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Original Research Article

Gallbladder Diseases: Assessment of Risk Factors and Association with Type 2 Diabetes Mellitus in Tertiary Care Hospitals of Rawalpindi and Islamabad

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Abstract: Gallbladder diseases are among the most common gastrointestinal conditions encountered in outpatient settings, with some evidence suggesting a higher prevalence among individuals with diabetes mellitus. This cross-sectional study aimed to identify risk factors associated with gallbladder diseases, particularly cholelithiasis and cholecystitis, and to evaluate the relationship between type 2 diabetes mellitus and gallbladder disease in symptomatic patients. The study was conducted over six months across multiple tertiary care hospitals in Rawalpindi and Islamabad and included 254 symptomatic patients presenting to surgical departments. Data were collected using a structured questionnaire, and statistical analysis was performed using SPSS version 27. The majority of participants were female (72.8%) and over 45 years of age (53.1%), with 53.9% having a normal body mass index. Type 2 diabetes mellitus was present in 24.8% of patients, and gallbladder disease was detected on ultrasound in 82.3% of cases. A significant association was observed between gallbladder disease and the use of estrogen–progestin medications ($p = 0.010$). No significant associations were found with diabetes mellitus, age, gender, body mass index, smoking status, physical activity, hypertension, lipid-lowering medication use, family history of diabetes, or parity. The findings indicate that type 2 diabetes mellitus is not significantly associated with gallbladder disease among symptomatic patients in this regional population, while hormonal medication use may represent an important risk factor.

Keywords: Cholelithiasis, Estrogen–Progestin Therapy, Gallbladder Disease, Type 2 Diabetes Mellitus.

INTRODUCTION

Studies reveal that Gallbladder Diseases are one of the most common gastrointestinal diseases in outpatient departments [1]. Globally gallstone prevalence in adult population is 10-20%, predominantly affecting female population and risk increases with advancing age [2]. According to the latest International Diabetes Federation (IDF) data, the estimated number of people suffering from Diabetes Mellitus Worldwide is 537 million individuals, with up to 7 million individuals being reported in Pakistan only. This number is expected to increase to 643 million by 2030 [3]. Previous studies have demonstrated multiple risk factors associated with gallbladder diseases including age, race, pregnancy, gender, obesity, diabetes and high total cholesterol [4]. Premenopausal women seem to have a higher risk, partly due to sex hormones, oestrogen in particular, increased biliary cholesterol secretion and super saturation of bile, and partly due to pregnancy as a major risk factor for gallstone formation [5].

Wide variety of complications arising from gallstone diseases include biliary colic, acute cholecystitis, choledocholithasis, acute pancreatitis and cholangitis [6]. In addition to other complications seen in DM type II patients, autonomic neuropathy is one of the pathological states with a lot of clinical manifestations [7]. It leads to a hypotonic gallbladder, resulting in stasis and ultimately diseases like cholecystitis and cholelithiasis develop [8]. Vagal neuropathy is the

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underlying mechanism for development of hypotonic gallbladder [9].

Studies have shown that there is no definitive evidence that diabetes increase the incidence of cholelithiasis but cholecystitis seems to be more common and severe in diabetic patients [10]. Cholelithiasis arise from metabolic, genetic and environmental factors that change bile composition and increase stone formation whereas cholecystitis occur as a result of inflammation and ischemia when a gallstone obstructs cystic duct [11]. Diabetics patients undergoing Laparoscopic cholecystectomy have significantly increased risk of acquiring postoperative wound infections than non-diabetics, predominantly with poor glycemic control [12]. Poorly controlled diabetes is linked with increased incidence of emergency cholecystectomy, intraoperative complications, shifting from laparoscopic to open surgery and decreased overall favorable outcomes as compared to non-diabetic patients [13].

Although national studies confirm a high prevalence of type 2 diabetes in Pakistan and some local researches provide information about gallbladder diseases, there is limited data specifically examining the association between type 2 diabetes and gallbladder diseases in Rawalpindi and Islamabad region [14, 15]. It aims to find the association of NIDDM with gallbladder diseases in both genders and ascertain the prognostic factors concerning the pathologies. Bridging the knowledge gap for better healthcare services and improved quality of life is the foremost aspect of this study. It highlights the importance of educating future healthcare providers on gallbladder diseases, particularly those with a history of NIDDM, in particular.

METHODS

A cross-sectional study was conducted at the DHQ Hospital, Benazir Bhutto Hospital (BBH), Holy Family Hospital (HFH), Fouji Foundation Hospital, and Rawal General and Dental Hospital. Data collection was conducted over a six-month period, from January 2025 to June 2025. The methodology and reporting of this study adhere to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies [16].

The sample size was calculated using the formula for single population proportion, taking a gallstone prevalence of 13.6% from prior studies of Iraq [17], with a 5% margin of error, 95% confidence level, and adjusting for a 10% non-response rate, resulting in a final target sample of 254 patients with gallbladder diseases presenting to the surgical departments of these allied hospitals. This is a mixed population of diabetics and non-diabetics from which the diabetic subset was analyzed. Since missing, the demographic information was excluded. The final 254 questionnaires were analyzed for this study.

A non-probability convenience sampling was used to recruit participants. Although this sampling technique introduces bias in study but it is cost effective and less time consuming. The bias could have come from the investigators selecting patients on the basis of severity of symptoms. Patients who consented to and completed the questionnaire were included, while those who declined, submitted incomplete responses, or had previously undergone cholecystectomy were excluded. Data were collected using a structured Google Form questionnaire, which consisted of five main sections: Section A (socio-demographic characteristics; questions 1–8), Section B (family history; questions 9–11), Section C (past medical/surgical history; questions 12–25), Section D (diabetes history; questions 26–39), and Section E (risk factors; questions 41–46). Investigators interviewed the patients and recorded data in Google forms. Ethical approval was obtained from the Institutional Review Committee (IRC) of Rawalpindi Medical University & Allied Hospitals Rawalpindi, Pakistan [Ref. No: 1247/IREF/RMU/2025].

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 27. Continuous data are reported as mean and standard deviation, and compared using independent sample t-tests. Categorical data is reported as gross numbers and percentages (n; %) and compared using chi-squared tests. A p-value of < 0.05 is considered significant.

RESULTS

A total of 254 participants were included in the study (Table 1). The majority of respondents were female (185; 72.8%), while 69 (27.2%) were male. Most participants were over the age of 45 years (135; 53.1%), with the largest age subgroup being 36–45 years (79; 31.1%), followed by 46–55 years (66; 26.0%). Regarding nutritional status, 137 (53.9%) participants had a normal body mass index (BMI), 61 (24.0%) were overweight, and 24 (9.4%) were classified as obese (Figure 1). A smaller proportion, 32 (12.6%), were underweight. In terms of educational background, 85 (33.5%) participants had completed secondary education, 65 (25.6%) had received primary education, while 17 (6.7%) reported tertiary-level education. A total of 57 (22.4%) were grouped under 'other' education, and 30 (11.8%) had no formal education.

Table 1: Socio-demographic and baseline clinical characteristics of study participants (n = 254)

Variable	Frequency (%)
Gender	
Male	69 (27.2)
Female	185 (72.8)
Age group	
25–35 years	40 (15.7)
36–45 years	79 (31.1)
46–55 years	66 (26.0)
>55 years	69 (27.2)
BMI category	
Normal	137 (53.9)
Overweight	61 (24.0)
Obese	24 (9.4)
Underweight	32 (12.6)
Educational level	
No formal education	30 (11.8)
Primary education	65 (25.6)
Secondary education	85 (33.5)
Tertiary education	17 (6.7)
Other	57 (22.4)
Family history of DM	
Yes	117 (46.1)
No	137 (53.9)
Type 2 Diabetes Mellitus	
Yes	63 (24.8)
No	191 (75.2)

A positive family history of diabetes mellitus was reported by 117 (46.1%) participants. Type 2 diabetes mellitus was present in 63 (24.8%) individuals (Figure 2). Ultrasonographic examination revealed that 209 (82.3%) participants had gall-bladder disease, whereas 45 (17.7%) had a normal gall-bladder appearance. This finding suggests a high burden of gallbladder pathology in the study population.

Lifestyle and metabolic characteristics were assessed across the cohort (Table 2). The majority of participants were non-smokers (223; 87.8%), while 31 (12.2%) reported current or former smoking. A substantial proportion, 163 (64.2%), engaged in regular physical activity of at least 30 minutes per day, whereas 91 (35.8%) did not. Hypertension was present in 82 (32.3%) individuals, while 31 (12.2%) were using lipid-lowering medications.

Table 2: Distribution of lifestyle, metabolic, and reproductive characteristics

Variable	Yes n (%)	No n (%)
Smoker	31 (12.2)	223 (87.8)
Physically active ≥30 min/day	163 (64.2)	91 (35.8)
Hypertensive	82 (32.3)	172 (67.7)
Uses cholesterol medication	31 (12.2)	223 (87.8)
Uses oral contraceptive pills	7 (2.8)	247 (97.2)
History of estrogen–progestin use	45 (17.7)	209 (82.3)

Only 7 (2.8%) participants reported the use of oral contraceptive pills, while 45 (17.7%) had used estrogen–progestin drugs for non-contraceptive purposes. Among female participants, parity was distributed as follows: 42 (22.7%) had 0–2 children, 89 (48.1%) had 3–5 children, and 52 (28.1%) had more than 5 children.

To examine potential associations between gallbladder disease and the studied risk factors, chi-square tests were performed (Table 3). A statistically significant association was found between the use of estrogen-progestin medications and the presence of gallbladder disease ($p = 0.010$). Participants who had a history of using these hormonal agents showed a notably higher frequency of gallbladder pathology (95.6%) compared to those who did not (79.4%). No statistically significant associations were observed between gallbladder disease and other variables, including sex ($p = 0.779$), age group ($p = 0.190$), BMI category ($p = 0.173$), family history of diabetes ($p = 0.815$), smoking status ($p = 0.216$), hypertension ($p = 0.450$), use of cholesterol-lowering medication ($p = 0.287$), or physical inactivity ($p = 0.765$). Among female respondents, no

significant association was observed between parity and gallbladder disease (p = 0.693).

Table 3: Bivariate association between gall-bladder disease and selected variables

Variable	Category	GBD Present n (%)	GBD Absent n (%)	χ^2	p-value
Gender	Male	56 (81.2)	13 (18.8)	0.078	0.779
	Female	153 (82.7)	32 (17.3)		
Age Group	25–35 years	35 (87.5)	5 (12.5)	4.764	0.190
	36–45 years	66 (83.5)	13 (16.5)		
	46–55 years	55 (83.3)	11 (16.7)		
	>55 years	53 (76.8)	16 (23.2)		
BMI Category	Underweight	23 (71.9)	9 (28.1)	4.980	0.173
	Normal	112 (81.8)	25 (18.2)		
	Overweight	53 (86.9)	8 (13.1)		
	Obese	21 (87.5)	3 (12.5)		
Family History of Diabetes	Yes	96 (82.1)	21 (17.9)	0.055	0.815
	No	113 (82.5)	24 (17.5)		
Smoking Status	Yes	24 (77.4)	7 (22.6)	1.532	0.216
	No	185 (83.0)	38 (17.0)		
Hypertension	Yes	70 (85.4)	12 (14.6)	0.571	0.450
	No	139 (80.8)	33 (19.2)		
Cholesterol Medication Use	Yes	24 (77.4)	7 (22.6)	1.135	0.287
	No	185 (83.0)	38 (17.0)		
Estrogen–Progestin Use	Yes	43 (95.6)	2 (4.4)	6.610	**0.010**
	No	166 (79.4)	43 (20.6)		
Physical Activity <30 min/day	Yes	76 (83.5)	15 (16.5)	0.089	0.765
	No	133 (81.6)	30 (18.4)		
Parity (among females)	0–2 children	42 (79.2)	11 (20.8)	0.734	0.693
	3–5 children	89 (87.3)	13 (12.7)		
	>5 children	52 (86.7)	8 (13.3)		

The relationship between type 2 diabetes mellitus and gallbladder disease was also evaluated. Among diabetic participants, 87.3% (55 out of 63) had gallbladder disease, compared to 80.6% (154 out of 191) among non-diabetics. However, this difference was not statistically significant ($\chi^2 = 1.447$, df = 1, p = 0.229), indicating that the presence of type 2 diabetes mellitus was not associated with an increased risk of gallbladder disease in this sample.

DISCUSSION

In the Rawalpindi and Islamabad region, limited studies have specifically assessed risk factors in symptomatic gallbladder patients. While gallbladder diseases such as cholelithiasis and cholecystitis are common among asymptomatic individuals, this study aimed to identify risk factors in symptomatic patients.

Our findings revealed a significant association between the use of oral contraceptive pills (OCPs) and the development of gallbladder disease. However, no significant correlation was found between gallbladder disease and smoking, body mass index (BMI), type 2 diabetes mellitus, sex, age group, family history of diabetes, hypertension, cholesterol-lowering drugs, physical inactivity, or parity. This study focused particularly on having type 2 diabetes mellitus among symptomatic individuals. The lack of association between type 2 diabetes and gallbladder disease maybe due to low statistical power, particularly given the relatively small number of diabetic subjects (n=63). In contrast, previous studies in Rawalpindi and Islamabad included both symptomatic and asymptomatic participants, which may explain the variation in findings.

In this study, 82.3% of symptomatic patients showed gallbladder pathology on imaging modalities such as ultrasound and CT scans. This prevalence is comparable to an ICU-based study, where 84% of patients exhibited sonographic abnormalities despite the absence of symptoms, indicating undiagnosed early-stage disease [18]. Although gender was not significantly associated with gallbladder disease, the majority of participants were female (72.8%), with males comprising 27.2%. This is a limitation of the study that more of the symptomatic female patients were found in the surgical wards. However, among these female patients, OCP as a risk factor proved significant.

Our results align with a study from Iraq regarding hypertension. A p-value of 0.450 in our study indicates no significant association between hypertension and gallbladder disease, consistent with the Iraqi study's findings [19]. Although both conditions may coexist as components of metabolic syndrome, they

develop through distinct pathophysiological mechanisms.

A significant association was noted between gallbladder disease and estrogen–progestin medication use. Supporting this, a 2024 review encompassing 925 articles concluded that long-term hormone therapy (HT) increases the risk of gallstone formation [20]. Estrogen therapy elevates biliary cholesterol saturation in both sexes by enhancing hepatic cholesterol uptake and synthesis, leading to bile supersaturation, cholesterol crystal formation, and ultimately gallstone development. However, this effect does not apply to HT used in cases of hypogonadism or surgical menopause.

Regarding lifestyle factors, no significant association was found between gallbladder disease and either physical inactivity or smoking. A p-value of 0.216 was observed for smoking in our study. A 2023 study from Peshawar supports this finding [21], although a 2018 study in the Indian Journal of Community Health suggested a potential link between tobacco use and gallbladder disease through its effects on HDL cholesterol, prostaglandin synthesis, and mucus production. These findings, however, were not reflected in our sample. Since our sample has a majority female gender and there are cultural, social, and moral restraints on smoking in women, a potential association couldn't be found.

In Pakistan, some studies have associated abnormal lipid profiles, particularly elevated triglyceride levels, with cholelithiasis [22]. However, links between statin use and gallbladder disease are primarily based on international research [23]. While our study did not find a significant association between parity and gallbladder disease, previous literature suggests a positive correlation [24].

This study is distinct in its exclusive focus on symptomatic gallbladder patients from the Rawalpindi and Islamabad region, which may account for the differences in observed associations. Imaging modalities, comprehensive data collection, and statistical rigor are strong features of our study. However, there are certain limitations. Future longitudinal studies with a larger and more diverse sample, including a higher proportion of obese individuals (currently 9.4% of our sample and OCP users, 2.8%), are recommended to enhance the generalizability of findings.

The study has limited generalizability, which does not reflect the risk profile of broader or asymptomatic patient, also convenience sampling was used data collection which introduces selection bias and limits generalizability of findings. Univariate analysis was performed, due to which certain confounders like age, gender, physical inactivity, obesity may interfere with the findings as they were not adjusted. Our study design is cross-sectional which limits to determine the temporal relationships between variables. For future researchers, including asymptomatic controls is suggested. That way, the public health care gap will be bridged better.

CONCLUSION

This study underscores the need to revisit commonly held assumptions regarding the role of type 2 diabetes in gallbladder disease. While estrogen–progestin therapy emerged as a significant risk factor, other expected associations, such as with BMI, diabetes, and hypertension, were not statistically significant in symptomatic patients. These findings call for more focused public health screening strategies that go beyond diabetes status alone. Future studies should adopt a broader design—ideally multicenter, longitudinal, and inclusive of asymptomatic individuals—to enhance the applicability of results and inform region-specific clinical guidelines. Tailored awareness and screening protocols, especially for hormone therapy users, may improve early diagnosis and management outcomes.

Competing Interests: The authors declare no competing interests.

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Ethics Approval

The study was performed in accordance with the relevant guidelines and regulations and approved by the Institutional Review Board RSRS, Rawalpindi Medical University & Allied Hospitals Rawalpindi, Pakistan, Institutional Review Board, Pakistan, with a Reference Number 1247/IREF/RMU/2025. Participants gave informed consent to participate in the study before taking part.

Research registration unique identifying number (UIN)

1. Name of the registry: Research Registry.
2. Unique identifying number or registration ID: researchregistry11385
3. Hyperlink to specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry/#home/registrationdetails/687cdc0086129f02e9b9468e/

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