Original paper

The association between diabetes and gallstones: a nationwide population-based cohort study

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Gastroenterology Rev 2023; 18 (3): 292–299
DOI: https://doi.org/10.5114/pg.2023.131395

Key words: diabetes mellitus, cholelithiasis, gallstones, association.

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Abstract

Introduction: Evidence regarding the association between diabetes mellitus (DM) and cholelithiasis is still inconsistent.

Aim: To examine the association between diabetes and gallstones and the commonly associated factors in a nationwide population-based cohort investigation.

Material and methods: The demographic and outcome variable data were extracted from the National Health and Nutrition Examination Survey (NHANES) database for the years 2017–2018.

Results: A total of 5376 individuals were included in the final analysis, with a mean age of 51.3 ±17.8 years. Females constituted 51.5% of the included individuals, and the overall mean body mass index (BMI) was 29.8 ±7.4 kg/m^2. The prevalence of diabetes was 16.2% among the included individuals, with a mean age of 50.6 ±13.6 years at diagnosis of diabetes, and only 4.5% were taking insulin. The prevalence of cholelithiasis was 11.2%, with a mean age of 44.4 ±16.1 years at diagnosis, and 11.3% had previous cholecystectomy (gallbladder surgery.) There was a significant increase in gallstone rates among diabetic patients as compared to non-diabetics in the unadjusted (OR = 2.30; 95% CI: 1.89–2.79; $p < 0.001$) and adjusted (OR = 1.52; 95% CI: 1.20–1.92; $p < 0.001$) models. Moreover, this association was not time-dependent where the "age when first told you had diabetes" did not show a significant influence on the gallstone rate, whether in unadjusted (OR = 1.01; 95% CI: 1.00–1.02; $p = 0.221$) or adjusted (OR = 1.01; 95% CI: 0.99–1.03; $p = 0.395$) models. Furthermore, insulin usage was found to be a significant predictor of cholelithiasis, whether in unadjusted (OR = 2.39; 95% CI: 1.74–3.28; $p < 0.001$) or adjusted (OR = 1.52; 95% CI: 1.05–2.19; $p = 0.026$) models.

Conclusions: DM and insulin therapy are possible risk factors for developing cholelithiasis.

Introduction

Diabetes mellitus (DM) is a syndrome characterized by hyperglycaemia, which leads to damage to the body's tissues. Diabetes is also one of the world's most common diseases, and it exerts severe healthcare burdens due to various associated complications such as nephropathy, neuropathy, retinopathy, peripheral vascular disease, and ischaemic heart disease. Estimates show that around 382 million individuals suffered from DM globally in 2013, and the numbers are expected to increase every year, reaching 592 million patients in 2035 [1]. The incidence of the 2 main types of diabetes, type 1 (T1DM) and type 2 (T2DM), is 15% and 85%, respectively [1]. T1DM results from insulin deficiency, while T2DM results from insulin resistance. In addition, current evidence suggests that DM is associated with the development of gallstones, which was found attributable to impaired gallbladder emptying and decreased bile salt secretion from the gallbladder [2–6].

Gallstones are crystalline deposits that are observed within the cavity of the gallbladder in some patients. Cholelithiasis, the disease of gallstones, affects up to 25% of adults globally [7, 8]. It has been reported that cholelithiasis is the most common gastrointestinal

disorder, frequently observed within ambulatory clinics. Diagnosis can be quickly established using abdominal ultrasonography, reported with a sensitivity rate of 90% [9]. Patients with cholelithiasis can develop severe and even life-threatening complications from the disease, including acute pancreatitis, acute cholecystitis, and obstructive jaundice with varying incidence rates [10–13].

Acute cholangitis or acute pancreatitis is the most deadly, with an estimated mortality rate of 20% for patients suffering their first episode [14]. In addition, surgery is required in up to 2% of the cases per year, representing a heavy burden on healthcare resources associated with managing this disease [15]. Investigators have identified multiple risk factors associated with the development of cholelithiasis, such as increased body mass index, reduced physical activity, high triglycerides, hyperinsulinaemia, and even insulin resistance, which may be associated with an increased risk of cholelithiasis [16–21]. In this context, evidence regarding the association between DM and cholelithiasis is still inconsistent among studies, probably indicating that the risk of developing cholelithiasis is multifactorial [22–26]. Therefore, risk factors for developing gallstones must continue to be identified and eliminated to reduce healthcare burdens on patients and the healthcare system.

Aim

Our study aims to evaluate the association between diabetes mellitus and gallstones and common risk factors in a nationwide population-based cohort investigation.

Material and methods

Data sources

The data reported from the National Health and Nutrition Examination Survey (NHANES) database from 2017 to 2018 were extracted for this study. Administrators of the database collected the data, and each patient's data was reported for usage for research purposes without identifying variables.

Study variables

Demographic variables were extracted, including sex, age, marital status, educational level, and race. Moreover, the outcomes of interest were collected, including diabetes diagnosis, insulin use, age at diabetes mellitus diagnosis, cholelithiasis diagnosis, age at cholelithiasis diagnosis, and need for surgery due to cholelithiasis. Comorbidities such as heart failure, stroke, coronary artery disease, angina pectoris, heart attack, and cancer were also analysed.

All patients who had a known diagnosis of diabetes mellitus and cholelithiasis were included. Those with missing data, borderline diabetes, and individuals who gave a "do not know" answer to the outcomes of interest were excluded.

Statistical analysis

R software version 4.1.0 was used for the analysis of the data. All the categorical data were analysed using the χ^2 test, while all the continuous data were analysed using the Mann-Whitney H test in accordance with the normality of the data distribution. We further performed a logistic regression analysis interpreted as odds ratio (OR) and 95% confidence interval (CI) to test the association between our outcomes of interest. The logistical regression was done using 2 models, one was unadjusted, and the other was adjusted for potential covariates, including age, gender, race, marital status, educational level, body mass index (BMI), and all reported comorbidities.

Results

Sociodemographic characteristics

A total of 5376 individuals were included in the final analysis, with a mean age of 51.3 ±17.8 years. Females constituted 51.5% of the included individuals, with an overall mean BMI of 29.8 ±7.4 kg/m^2. Non-Hispanic White was the most common race with 34.9% of the included patients, followed by Non-Hispanic Black (23.1%), other races – including multi-racial (19.2%), and Mexican Americans (131.3%), respectively. Of the included patients, 49.1% were married and 32.1% had some college courses or associate degrees. There were significant differences between patients with reported cholelithiasis and those who were not in all reported sociodemographic characteristics (Table I). Similarly, there were significant differences between patients with diabetes and those who were not in all reported sociodemographic characteristics, except for race (Table II).

Patient characteristics

The prevalence of diabetes was 16.2% among the included individuals, with a mean age of 50.6 ±13.6 years at diagnosis of diabetes, and only 4.5% were taking insulin. The prevalence of cholelithiasis was 11.2%, with a mean age of 44.4 ±16.1 years at the time of diagnosis, and 11.3% had a previous cholecystectomy (gallbladder surgery.) For cardiovascular disease, heart failure was present in 3.6%, coronary artery disease was present in 4.8%, angina pectoris was present in 3.0%, and myocardial infarction was present in 4.9% of patients. Moreover, 4.9% of the included patients

Table I. Sociodemographic characteristics of the included patients – Stratified by Call stone status

Variables	Gallstones						*P*-value
	No		Yes		Total		
	n	%	*n*	%	*n*	%	
Age, mean ± SD	50.3 ±17.8		59.2 ±15.9		51.3 ±17.8		< 0.001*
Body mass index [kg/m^2] mean ± SD	29.4 ±7.1		33.1 ±8.4		29.8 ±7.4		< 0.001*
Gender:							
Female	2336	48.9	432	71.4	2768	51.5	< 0.001*
Male	2438	51.1	173	28.6	2611	48.5	
Race:							
Non-Hispanic White	1608	33.7	270	44.6	1878	34.9	< 0.001*
Non-Hispanic Black	1141	23.9	102	16.9	1243	23.1	
Other race – including multi-racial	948	19.9	87	14.4	1035	19.2	
Mexican American	633	13.3	85	14.0	718	13.3	
Other Hispanic	444	9.3	61	10.1	505	9.4	
Marital status:							
Married	2333	48.9	304	50.2	2637	49.1	< 0.001*
Never married	913	19.1	69	11.4	982	18.3	
Divorced	540	11.3	78	12.9	618	11.5	
Living with partner	464	9.7	39	6.4	503	9.4	
Widowed	348	7.3	89	14.7	437	8.1	
Separated	171	3.6	26	4.3	197	3.7	
Educational level:							
Some college courses or AA degree	1516	31.8	207	34.2	1723	32.1	< 0.001*
High school graduate GED or equivalent	1134	23.8	150	24.8	1284	23.9	
College graduate or higher	1139	23.9	132	21.8	1271	23.7	
12th grade without diploma or less	973	20.4	116	19.2	1089	20.3	

**Statistically significant; SD – standard deviation, AA – associate degrees, GED – General Education Development.*

had a history of stroke, and 10.3% of patients reported a history of cancer/malignancy (Table III).

Association between diabetes and gallstones

There was a significant increase in gallstone rates among diabetic patients as compared to non-diabetics in the unadjusted (OR = 2.30; 95% CI: 1.89–2.79; $p < 0.001$) and adjusted (OR = 1.46; 95% CI: 1.12–1.89; $p = 0.004$) models. Moreover, this association was not time-dependent where the duration of diabetes did not show a significant influence on the gallstone rate, whether in unadjusted (OR = 0.99; 95% CI: 0.98–1.01; $p = 0.194$) or adjusted (OR = 1.01; 95% CI: 0.99–1.02; $p = 0.285$) models. Furthermore, age, BMI, female gender, black race, higher education, angina, stroke, and cancer were all significant independent predictors persisting in the multivariate model (Table IV).

Discussion

Diabetes mellitus is one of the world's most costly diseases and is responsible for significant comorbidity and mortality. Despite the rising incidence of DM globally, a noticeable reduction in its complications has been reported in the past decade [27]. Contemporary research has focused on the association between diabetes and the risk of complicated cholelithiasis. However, there is a heterogeneity of data in these studies, and the prevalence of cholelithiasis varies across populations, from 5% to 33% [28–31]. We provide the first and largest study for the US population, investigating all other factors that may affect the studies association.

Our study demonstrated a 46% increase in the odds of developing gallstones in patients with diabetes after the adjustment of all available covariates (OR = 1.52; 95% CI: 1.05–2.19). A similar observation was reported by the retrospective cohort of Chen *et al.* that reported

Table II. Sociodemographic characteristics of the included patients – Stratified by Call diabetic status

Variables	Diabetes mellitus				*P*-value
	Yes		No		
	n	%	*n*	%	
Age; mean ± SD	63.7	12.2	48.9	17.8	< 0.001*
Body mass index [kg/m^2]; mean ± SD	32.4	7.8	29.3	7.1	< 0.001*
Gender:					
Male	474	54.5	2137	47.4	< 0.001*
Female	396	45.5	2372	52.6	
Race:					
White	303	34.8	1575	34.9	0.651
Black	199	22.9	1044	23.2	
Other Hispanic	75	8.6	430	9.5	
Mexican American	129	14.8	589	13.1	
Other race – including multi-racial	164	18.9	871	19.3	
Marital status:					
Married	488	56.1	2149	47.7	< 0.001*
Never married	73	8.4	909	20.2	
Divorced	121	13.9	497	11	
Living with partner	37	4.3	466	10.3	
Widowed	112	12.9	325	7.2	
Separated	39	4.5	158	3.5	
Educational level:					
College graduate or higher	163	18.8	1108	24.6	< 0.001*
Some college courses or AA degree	264	30.4	1459	32.4	
12th grade without diploma or less	240	27.6	849	18.9	
High school graduate GED or equivalent	201	23.2	1083	24.1	
Gallstones:					
Yes	171	19.7	434	9.6	< 0.001*
No	699	80.3	4075	90.4	

**Statistically significant; SD – standard deviation, AA – associate degrees, GED – General Education Development.*

a 55% increase in the incidence of gallstone formation in patients with type 2 diabetes mellitus. However, this study reported an inverse relationship between type 1 diabetes mellitus, where the odds of cholelithiasis were reduced by 52% compared to nondiabetic controls. The results of Chen *et al.* regarding type 1 diabetes mellitus were attributed to the younger age of patients with type 1 diabetes mellitus and the subsequent low prevalence of comorbidities compared to patients with type 2 diabetes mellitus, which were known risk factors for gallstone formation [29]. Furthermore, in an Italian population-based study, a higher prevalence of cholelithiasis was found in obese patients with type 2 diabetes mellitus compared to lean subjects with normal glucose tolerance, lean subjects with type 2 diabetes mellitus, and obese normal glucose tolerance groups, at 23%, 9%, 17%, and 14%, respectively [30].

In a case-control study in Iran, a significantly higher prevalence of gallstones was found in diabetic patients than in nondiabetics (33% vs. 17%). The risk was further elevated with the longer duration of diabetes mellitus (> 10 years) or with poor control with haemoglobin A_{1c} (HbA_{1c}) levels (8 and higher) [28]. This was supported by the fact that diabetes control can affect the incidence of cholelithiasis. A retrospective cohort study demonstrated a significant reduction in gallstone formation among diabetic patients with long-term use of metformin [32]. In addition, Liu *et al.* observed that around 10% of diabetic patients had symptomatic cholelithiasis requiring surgical intervention compared to 8% of the nondiabetic

Table III. History of different co-morbidities among the included patients

Variables		*N*	%
Diabetes mellitus (DM)	No	4509	83.8
	Yes	870	16.2
Age on first DM diagnosis; mean ± SD		50.6 ±13.6	
Currently taking insulin	No	5136	95.5
	Yes	242	4.5
Ever had gallstones	No	4774	88.8
	Yes	605	11.2
Age on first gallstone diagnosis; mean ± SD		44.4 ±16.1	
Ever had a gallbladder surgery	No	4767	88.7
	Yes	609	11.3
Ever had heart failure	No	5169	96.4
	Yes	193	3.6
Ever had coronary heart disease	No	5104	95.2
	Yes	259	4.8
Ever had angina pectoris	No	5193	97.0
	Yes	158	3.0
Ever had heart attack	No	5105	95.1
	Yes	265	4.9
Ever had stroke	No	5108	95.1
	Yes	261	4.9
Ever had cancer/malignancy	No	4821	89.7
	Yes	556	10.3

patients. This risk was further increased in diabetic females than in diabetic males [33].

Insulin is the primary therapeutic modality for uncontrolled type 2 diabetes and type 1 diabetes [34]. In animal models of insulin resistance, hepatic insulin resistance was implicated in gallstone formation. In this model, insulin resistance increases the heterodimeric cholesterol transporters responsible for regulating cholesterol secretion. Furthermore, an enzyme involved in bile acid synthesis, *Cyp7b1,* which has a protective effect against gallstone formation, was significantly downregulated [35]. Our analysis demonstrates that patients currently on insulin therapy had a higher odds ratio of developing cholelithiasis. A similar observation was reported in an Italian case-control study, in which participants with high insulin levels were associated with a higher prevalence of gallstones [36].

Diabetes is associated with comorbidities, particularly obesity and hypercholesterolaemia, which are known risk factors for cholelithiasis in previously predisposed individuals [37, 38]. Diabetes affects the biliary tract via microvascular and neurologic complications, potentiating a reduction in gallbladder (GB) blood supply, reducing GB emptying, raising the risk of infection, and increasing the concentration of bile, which may lead to infection and the development of cholelithiasis [39]. Diabetes has also been implicated in alterations of gastrointestinal hormones that affect gallbladder emptying. This may allow bile stasis, precipitating cholelithiasis [40]. Lastly, the dysfunction of the sphincter of Oddi in patients with DM may increase the risk of bile concentration and subsequent cholelithiasis [41].

This analysis suggests that insulin use may significantly predict cholelithiasis development in diabetic patients. One might conclude that these data support the initiation of non-insulin therapies as first-line, to reduce the risk of developing cholelithiasis. However, there is little evidence regarding the effect of these therapies

on the development of cholelithiasis. Further research should be directed regarding the association of these drugs with cholelithiasis.

One of the study's main strengths includes a large sample size of patients. Furthermore, our results were consistent in both the adjusted and unadjusted analyses. We also investigated whether time dependency and insulin intake are associated with gallstones, which are essential parameters that can affect the development of any diabetic complication and were not

Table IV. Logistic regression of the association gallstones and different predictors

Variables		OR (univariable)	OR (multivariable)
Diabetes	No	–	–
	Yes	2.30 (1.89–2.79, $p < 0.001$*)	1.46 (1.12–1.89, $p = 0.004$*)
Duration of diabetes		0.99 (0.98–1.01, $p = 0.194$)	1.01 (0.99–1.02, $p = 0.285$)
Taking insulin now	No	Reference	
	Yes	2.39 (1.73–3.25, $p < 0.001$*)	1.17 (0.77–1.74, $p = 0.457$)
Age		0.97 (0.97–0.98, $p < 0.001$*)	0.97 (0.97–0.98, $p < 0.001$*)
Body mass index [kg/m^2]		0.94 (0.93–0.95, $p < 0.001$*)	0.94 (0.93–0.95, $p < 0.001$*)
Gender	Male	Reference	
	Female	0.38 (0.32–0.46, $p < 0.001$*)	0.36 (0.29–0.44, $p < 0.001$*)
Race	Mexican American	Reference	
	Other Hispanic	0.98 (0.69–1.39, $p = 0.898$)	1.02 (0.70–1.50, $p = 0.921$)
	White	0.80 (0.61–1.03, $p = 0.093$)	1.18 (0.86–1.60, $p = 0.305$)
	Black	1.50 (1.11–2.03, $p = 0.009$*)	2.21 (1.55–3.14, $p < 0.001$*)
	Other race – including multi-racial	1.46 (1.07–2.01, $p = 0.018$)	1.38 (0.95–1.98, $p = 0.087$)
Marital status	Married	Reference	
	Widowed	0.51 (0.39–0.66, $p < 0.001$*)	1.18 (0.85–1.65, $p = 0.332$)
	Divorced	0.90 (0.69–1.18, $p = 0.447$)	1.04 (0.77–1.41, $p = 0.809$)
	Separated	0.86 (0.57–1.34, $p = 0.481$)	0.92 (0.57–1.52, $p = 0.725$)
	Never married	1.72 (1.32–2.28, $p < 0.001$*)	0.98 (0.71–1.35, $p = 0.883$)
	Living with partner	1.55 (1.11–2.23, $p = 0.014$*)	0.99 (0.67–1.48, $p = 0.953$)
Educational level	12th grade without diploma or less	Reference	
	High school graduate GED or equivalent	0.90 (0.70–1.16, $p = 0.428$)	0.68 (0.50–0.92, $p = 0.014$*)
	Some college courses or AA degree	0.87 (0.68–1.11, $p = 0.270$)	0.69 (0.51–0.92, $p = 0.013$*)
	College graduate or higher	1.03 (0.79–1.34, $p = 0.833$)	0.65 (0.47–0.89, $p = 0.008$*)
Congestive heart failure	No	Reference	
	Yes	2.29 (1.59–3.23, $p < 0.001$*)	0.89 (0.55–1.42, $p = 0.643$)
Coronary heart disease	No	Reference	
	Yes	2.30 (1.68–3.11, $p < 0.001$*)	1.28 (0.81–1.98, $p = 0.277$)
Angina pectoris	No	–	–
	Yes	3.52 (2.46–4.98, $p < 0.001$*)	2.39 (1.52–3.73, $p < 0.001$*)
Heart attack	No	Reference	
	Yes	1.76 (1.25–2.41, $p = 0.001$*)	1.01 (0.64–1.58, $p = 0.950$)
Stroke	No	Reference	
	Yes	2.39 (1.75–3.22, $p < 0.001$*)	1.47 (1.00–2.12, $p = 0.044$*)
Cancer or malignancy	No	Reference	
	Yes	2.37 (1.89–2.96, $p < 0.001$*)	1.41 (1.07–1.84, $p = 0.012$*)

*OR – odds ratio, *statistically significant, AA – associate degrees, GED – General Education Development.*

adequately reported by previous investigations. We also acknowledge several limitations that should be considered. Variables from the NHANES database are self-reported and subject to recall bias that cannot be avoided. The data regarding the type of diabetes mellitus (type 1 and type 2) and the duration of diabetes were not reported for all patients in our study. Finally, very few patients reported the current levels of HbA_{1c}; therefore, the effect of diabetes control on cholelithiasis could not be examined.

Conclusions

There is an association between developing cholelithiasis and diabetes. Moreover, patients on insulin therapy showed greater odds of developing gallstones than patients who did not. Further investigation is needed to discover the role of insulin therapy, its duration, and dose in the development of gallstones.

Conflict of interest

The authors declare no conflict of interest.

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Received: 10.03.2022
Accepted: 21.06.2022