Clinical and therapeutic features of acute cholecystitis in diabetic patients

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Abstract. The present study aimed to compare the clinical, paraclinical, intraoperative findings, and postoperative complications in acute cholecystitis in diabetic patients vs. non-diabetic patients. A 2-year retrospective study was performed on the patients who underwent emergency cholecystectomy for acute cholecystitis between 2017 and 2019 at the 4th Department of Surgery, Emergency University Hospital Bucharest. The diabetic subgroup numbered 46 eligible patients and the non-diabetic one 287 patients. Demographics, the severity of the clinical forms, biological variables (including white cell count, urea, creatinine, coagulation and liver function tests) comorbidity status, surgical approach, postoperative complications, and hospital stay were analyzed. Statistical analyses were performed to assess comparative results between the aforementioned data (SPSS V 13.0). The CCI and ASA risk classes were increased in the diabetic group, with 34.78% of patients having 3 or more associated comorbidities. No statistically significant associations were demonstrated between diabetes and the severity of the cholecystitis and risk for conversion. Postoperatively both minor complications such as surgical site infections and major cardiovascular events were more common in the diabetic subgroup (P=0.0254), well associated with the preoperative status and baseline cardiovascular comorbidities. Laparoscopic cholecystectomy is a safe procedure for diabetic patients, which can provide the best outcomes, by decreasing the risks of surgical wounds. Attentive perioperative care and good glycemic control must be provided to minimize the risk of complications.

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Introduction

With a rising prevalence of diabetes mellitus (DM) in the worldwide population, increased awareness of the multifaceted clinical spectra of biliary conditions in diabetic patients could lead to early diagnosis and improved outcomes (1). Contrary to the famous quote of William Mayo stating that 'there is no innocent gallstone', recent studies on the natural history of cholelithiasis indicate that less than one-third of the patients having gallstones will eventually become symptomatic (2-4). Although the same observation applies in patients suffering from DM, these tend to develop more severe complications, have longer hospital stays, and higher fatality rates (5). As a result, before the era of evidence-based medicine, for numerous generations of surgeons the logic-driven temptation to recommend prophylactic cholecystectomies in this category of patients became a perpetuated paradigm (6).

Even today there are numerous controversial aspects related to the diagnosis and management of gallstones and acute cholecystitis in diabetic patients in whom classical symptoms have different clinical connotations. These are attributed to diabetic neuropathy, impaired host response to infection, and various structural tissue damage caused by long term exposure to hyperglycemia (7). Although empirical evidence reported by surgeons and physicians over time suggested that special care should be taken when managing diabetic patients with biliary conditions there are no widely accepted guidelines on the matter. Perhaps this is due to the great variability in clinical presentations and response to treatment.

Attempting standardization of assessment and establishment of prognostic factors to support clinical decisions for acute cholecystitis in general, the Japanese Society of Gastroenterology published the Tokyo Guidelines in 2013, revised later in 2018 (TG 13/18) (8) which were used in the present for various stratifications of the cohorts.

The present study aimed to compare the clinical, paraclinical, intraoperative findings, and postoperative complications in acute cholecystitis in diabetic vs. non-diabetic patients.

Materials and methods

Study design. A 2-year retrospective study was performed on the patients who underwent emergency cholecystectomy for acute cholecystitis between January 2017 and December 2019 at the 4th Department of Surgery, Emergency University Hospital, Bucharest, Romania. A total of 333 patients, aged between 18-91 years were identified. The study group was divided into two subgroups based on the presence of DM. The diabetic subgroup numbered 46 eligible patients and the non-diabetic one 287 patients. Data were collected from observation charts and postoperative notes.

The inclusion criteria for the study consisted of: i) Emergency admission for acute cholecystitis followed by cholecystectomy later than 72 h from the admission; and ii) accurate documentation of the clinical and paraclinical data pertaining to the calculation of the Tokyo criteria, American Society of Anesthesiologists (ASA) Physical Status Classification (9) and Charlson Comorbidity Index (CCI) (10).

Exclusion criteria were: i) Associated pancreatitis or ii) any malignancy (Table I).

Data comparison and statistical analysis. Demographics, the severity of the clinical forms, biological variables [white cell count (WCC), urea, creatinine, coagulation, and liver function tests (LFTs)] comorbidity status, surgical approach, postoperative complications, and hospital stay were analyzed.

Statistical analyses were performed to assess comparative results between the aforementioned data. For descriptive analysis, the medians, means, and standard deviations were used. Pearson chi-square or Fisher exact test (if the number of observations in the cells was <5) and ANOVA test were used to evaluate associations between different variables. Relative risk and odds ratio for diabetic vs. non-diabetic patients were calculated for the following outcomes: major complications, surgery-related complications, in-hospital infection (SPPSS 13.0 version; SPSS, Inc.).

The study was released from the formal consent of the ethical board due to its retrospective nature.

Results

General data and comorbidities. Among the 46 diabetic patients, the sex ratio was almost equal, while in the control group there was a definite predominance for the female sex, with an F:M ratio of 3:1 (P<0.001) There were no significant differences between the diabetic and the non-diabetic group regarding the early/delayed presentation to Emergency Room. The CCI and ASA risk classes were increased in the diabetic group, with 34.78% of patients having 3 or more associated comorbidities. A statistically significant association was identified between the presence of DM and arterial hypertension (P<0.001) and ischemic cardiopathy (P=0.0043) (Table II).

Preoperative assessment included clinical and paraclinical exploration. Ultrasound examinations confirmed the presence of gallbladder stones and evaluated the thickness of the gallbladder wall: Double contour and pericholecystic fluid were markers for severe local inflammation (Table III).

The incidence of the severe cases in diabetic patients was higher than the value of that recorded in non-diabetics, but the result was not statistically significant (P=0.058; Table III). While some researchers support the association of DM with severe clinical forms of acute cholecystitis (6,11,12) larger studies are required to resolve this controversy.

Mean leucocyte levels were higher in DM patients despite a general belief that immune responses in diabetics are elicited in a slower and unpredictable manner. Since there was no association with the severity of the clinical form, it is considered that the number of leucocytes is linked to the chronic complications of DM as suggested by Moradi *et al* (13) and Coller (14), but the intimate mechanisms governing this remain partially unknown.

Intraoperative approach and outcomes. There were no statistically significant associations between the type of surgery and DM, most of the cases being performed laparoscopically. Although, the rate of conversion was higher in the diabetic group (13.2%) vs. the non-diabetic group (6.9%), which conformed well with the increased incidence of the severe forms of acute cholecystitis in the diabetic group (Table IV).

The ASA PS classification and CCI were significantly associated with the presence of DM (P=0.0012 and P<0.001, respectively; Table II). Surgery-related complications and major cardiovascular events were more common in the DM subgroup (P=0.0137 and P=0.013, respectively; Table IV). Healthcare-associated infections were slightly higher in the diabetic group but not statistically significant (Table IV).

Discussion

Specific physiopathological mechanisms of acute cholecystitis in diabetic patients. The present study revealed that the incidence of acute cholecystitis in diabetic patients was not sex-related with an even male to female proportion, markedly different from the general population where the female to male ratio is 4:1. Similar results have been reported by other authors (Kamaranos *et al* 55.4%, Pagliarulo *et al* 53.1%, Cho *et al* 46.36% and Ransohoff *et al* 51.12%), but to date a plausible mechanism has not been proposed (15-18). Some studies mention a higher degree of gallbladder distension and an increased wall tension secondary to kinetic disorders caused by microangiopathy and diabetic neuropathy. Metabolic disorders and DM-related gallstone formation may play a role that is not fully elucidated. In this regard, Aune and Vatten (19) published a meta-analysis on the role of DM as a risk factor for gallbladder diseases in which unequivocal data demonstrated the role of DM in the formation of biliary calculi. The mechanisms incriminated were related to insulin resistance

Table I. Tokyo Guideline (TG13/TG18) severity risk scale.

Grade III (severe) acute cholecystitis	Acute cholecystitis with organ/system dysfunction (renal, cardiovascular, hepatic, respiratory, neurologic, hematologic)
Grade II (moderate) acute cholecystitis	Acute cholecystitis associated with: i) WBC >18000/mmc ii) Palpable tender mass in the right upper abdominal quadrant iii) Marked local inflammation iv) Onset >72 h
Grade I (mild) acute cholecystitis	Acute cholecystitis which does not meet criteria for grade II or III

WBC, white blood cells.

Table II. General data in the diabetic and non-diabetic groups.

Factors	Diabetic group	Non-diabetic group	P-value
Total no. of subjects	46	287	
Females	26 (56.53%)	205 (71.42%)	**<0.001**
Males	20 (43.47%)	82 (38.58%)	
Age (mean ± SD) (min; max)	64±12.1 (35-88 years)	55±16 (18-91 years)	**<0.001**
Presentation			0.646
Early (<72 h)	16 (34.8%)	91 (31.7%)	
Delayed (>72 h)	30 (65.2%)	196 (68.3%)	
CCI (mean ± SD)	2.56±1.73	0.78±14	**<0.001**
CCI ≥4	14 (30.43%)	18 (6.27%)	
Diabetes			
Uncomplicated	24 (52.2%)		
With complications	22 (47.8%)		
Arterial hypertension	28 (60.8%)	78 (27.2%)	**<0.001**
Ischemic cardiopathy	21 (45.6%)	45 (15.6%)	**0.0043**
ASA ≥III	22 (47.8%)	68 (23.69%)	**0.0012**
ASA risk staging			
I	1	64	
II	24	109	
III	18	61	
IV	4	5	
V	0	2	

Bold indicates statistical significance. ASA, American Society of Anesthesiologists Physical Status Classification; CCI, Charlston Comorbidity Index.

and disorders of lipid metabolism leading to high levels of cholesterol and triglycerides. These are frequently associated with obesity in the metabolic syndrome associated with type 2 DM (20). In other studies, increased bile saturation indexes and hypo-motility of the gallbladder induced by a decrease of cholecystokinin receptors in the gallbladder wall were observed (21-23) causing reduced smooth muscle sensibility to humoral stimulation. All these pathological mechanisms provide logical explanations for the equal sex distribution of acute cholecystitis in diabetic patients, and this particularity is more than likely the result of their complementary and cumulative effect.

Postoperative cardiovascular complications risk in diabetic patients with acute cholecystitis. The present study determined statistically significant associations between cardiovascular comorbidities (arterial hypertension, ischemic cardiopathy), ASA score and CCI used in preoperative assessment of the surgical risk.

Ischemic heart disease has been revealed to be significantly associated with DM due to the occurrence of both large vessels (accelerated atherosclerosis) and microvascular disorders. Similar studies on outcomes of cholecystectomy in diabetic patients have confirmed the interdependency between DM and acute coronary syndromes (11,23).

Table III. Preoperative assessment of the diabetic and non-diabetic groups.

Factors	Diabetic group	Non-diabetic group	P-value
WBC >18000/mmc	7 (15.2%)	18 (6.27%)	0.0664
WBC (median ± SD)	11,859±5,593	9,603.47±5,443.04	**0.018**
Ultrasound: Double contour image	15 (32.6%)	64 (22.3%)	0.1273
Creatinine >2 mg/ml	6 (13%)	14 (4.85%)	**0.0164**
Creatinine	1.27±0.76	1.03±0.92	0.097
TG13/TG18			0.6562
Severe	6 (13.04%)	16 (5.57%)	0.058
Moderate	26 (56.52%)	182 (63.4%)	
Mild	14 (30.43%)	89 (31.01%)	
Main duct stones	7 (15.2%)	24 (8.3%)	0.1301
Angiocholitis	1	3	

Bold indicates statistical significance. WBC, white blood cells; TG13/TG18, Tokyo Guideline severity risk scale.

Table IV. Surgical approach and outcomes in diabetic vs. non-diabetic groups.

Parameters	Diabetic group	Non-diabetic group	P-value
Type of surgery			0.1275
Laparoscopic cholecystectomy	38 (82.6%)	256 (89.2%)	
Conversion	6 (13.2%)	20 (6.9%)	
Open cholecystectomy	2 (4.34%)	11 (3.8%)	
Severe forms	7 (15.2%)	27 (9.4%)	0.368
Gangrenous	3	14	
Piocholecystitis	3	6	
Pericholecystitis	1	3	
Biliary peritonitis	0	4	
Hospital days	6.7±5.3	6.39±5.89	0.695
Post-surgery hospitalization	4.3±4.8	3.77±3.59	0.398
Surgery-related complications (treated conservatively)	6 (13.04%)	12 (3.83%)	**0.0137**
Hemorrhage	3	7	
Bile leak	2	3	
SSI	1	2	
Major complications	6 (13.04%)	3 (2.4%)	**0.013**
Death	1 (sepsis)	2 (stroke)	
Stroke	0	2	
Acute myocardial infarction	5	1	
Nosocomial infections (*Clostridium*, lower urinary tract infections)	9 (19.5%)	33 (11.49%)	0.12

Bold indicates statistical significance. SSI, surgical site infections.

Moreover, other systemic complications have been revealed to be associated with DM including respiratory, renal decompensation, sepsis, and systemic infections (11,12,15,17). In the present study, there were no pulmonary and renal complications, and the hospital-acquired infection rates did not differ between the 2 study groups. Yet, the only death in the diabetic group was due to sepsis.

In a meta-analysis published by Łącka *et al* (11), mortality was revealed to be higher in diabetic patients in several studies (24,25), while others found similar rates in comparison to non-diabetic patients (26-29). One explanation may be that some of the cited studies are more than 20 years old, and the development and skills in laparoscopic surgery, as well as in intensive care, would have improved the outcomes of this vulnerable category of patients. Careful preoperative preparations, meticulous intraoperative surgical techniques, and cautious postoperative care are extremely important for preventing these severe events (29).

Impaired surgical wound healing in diabetics. In the present study, the postoperative complications related to surgery were higher in the diabetic group. These aspects can be correlated to the stiffness of the vascular wall, which leads to prolonged bleeding and tissular hypoxia, as well as impaired wound healing secondary to chronic hyperglycemia (12,30-32).

Moreover, septic site infection and wound dehiscence were encountered to be more frequent in diabetic patients (28-32). In this regard, the advantages of the laparoscopic approach are extremely important, in preventing perioperative morbidity.

Severity forms and risk for conversion in diabetic patients. The present study supports the evidence according to which laparoscopic cholecystectomy remains the gold standard of treatment for diabetic patients with acute cholecystitis, considering the similar conversion rates with non-diabetic patients and no special intraoperative requirements or adjustments of techniques.

Some studies have published data revealing a higher incidence of severe cases of acute gangrenous or emphysematous cholecystitis in diabetic patients (6,12), but this is not unanimously accepted. A possible explanation for the inconsistencies in study results may be related to insufficient documentation of the comorbidities and severe cases in clinical notes. The duration of DM may play a role in the development of severe cases considering that the microvascular and macrovascular complications and neuropathic changes are directly proportional to the duration of the uncontrolled hyperglycemia (33,34). Chronically elevated blood sugar levels alter the immune response and render the diabetic more susceptible to infections by various mechanisms such as glycosylation of the complement proteins, inhibition of immunoglobulin-mediated opsonization of bacteria, inhibition of neutrophil migration phagocytosis, and apoptosis (35-37). Hence the pivotal role of tight glycemic control, between 100 and 140 mg/ml, in the reduction of healthcare-associated infections and speedy surgical site healing (38).

Surgical management of acute cholecystitis in diabetic patients. Several studies have reported that diabetic patients are more predisposed to severe forms of acute cholecystitis, suggesting that even silent gallstones should be addressed surgically (6,12). In a recent metanalysis on 40 studies regarding the clinical features and outcomes of acute cholecystitis in diabetic patients, Łącka *et al* (11) concluded that there is not enough evidence to recommend elective cholecystectomy as a routine in patients with DM. The present study also supports this conclusion, as there were no particular differences regarding the severity and surgical approach in diabetic vs. non-diabetic patients.

Once the gold standard for the treatment of acute cholecystitis, interval cholecystectomy is increasingly abandoned in favor of index admission laparoscopic cholecystectomy (39). This is due to studies that revealed that in trained hands early cholecystectomy is as safe as delayed surgery and that after one episode of cholecystitis the risk of developing calculi-related complications is 14% at 6 weeks, 19% at 12 weeks, and 29% at one year following discharge (39-44). Traditionally, critically ill surgical patients with acute cholecystitis should be temporized with percutaneous cholecystostomy, but there are data suggesting that in patients with organ failure, temporizing is associated with poorer outcomes and higher mortality compared to those in whom surgery is not deferred (40-42).

In conclusion, diabetic patients with acute cholecystitis are more predisposed to postoperative systemic- and surgical-related morbidity. Laparoscopic cholecystectomy is a safe procedure for diabetic patients, which can provide the best outcomes, by decreasing the risks of surgical wounds. Attentive perioperative care and good glycemic control must be provided to minimize the risk of complications.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SAB, DS, AMD and ADS contributed to the conception and design of this study. CA, SAB, AMT, BS, AMD, DS and CB were responsible for the data collection and analysis. SAB, DS, CDB, BS, IM, VA and DaS were in charge of drafting the manuscript. DaS, CDB, RIS, GCS, VA, IM revised the manuscript critically for important intellectual content. All authors read and approved the final version.

Ethics approval and consent to participate

The study was released from the formal approval of the ethical board due to its retrospective nature. All patients had previously signed an informed written consent concerning hospitalization and investigations.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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