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ORIGINAL ARTICLE

ASSOCIATION BETWEEN BILIARY DISEASE, INCLUDING ACUTE CHOLECYSTITIS AND DIPEPTIDYL PEPTIDASE 4 INHIBITORS USE IN PATIENTS WITH TYPE 2 DIABETES MELITTUS

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a global health challenge associated with multiple significant complications. Recent studies suggest that use of dipeptidyl peptidase 4 (DPP-4) inhibitors, may be linked to acute cholecystitis and biliary dysfunction. Understanding this association is important, as biliary complications may adversely affect patient outcomes.

Objective: To explore the association between biliary diseases, including acute cholecystitis, in patients with type 2 diabetes mellitus treated with DPP-4 inhibitors.

Material and Methods: This cross-sectional study was conducted between Nov 2022 to August 2024 at PAF Hospital, Islamabad. The study population had two qual groups of 350 patients each comprising type 2 diabetic patients receiving DPP-4 inhibitors and those receiving other ant diabetic medications. The data regarding demographic characteristics and biliary outcomes were collected from their medical records using a structured questionnaire and analyzed using SPSS version 25 to find the association between biliary disease and use of DPP4 inhibitors.

Results: Patients receiving DPP-4 inhibitors showed a significantly higher frequency of acute cholecystitis compared to those receiving other antidiabetic medications (16.0% vs 10.0%, p=0.027; OR=1.71, 95% CI: 1.09–2.68). There were also higher frequencies of gallstones (22.0% vs 16.0%, p=0.153; OR=1.48, 95% CI: 0.99–2.20)and biliary sludge (24.0% vs 18.3%, p=0.076; OR=1.41, 95% CI: 0.97–2.05)in the DPP-4 inhibitor group; however, these differences were not statistically significant.

Conclusion: Our findings suggests an association between use of DPP-4 inhibitors and a higher frequency of acute cholecystitis and biliary disease in patients with type 2 diabetes mellitus, warranting careful monitoring in clinical practice.

Keywords: Acute cholecystitis, Biliary disease, Dipeptidyl peptidase 4 inhibitors, Type 2 diabetes mellitus .
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Introduction:

Type 2 diabetes mellitus (T2DM) is currently a major health challenge globally effecting millions of populations. According to an estimate by IDF (International Diabetes Federation), approx. 537 million people are afflicted with DM worldwide.[1] It is a chronic disease consisting mainly of insulin resistance and pancreatic beta-cell dysfunction that results in hyperglycemia with multiple associated secondary complications.[2]Biliary disease, specifically acute Cholecystitis has recently become prominent in the literature and should be especially concerning due to its significant morbidity as well potentially-life threatening nature.[3] The main etiology of acute cholecystitis is related to gallstones, which obstruct the cystic duct but in diabetic patients there might be other factors that trigger the pathology.

T2DM management, on the other hand, usually involves a multifaceted approach that includes lifestyle

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and dietary changes accompanied by pharmacological interventions.[4] Dipeptidyl Peptidase-4 (DPP- 4) inhibitors recently emerged as antidiabetic group, are conveniently chosen because of their reasonable glycemic control with a favorable safety profile.[5]Sitagliptin, saxagliptin and linagliptin are the DPP-4 inhibitors which reduce degradation of Incretins by inhibiting enzyme Dipeptide Peptidase. Circulatory glucose concentrations are countered by insulin release and glucagon suppression, which are under stimulator control of counter-regulatory hormones.[5-6] However, more recent studies have provided evidence of cholecystitis mainly by DPP-4 inhibitor use.

Diabetics have a well-documented high rate of biliary disease worldwide. A study by Ratheesh Ret al. (2023) reported gallstones and cholecystitis as being more frequent diagnostic entities among diabetic patients than in non-diabetic individuals.[7]Another study by Faillie, Jean-Luc et al. (2017) in particular looked at the effect of DPP-4 inhibitors on biliary disease and found a slightly increased risk for gallbladder-related events among DPP-4 users.[8]Recent meta-analyses and systematic reviews have tried to estimate the risk of DPP-4 inhibitors. To illustrate, a study-level meta-analysis done by He L, Wang J and others included 184 randomized controlled trials and concluded that DPP-4 inhibitors are significantly associated with an increased risk of biliary disease, including cholecystitis.[9]Although these global studies give us a truly broad overview of potential risks, they also emphasize the importance that regional and local investigations are necessary to understand patient populations as well as healthcare practices. These findings suggest the necessity for additional work serving to determine potential mechanisms by which DPP-4 inhibitors might affect biliary pathology.

Diabetes is already an endemic in Pakistan and is said to be affecting as many as 26.3 per cent of the population.IDF survey indicates approx. 31 million of the total population being affected by Type 2 DM (IDF, 2021).[10]Research done on patients in Sindh, Karachi showed similar trends of increased incidence of gallstones and cholecystitis in Diabetic patients.[11]Despite these observations, there has been very scant literature that has done a formal test to support these assertions. Therefore, the purpose of this study is systematically examining this link within the context of the local population and produce empirical evidence that could be helpful to clinicians in Pakistan. To the best of our understanding, this study is novel because it seeks to fill a significant void in the existing body of knowledge regarding the effects of DPP-4 inhibitors on biliary compartments, with specific focus on the Pakistani populace. DPP-4 inhibitors are often prescribed due to the proven benefits among patients with diabetes; thus, analyzing the risks of biliary disease related to their usage is a requirement. The premise of this work could prevent a more considerable number of diabetic patients from carrying this burden of biliary disease by using the study's findings to develop better clinical directives and patients' treatment plans.

Material and Method:

Place & duration: This cross-sectional study was conducted at the department of Medicine, Pakistan Air Force Hospital, Islamabad, from November 2022 to August 2024 after getting approval from Institutional Ethical Review Committee.

Study Population and Sample Size: Sample size was calculated using the WHO sample size calculator for comparison of two proportions. Taking the incidence of cholecystitis as 36% among patients receiving DPP-4 inhibitors and 25% among the controls, a 95% confidence level and 85% study power, the minimum required sample size was 620 (310 participants in each group); however, to compensate for potential missing data, incomplete records, and participant attrition, we inflated the sample size by approximately 13%, which resulted in a final sample size of 700 participants (350 patients allocated to each group).[12]

Inclusion criteria: A total of 350 patients aged between 18-75 years, attending the diabetic clinic of the unit with a confirmed diagnosis of T2DM, and receiving DPP-4 inhibitors for at least last six months were included in the study group. The enrolled patients were required to have a complete medical record, and relevant laboratory and radiological investigations. Similarly, the control group comprised 350 patients, belonging to same age group, with a confirmed diagnosis of T2DM, and receiving non-incretin antidiabetic medications for at least six months.

All participants provided written informed consent prior to their enrollment.

Exclusion criteria: Patients with type 1 diabetes mellitus, taking GLP-1 receptor agonists or those taking any other incretin-based drugs were excluded. Moreover, patients who had undergone biliary surgery or had a history of gallbladder disease prior to initiating antidiabetic therapy, with severe systemic illness (such as malignancy), moderate-to-severe renal impairment or significant hepatic dysfunction were also excluded. Pregnant or lactating women were also in the exclusion list.

Data collection: A structured questionnaire was used to collect the data with trained investigators. The questionnaire comprised of demographic data, medical history, duration of T2DM, medication history, lifestyle parameters and history of biliary disease. Clinical information was confirmed from the database of hospital's electronic medical records. All the laboratory investigations, imaging characteristics, and treatment records were further reviewed for confirmation of variables and outcomes pertinent to the study.

Biliary disease was defined as the presence of gallstones, biliary sludge or acute cholecystitis in the medical record.

The diagnosis of acute cholecystitis was made when typical clinical features (right upper quadrant pain, fever, and/or positive Murphy's sign) were accompanied by laboratory markers of inflammation and ultrasonography findings that suggested a diagnosis of gallbladder inflammation, consistent with current clinical practice guidelines. The primary imaging modality for diagnosis was ultrasonography.

Study Outcomes: The primary outcome of the study was the presence of biliary disease, including gallstones and biliary sludge, and the occurrence of acute cholecystitis.

Data analysis: Data were analyzed using SPSS 25. Continuous variables including age, duration of diabetes, and duration of DPP-4 inhibitor use, were presented as Mean ± standard deviation (SD), while categorical variables, including gender, socioeconomic status, physical activity level, gallstones, biliary sludge, and acute cholecystitis, were expressed as frequencies and percentages. Comparisons of the primary outcomes between the two groups were performed using the Chi-square test. The association between DPP-4 inhibitor use and biliary outcomes was assessed using Odds ratios (ORs) with 95% confidence intervals (CIs). A p-value of ≤0.05 was taken as statistically significant.

Results:

A total of 700 T2DM patients were enrolled in this study, where each group had 350 patients.

Summary of demographic and clinical characteristics of patients receiving DPP-4 inhibitors and those receiving other antidiabetic medications are shown in Table-1.

Table-1: Demographic and clinical characteristics n = 700

demographic and clinical characteristics		DPP-4 Inhibitors (n=350)	Other medication (n=350)
Age (Mean ± SD) years		52.5 ±13.3	54.0 ± 13.2
Gender	Male n (%)	185(52.9 %)	172(49.1%)
	Female n)	165(47.1%)	178(50.9%)
Socioeconomic status	Low n (%)	99(28.3%)	109(31.1%)
	Middle n %)	184(52.6%)	169(48.3%)
	High n (%)	67(19.1%)	72(20.6%)
Physical Activity level	Sedentary n(%)	141(40.3%)	141(40.3%)
	Moderate n(%)	142(40.6%)	135(38.6%)
	Active n (%)	67(19.1%)	74(21.1%)
Duration of Diabetes (Mean ± SD) years		10.1 ± 5.4	10.5 ± 5.5
Duration of DPP-4 inhibitors use (Mean ± SD) years		1.8 ± 0.7	N/A

The results of primary outcomes showed that patients receiving DPP-4 inhibitors had a significantly higher frequency of acute cholecystitis compared to those receiving other antidiabetic medications. Similarly, higher frequencies of gallstones and biliary sludge were also observed in the DPP-4 inhibitor group; however, these differences were not statistically significant, as shown in Table-2.

Table-2: Frequency of biliary disease n = 700

Outcome	DPP-4 inhibitors (n=350)	Other Drugs (n=350)	OR (95% CI)	p-value
Gallstones	77 (22.0%)	56 (16.0%)	1.48 (0.99–2.20)	0.153
Biliary Sludge	84 (24.0%)	64 (18.3%)	1.41 (0.97–2.05)	0.076
Acute cholecystitis	56 (16.0%)	35 (10.0%)	1.71 (1.09–2.68)	0.027

Discussion:

We aimed to study the association of DPP-4inhibitors with biliary disease and acute cholecystitis among T2DM patients. Results from our data revealed that the rates of biliary diseases including acute cholecystitis were higher in T2DM patients using DPP-4 inhibitors. Hence DPP-4 inhibitors usage was significantly associated with a higher risk of either condition. These observations underscore the importance of paying attention to the state of biliary health in patients with diabetes who are on DPP-4 inhibitors' treatment. Thus, it is recommended to follow up such research with prospective studies to elucidate the direct link and factors that underlie such a connection.

Recent researches have exposed a connection between DPP-4 inhibitors and problems related to biliary functions.

In line with our results, Shapiro SB et al., in a large population-based cohort study from the UK showed that the use of DPP-4 inhibitors was associated with significantly higher risk of gallbladder and bile duct disease compared to SGLT-2 inhibitors (HR 1.46; 95% CI 1.17–1.83).[13]

A recent meta-analysis by Yu M et al. comprising 75 randomized controlled trials with 97,150 patients showed a significant association with gallbladder or biliary diseases (RR 1.38, 95% CI 1.08–1.75) but no association with cholelithiasis or other biliary disease. The risk was higher for older patients and those who had been on DPP-4 inhibitors for a longer duration. The results were similar to our findings showing a significantly higher prevalence of acute cholecystitis in patients with DPP-4 inhibitors, and no differences were seen in the prevalence of gallstones and biliary sludge.[14]

Similar results were shared by He L et al. in large systematic review and meta-analysis of 82 randomized controlled trials (RCTs) with 104,833 patients, DPP-4inhibitorswere shown to be associated with a significantly elevated risk of gallbladder or biliary diseases (OR 1.22, 95% CI 1.04–1.43; P=0.02), most

prominently acute cholecystitis (OR 1.43, 95% CI 1.14–1.79; P=0.004). There was no significant increase in the risk for cholelithiasis or other biliary disorders. More specifically, the association seemed to be stronger for those who had been on the DPP-4 inhibitors the longest. These findings are similar to our results, showing that users of DPP-4 inhibitors had a significantly higher occurrence of acute cholecystitis, and of gallstones and biliary sludge, but not significantly.[12]

Dong YH et al. in a large retrospective cohort study conducted in the Taiwan investigated 78,253 propensity score matched patients with T2DM and identified a higher risk of biliary-related diseases with incretin-based therapy than with SGLT2 inhibitors. Using GLP-1RA was significantly associated with higher risks of composite biliary disease (HR 1.27, 95% CI 1.05–1.53), acute cholecystitis or cholecystectomy (HR 1.29, 95% CI 1.04–1.58), and choledocholithiasis (HR 1.74, 95% CI 1.23–2.46) in the intention-to-treat analysis. This heightened risk was more pronounced in older patients, women and patients with longer treatment exposure. While this study compared GLP-1 receptor agonists rather than DPP-4 inhibitors, the study results are in line with the increased incidence of biliary complications found with incretin-based therapy, which is similar to the much higher incidence of acute cholecystitis observed among DPP-4 inhibitor users in our study.[15]

In contrast to above findings, some studies have not found any safety signal with DPP-4 inhibitors. In a study by Yang YS et al. concluded no significant association of DPP-4 I and a higher risk of recurrent acute pancreatitis (HR 0.68, 95% CI 0.42–1.09). Hence, the authors concluded that DPP-4inhibitorsdemonstrates a neutral safety profile, highlighting the ongoing controversy regarding the adverse effects of incretin-based therapies.[16]

Importantly, our study provides regional data from Pakistan which is a gap in the literature.

The increased risk of biliary disease and acute cholecystitis may represent adverse reactions to DPP-4 inhibitors that healthcare providers should be aware of when prescribing these agents. Again, careful treatment plans tailored to the respective individual with T2DM but also considering their most likely future way of living is necessary for effective management.

In the context of T2DM's worldwide eruption and complications, these results are relevant for health-promotion strategies designed to help decrease diabetes. These risks can be minimized through patient education regarding potential side effects and the promotion of a healthy lifestyle. Moreover, this research addresses a Pakistani population and is relevant for other low- to middle-income countries experiencing diabetes epidemic pressures with scarce healthcare resources.

Future research might consider longitudinal studies to determine causality of DPP-4 inhibitors with biliary disease. Further studies on the mechanisms are warranted to uncover the underlying biological pathways. Researching the effects of different lengths and doses of DPP-4 inhibitors in Pakistani population may offer further guidance as to which treatment strategies are preferable with a balanced level of risk.

This study has several novel aspects. It provides an integrated representation of demographic, clinical and Lab characteristics to give a broad view on the risk profile for use with DPP-4 inhibitors in treatment of T2D. This also makes the data from Pakistan a practical addition for similar healthcare professionals working in other countries and facing comparable stress. This multivariable approach highlights the importance of broader patient health parameters for cost-benefit analysis.

This study has certain limitations. The results of this single-center, hospital-based study and among patients attending a diabetic outpatient clinic may not be representative of the general population of type 2 diabetes mellitus patients. In addition, the cross-section design does not allow for a causal association between the use of DPP-4 inhibitors and biliary disease.

Conclusion:

Recent studies point towards a relatively large risk of biliary disease and acute cholecystitis during DPP-4 inhibitor use in patients with T2DM. These results demonstrate the importance of close surveillance along with an individualized treatment strategy. There is the need for future longitudinal studies, mechanistic insights and detailed analyses of doses regimens before reaching definitive conclusions on how indeed DPP-4 inhibitors causes these pathologies. Filling in these important gaps with well-conducted research will lead to more effective strategies for mitigating the risks of DPP-4 inhibitors, and - hopefully-better patient care and outcomes.

Disclaimer: NO

Conflict of interest: NO

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