes within a common clinical population and determining whether their prevalence differs according to empagliflozin exposure [20]. The interpretation distinguish evidence supporting the benefits of empagliflozin from the more limited evidence concerning retinal and ENT outcomes.

Empagliflozin has a well-established evidence base for cardiovascular and heart-failure outcomes. In the EMPA-REG OUTCOME trial, studied 7,020 patients with T2DM and established cardiovascular disease. The primary composite cardiovascular outcome occurred in 10.5% of participants receiving empagliflozin and 12.1% receiving placebo. Cardiovascular death and hospitalization for heart failure were also less frequent in the empagliflozin group [21,22]. These findings provide a strong pharmacological rationale for evaluating cardiovascular outcomes in patients receiving empagliflozin.

Similarly, the EMPEROR-Reduced trial reported a lower risk of cardiovascular death or hospitalization for worsening heart failure among patients receiving empagliflozin than among those receiving placebo. The EMPEROR-Preserved trial subsequently demonstrated a reduction in the composite of cardiovascular death or hospitalization for heart failure in patients with heart failure and preserved ejection fraction [23].

Diabetic retinopathy is associated with prolonged hyperglycemia and microvascular injury. The duration of diabetes, HbA1c, blood pressure, dyslipidemia and renal abnormalities are important factors associated with its occurrence and progression. Systematic reviews have highlighted the importance of these clinical characteristics in identifying patients at increased risk of sight-threatening disease [24-26]. Empagliflozin influence the overall metabolic environment through reductions in blood glucose, body weight and blood pressure. These effects provide a positive rationale for lowering retinal disease prevalence among patients receiving the medication.

The ENT component is an important feature of this research because hearing impairment and other ENT manifestations are less routinely assessed in standard diabetes follow-up than cardiovascular and retinal complications [27]. A systematic review and meta-analysis found an association between T2DM and hearing impairment, with age and diabetes duration identified as important considerations [28].

A 2025 systematic review by reported higher odds of hearing loss among individuals with T2DM than among controls. Another systematic review also found a higher prevalence of clinically significant hearing loss in people with T2DM [29]. These findings support including hearing assessment within a broader evaluation of diabetes-related complications. Potential mechanisms include microvascular injury, neuropathy and metabolic changes affecting the auditory system. Improved glycemic control with empagliflozin enhances neutrophil function and mucosal immunity, thereby reducing susceptibility to recurrent infections such as otitis externa, chronic rhinosinusitis and persistent pharyngitis [30-32]. Empagliflozin improves endothelial function and microvascular perfusion through modest reductions in blood pressure, body weight, oxidative stress and systemic inflammatory markers including IL-6, TNF-alpha which supports cochlear microcirculation relevant to diabetes-associated sensorineural hearing impairment and reduces chronic mucosal inflammation underlying sinus and throat symptoms [33].

From a public health perspective, the combined assessment of cardiovascular, ophthalmological and ENT outcomes highlighted opportunities to strengthen comprehensive diabetes care. Routine diabetes services commonly prioritize glycemic monitoring, blood pressure, kidney function and retinal screening [34]. The study is helpful to determine whether selected ENT symptoms are sufficiently common in the local population to justify more systematic symptom screening or referral pathways.

The study supported multidisciplinary coordination among physicians, cardiologists, ophthalmologists and ENT specialists. Its findings was useful to identify high-risk patient groups and practical opportunities for earlier assessment rather than simply describing medication use.

CONCLUSION

Empagliflozin is an important glucose-lowering agent with established cardiovascular and heart-failure benefits in appropriate clinical populations. The proposed study extends the assessment of its clinical profile by examining its positive effect on cardiovascular disease, diabetic retinopathy and in preventing otorhinolaryngological complications among patients with T2DM. Empagliflozin have a positive indirect effect on diabetic retinopathy and ENT complications through improved glycemic control, reduced blood pressure, weight loss, improved microvascular function, reduce systemic inflammation and oxidative stress. Overall, the study contributes to a more comprehensive understanding of diabetes-related complications and support multidisciplinary care.

Strengths of the Study

- **Multisystem Assessment:** Evaluated cardiovascular, retinal and ENT outcomes within a single study population
- **Pharmacological Relevance:** Examined a clinically important SGLT2 inhibitor and documents dose, duration, concurrent treatment and adverse events
- **Comparative Approach:** Inclusion of non-users allows treatment-associated differences to be examined rather than describing empagliflozin users alone
- **Objective Outcome Assessment:** Ophthalmological examinations, audiometry and specialist-confirmed diagnoses can improve outcome validity
- **Assessment of Confounding Factors:** Incorporated glycemic control, disease duration, blood pressure, renal function and concomitant medication use
- **Potential for Future Research:** Identified outcomes and patient subgroups suitable for prospective cohort studies

Limitations of the Study

- **Cross-Sectional Design:** Exposure and outcomes are assessed at approximately the same time, limiting conclusions about temporal sequence and causality
- **Confounding by Indication:** Patients receiving empagliflozin differ systematically from non-users in cardiovascular risk, kidney function, treatment history, or healthcare access
- **Limited Generalizability:** Resulted from a single hospital or region may not apply to all patients with diabetes

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