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Original Research Article

PREVALENCE OF ASYMPTOMATIC GALL BLADDER STONES USING ULTRASONOGRAM IN DIABETIC PATIENTS WITH CARDIAC AUTONOMIC NEUROPATHY

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ABSTRACT

Background: Diabetes mellitus is associated with multiple systemic complications, including cardiac autonomic neuropathy (CAN), which can impair gallbladder motility and predispose to gallstone formation. This study aimed to determine the prevalence of asymptomatic gallbladder stones in diabetic patients using ultrasonography and to assess their association with CAN.

Materials and Methods: This cross-sectional study was conducted at a tertiary care center in Chennai over six months. A total of 166 diabetic patients were included based on predefined inclusion and exclusion criteria. Clinical evaluation, biochemical investigations, and ultrasonography were performed. CAN was assessed using Ewing's battery of autonomic function tests. Data were analyzed using SPSS, and statistical significance was set at $p < 0.05$.

Results: Among 166 participants, 53.6% were aged 40–50 years, with females constituting 52.4%. Asymptomatic gallstones were present in 20.5% (34/166). CAN was observed in 19.9%, including early (6.6%), definitive (9.6%), and severe (3.6%). All CAN-positive patients (33/33, 100%) had gallstones, compared to only 0.75% (1/133) among CAN-negative individuals ($p < 0.001$). Among gallstone-positive cases, definitive CAN was most common (47.1%). Significant differences were observed in biochemical parameters including blood sugar ($p = 0.007$), urea ($p = 0.029$), and creatinine ($p = 0.036$). Autonomic function tests also showed significant variation across CAN categories ($p < 0.001$).

Conclusion: A strong association exists between CAN and asymptomatic gallstones in diabetic patients, with increasing prevalence across severity stages. Early screening using ultrasonography may aid in timely detection and prevention of complications.

Keywords: Diabetes Mellitus, Cholelithiasis, Autonomic Nervous System Diseases, Ultrasonography, Gallbladder.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is a major global health concern and is associated with a wide spectrum of microvascular and macrovascular complications that significantly contribute to morbidity and mortality.[1,2] Among these complications, diabetic autonomic neuropathy is a common yet frequently under-recognized condition that affects multiple organ systems. Cardiac autonomic neuropathy (CAN), one of the most clinically significant forms, involves impairment of autonomic control over heart rate and vascular dynamics and is associated with adverse cardiovascular outcomes.[3,4] Beyond its cardiovascular effects, autonomic neuropathy also plays an important role in gastrointestinal dysfunction, including abnormalities in gallbladder motility.

The gallbladder is an essential component of the biliary system, responsible for the storage and regulated release of bile during digestion. Its function is largely controlled by autonomic innervation, particularly parasympathetic stimulation via the vagus nerve. In patients with diabetes, especially those with autonomic neuropathy, this neural regulation becomes impaired, resulting in decreased gallbladder contractility and delayed emptying. Such dysfunction leads to bile stasis, which promotes cholesterol supersaturation and nucleation, thereby increasing the risk of gallstone formation.[5,6] Over time, these changes can culminate in gallbladder enlargement and reduced responsiveness to physiological stimuli.

Gallstones are one of the most common gastrointestinal disorders, and their prevalence is known to be higher in diabetic individuals compared to the general population. Many cases remain asymptomatic and are often detected incidentally during imaging studies. Despite the absence of symptoms, asymptomatic gallstones are clinically relevant as they may progress to complications such as acute cholecystitis, choledocholithiasis, or pancreatitis. Therefore, identifying at-risk populations is crucial for early detection and prevention of adverse outcomes.[7,8].

Ultrasonography is the preferred imaging modality for evaluating gallbladder pathology due to its safety, non-invasiveness, cost-effectiveness, and high diagnostic accuracy. It enables reliable detection of gallstones and assessment of gallbladder volume, which indirectly reflects gallbladder motility. In diabetic patients, especially those with autonomic dysfunction, ultrasonographic findings may reveal subclinical gallbladder abnormalities even in the absence of symptoms.[9].

Several studies have demonstrated an association between diabetes mellitus and gallstone disease, with factors such as duration of diabetes, poor glycemic control, obesity, and dyslipidemia contributing to increased risk However, studies specifically evaluating the relationship between CAN and asymptomatic gallstone formation in the Indian population remain limited, and the magnitude of this association across CAN severity grades has not been well characterized. Exploring this association is important, as autonomic dysfunction may represent a key mechanistic link between metabolic disturbances and gallbladder pathology.[4,10].

Therefore, the present study was undertaken to determine the prevalence of asymptomatic gallbladder stones using ultrasonography in diabetic patients and to evaluate their association with CAN. The objectives of the study were to identify diabetic patients with asymptomatic gallstones and to assess the relationship between the presence of CAN and gallstone formation.

MATERIALS AND METHODS

Study Design and Setting: This cross-sectional study was conducted at Government Kilpauk Medical College, Chennai, over a period of six months following approval from the Institutional Ethics Committee and written informed consent was obtained from all participants prior to enrolment (ECR/1385/Inst/TN2020).

Study Population: A total of 166 patients with known or established diabetes mellitus attending the Medicine and Diabetology outpatient department were included in the study after obtaining informed consent.

Inclusion & Exclusion Criteria

Patients with known or established diabetes mellitus were included in the study and Patients with liver and gallbladder disease, pregnancy, cholecystitis, chronic debility, and those who had undergone cholecystectomy were excluded from the study.

Sample Size calculation: The sample size was calculated using the standard formula for estimating a proportion:

$$n = \frac{Z^2 \times p \times q}{d^2}$$

Where:

n = required sample size

Z = standard normal variate at 95% confidence level (1.96)

p = expected prevalence of gallstones in diabetic patients = 20%

q = 1 − p (80%)

d = allowable error (6.2%)

Substituting the values:

$$n = \frac{(80}{(6.2)^2} n = \frac{3.84 \times 20 \times 80}{38.44} n = 166$$

Thus, the calculated sample size for the study was 166 participants.

Methods: All eligible diabetic patients were enrolled based on the inclusion and exclusion criteria. CAN was assessed using Ewing's battery of autonomic function tests. CAN was diagnosed and graded using Ewing's battery of five standardized cardiovascular reflex tests. CAN grading was defined as: Normal- all tests within normal limits; Early involvement- one parasympathetic test abnormal; Definitive involvement- two or more parasympathetic tests abnormal; Severe- additional sympathetic involvement with postural hypotension. Clinical evaluation included measurement of blood pressure in the sitting position after adequate rest, height using a wall-mounted stadiometer, and weight in fasting state without footwear. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Laboratory investigations included fasting and postprandial blood glucose, lipid profile, renal and liver function tests, and complete blood count. Autonomic function was assessed using Ewing's tests, including deep breathing test (E:I ratio), heart rate response to standing (30:15 ratio), Valsalva maneuver, blood pressure response to postural change, and sustained handgrip test. Ultrasonography of the abdomen was performed to detect gallbladder stones and assess gallbladder volume.

Statistical Analysis: Data were analyzed using SPSS software. Continuous variables were expressed as mean ± standard deviation and categorical variables as frequency and percentage. The prevalence of asymptomatic gallstones was calculated. Association between CAN (CAN) and gallstones was assessed using the Chi-square test. Differences across CAN categories were analyzed using ANOVA. A p value < 0.05 was considered statistically significant.

RESULTS

Most were aged 40–50 years (53.6%), with a near-equal gender distribution (females 52.4%, males 47.6%). Asymptomatic gallstones were present in 20.5%, while 79.5% had no gallstones. CAN was present in 19.9%, including early (6.6%), definitive (9.6%), and severe (3.6%) [Table 1].

Table 1: Demographic and Clinical Characteristics of Study Participants

Variable	Category	Frequency n(%)
Age Group	40-50 years	89 (53.6%)
	51-60 years	77 (46.4%)
Gender	Female	87 (52.4%)
	Male	79 (47.6%)
Gall Bladder Volume	Distended	34 (20.5%)
	Normal	132 (79.5%)
Gall Stones	Absent	132 (79.5%)
	Present	34 (20.5%)
Grading of Autonomic Neuropathy	Normal	133 (80.1%)
	Early involvement	11 (6.6%)
	Definitive involvement	16 (9.6%)
	Severe	6 (3.6%)

The mean weight, height, and BMI were 61.0 ± 11.2 kg, 160.1 ± 8.2 cm, and 23.83 ± 4.19 kg/m². Biochemical parameters were largely within normal limits, with mean total bilirubin 0.84 ± 0.02 mg/dL, ALT 25.25 ± 3.31 U/L, AST 19.93 ± 2.66 U/L, total protein 72.18 ± 6.88 g/L, albumin 2.20 ± 0.12 g/dL, and globulin 29.37 ± 3.99 g/L. Lipid profile showed mean triglycerides 185.1 ± 9.2 mg/dL and total cholesterol 203.73 ± 3.78 mg/dL. Autonomic function tests demonstrated a mean Valsalva ratio of 1.18 ± 0.04, R–R interval 17.62 ± 5.01, 30:15 ratio 0.99 ± 0.27, fall in systolic blood pressure 10.4 ± 7.2 mmHg, and rise in diastolic blood pressure 22.43 ± 5.17 mmHg [Table 2].

Table 2: Mean Anthropometric and Biochemical Parameters

Main Variable	Sub Variable	Mean ± SD
Anthropometric	Weight (kg)	61.0 ± 11.2
	Height (cm)	160.1 ± 8.2
	BMI	23.83 ± 4.19
Biochemical	Total bilirubin (mg/dl)	0.84 ± 0.02
	ALT (IU/L)	25.25 ± 3.31
	AST (U/L)	19.93 ± 2.66
	Total protein (g/L)	72.18 ± 6.88
	Albumin (g/dl)	2.20 ± 0.12
	Globulin (g/L)	29.37 ± 3.99
	Triglycerides (mg/dl)	185.1 ± 9.2
	Total cholesterol (mg/dl)	203.73 ± 3.78
Autonomic Function Tests	Valsalva ratio	1.18 ± 0.04
	R-R interval (beats/min)	17.62 ± 5.01
	30:15 ratio	0.99 ± 0.27
	Fall in systolic response (mmHg)	10.4 ± 7.2
	Increase in diastolic BP (mmHg)	22.43 ± 5.17

All patients with CAN (33/33, 100%) had gallstones, only 1of CAN-negative patients had gallstones [Table 3].

Table 3: Prevalence of Asymptomatic Gallstones by CAN Status

CAN Status	Total n	Gallstones Present n(%)	Gallstones Absent n(%)
CAN Positive (Early + Definitive + Severe)	33	33 (100%)	0
CAN Negative (Normal)	133	1 (0.75%)	132 (99.25%)

Among gallstone-positive patients, CAN was present in nearly all cases, predominantly definitive (47.1%), early (32.4%), and severe (17.6%), with only 2.9% normal. A similar significant association was seen in males and females (p < 0.001). Biochemical parameters also showed statistically significant differences across CAN categories, including blood sugar (p = 0.007), urea (p = 0.029), and creatinine (p = 0.036). All autonomic function tests differed significantly across CAN categories (p < 0.001) [Table 4].

Table 4: Association Between Asymptomatic Gallstones and CAN

Section	Variable / Category	Definitive	Early	Normal	Severe	P value
Gallstones vs CAN (All Participants)	Absent	0	0	132 (100.0%)	0	<0.001
	Present	16 (47.1%)	11 (32.4%)	1 (2.9%)	6 (17.6%)	
	Total	16 (9.6%)	11 (6.6%)	133 (80.1%)	6 (3.6%)	
Gallstones vs CAN (Males)	Normal	0	0	132 (100.0%)	0	<0.001
	Present	16 (47.1%)	11 (32.4%)	1 (2.9%)	6 (17.4%)	
Gallstones vs CAN (Females)	Absent	0	0	21 (100.0%)	0	<0.001
	Normal	0	0	52 (100.0%)	0	
	Present	4 (28.6%)	6 (42.9%)	1 (7.1%)	3 (21.4%)	
Biochemical Parameters vs CAN	Blood Sugar (mg/dL)	321.56 ± 87.11	328.36 ± 65.94	284.11 ± 54.48	323.83 ± 36.32	0.007
	Urea (mg/dL)	11.56 ± 3.65	15.55 ± 4.39	13.98 ± 3.97	11.67 ± 3.50	0.029
	Creatinine (mg/dL)	1.08 ± 0.12	0.97 ± 0.09	1.02 ± 0.11	0.97 ± 0.10	0.036
Autonomic Function Tests vs CAN	Valsalva Ratio	1.23 ± 0.04	1.18 ± 0.02	1.17 ± 0.03	1.23 ± 0.03	<0.001
	R-R Interval (beats/min)	8.94 ± 1.12	10.00 ± 1.55	19.71 ± 2.95	8.33 ± 1.03	
	30:15 Ratio	0.41 ± 0.31	1.10 ± 0.03	1.09 ± 0.03	0.23 ± 0.06	
	Fall in Systolic BP (mmHg)	22.44 ± 9.29	9.18 ± 1.25	7.89 ± 1.82	35.00 ± 2.90	
	Increase in Diastolic BP (mmHg)	23.19 ± 4.55	23.09 ± 5.17	22.93 ± 4.38	8.00 ± 1.27	

DISCUSSION

Diabetes mellitus is associated with metabolic disturbances affecting multiple systems, including the hepatobiliary tract,can impair gallbladder motility, leading to bile stasis and asymptomatic gallstone formation. This study aimed to assess the prevalence of asymptomatic gallstones in diabetic patients and their association with CAN. The findings showed a higher frequency of gallstones in patients with CAN, increasing with its severity. The results highlight the need for early screening in diabetic patients.

In our study, the study population consisted predominantly of middle-aged diabetic individuals with a slight female predominance, with a subset showing asymptomatic gallstones and a varying grades of CAN. Similarly, Ratheesh et al. reported a comparable demographic profile with females constituting 51.5% and a mean age of 51.3 ± 17.8 years, with gallstone prevalence of 11.2% and a significantly higher rate among diabetics compared to non-diabetics (OR = 2.30; $p < 0.001$, adjusted OR = 1.52; $p < 0.001$).[11] Similarly, Wang et al. in a large systematic review of over 32 million participants reported higher gallstone prevalence in females than males (7.6% vs 5.4%) with increasing age.[12] Similarly, Ning et al. further reported female sex, age above 50 years, and diabetes as significant risk factors.[13] These findings collectively suggest that the demographic profile of our study aligns with established risk patterns for gallstone disease.

In our study, anthropometric parameters were within normal limits, while biochemical values showed a tendency toward dyslipidemia, and autonomic function measures varied across participants. Similarly, Li et al. reported that each one-unit increase in triglyceride-glucose (TyG) index was associated with a 41% higher risk of gallstones (OR 1.41, 95% CI 1.07–1.86), particularly in individuals with total cholesterol >200 mg/dL.[14] Fu et al. further demonstrated significant positive associations between TyG-related indices (TyG-BMI, TyG-WC, TyG-WHtR) and gallstone disease.[15] Likewise, Gong et al. found a positive association between TyG index and gallstones (OR 1.10, 95% CI 1.01–1.21), with stronger effects in individuals with elevated lipid levels.[16] Although TyG indices were not directly measured in our study, the presence of elevated triglycerides and cholesterol in our population supports the role of metabolic imbalance in gallstone formation.

In our study, asymptomatic gallstones were predominantly observed in patients with CAN, with minimal occurrence in those without autonomic dysfunction. Similarly, a study by Shirale and Zawar, reported gallbladder disorders in 47.76% (32/67) of diabetic patients with autonomic neuropathy compared to 11.76% (4/34) without neuropathy.[17] Similarly, Hillson reported that autonomic neuropathy leads to impaired gallbladder emptying, bile stasis, and subsequent gallstone formation.[18] Similarly, Jones et al. also reported reduced gallbladder contraction due to autonomic dysfunction.[8] These findings suggest that autonomic neuropathy plays a central role in gallstone pathogenesis through impaired motility and bile stasis.

In our study, a significant association was observed between asymptomatic gallstones and CAN, with the association increasing across severity categories. Similarly, Channakeshavamurthy et al. reported that gallbladder volume was higher in patients with severe autonomic neuropathy (55.8 ± 9.9 ml) compared to those without neuropathy (18.5 ± 5.01 ml; $p < 0.05$).[19] Similarly, Karthikeyan et al. resulted that autonomic function tests such as Valsalva ratio and 30:15 ratio reliably differentiate stages of neuropathy.[20] Furthermore, Gogan et al. reported that CAN is an underdiagnosed complication with systemic implications.[4] These findings suggest that progressive autonomic dysfunction, along with metabolic abnormalities, contributes significantly to gallstone formation, emphasizing the importance of early detection and screening in diabetic patients.

This study demonstrates a strong association between CAN and asymptomatic gallstones in diabetic patients, with increasing prevalence across severity stages. These findings suggest that autonomic dysfunction and metabolic imbalance contribute to gallstone formation, highlighting the importance of early detection and screening.

Limitation: This study was limited by its cross-sectional design, which prevents establishing causality. The relatively small sample size and single-center setting may affect generalizability. Long-term outcomes and temporal relationships between CAN and gallstone formation could not be assessed. Future longitudinal, multicenter studies with larger sample sizes are needed to confirm causal relationships.

CONCLUSION

This study demonstrated a significant association between CAN and asymptomatic gallstone disease among patients with diabetes mellitus. The prevalence of asymptomatic gallstones was higher in patients with CAN, particularly among those with definitive and severe autonomic dysfunction. Alterations in autonomic function tests and metabolic parameters further supported the role of autonomic imbalance and metabolic disturbances in gallstone formation. CAN may contribute to impaired gallbladder motility and bile stasis, thereby increasing the risk of gallstone development in diabetic patients. Early screening and evaluation for gallstones in diabetic individuals with autonomic neuropathy may help in timely identification and prevention of related complications.

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