

# Acute cholecystitis in patients with diabetes mellitus – systematic review

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## Abstract

**Introduction:** According to the WHO, an estimated 422 million people are suffering from diabetes worldwide. Among them, the incidence of cholelithiasis is higher than in the healthy population. The aim of this literature review was to summarize the available evidence about acute cholecystitis in patients with diabetes. **Materials and methods:** This study adhered to the PRISMA guidelines. The course of hospitalization of patients with and without diabetes who underwent cholecystectomy due to acute cholecystitis was compared. Following information was abstracted from original studies: general study information, patient characteristics, complications, and recommendations for patients with diabetes. **Results:** Initial search provided 1632 results. After full text assessment, 40 studies met the inclusions criteria. Operative and postoperative complication rates were significantly higher among the diabetic patients. Diabetes is a risk factor for conversion from laparoscopic to open cholecystectomy method. The authors' opinions on elective surgery before the onset of acute cholecystitis symptoms are divided. **Conclusions:** Diabetic patients are at greater risk of developing complications. An individualized screening and treatment approach, as well as proper preparation of the diabetic patient for an elective cholecystectomy could have a positive effect on the outcome. However, the low quality of the data from the systematic review does not allow for meta-analysis, which is why we cannot draw strong conclusions.

**Keywords:** diabetes and metabolism · general surgery

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## Introduction

According to the latest World Health Organization data, an estimated 422 million people suffer from diabetes worldwide. The incidence of diabetes is increasing rapidly and it is estimated that the number of people with diabetes will double by 2030. Approximately 104 million new cases of gallbladder and bile duct pathologies are reported annually. Among people suffering from diabetes, the incidence of cholelithiasis is higher than in the healthy population and diabetes increases the risk of developing acute cholecystitis [1-5]. In this group of patients, complications of acute cholecystitis such as gangrenous cholecystitis, bacteriobilia, perforation and emphysematous cholecystitis are more frequent [3-5]. Therefore, acute cholecystitis seems to be a serious problem in diabetic population [6]. However, not many studies were published in the last 30 years on this matter. Moreover, it was reported that cholecystectomy in people with diabetes is related to a significantly higher number of intraoperative complications and almost 3 times higher number of postoperative complications [7]. Once again, the literature about these specific issues is limited.

The aim of this study was to systematically review the available evidence regarding acute cholecystitis in patients suffering from diabetes.

## Materials and methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We performed a systematic search of the PubMed and Web of Science databases to identify studies on acute cholecystitis in patients with diabetes mellitus published before September 1<sup>st</sup> 2019. Following search query was used: "(cholecystitis OR cholecystectomy) AND (diabetes OR diabetic) Articles written in languages other than English were excluded. Abstracts, case reports, conference papers, letters, and editorials were excluded during the initial screening of titles and citations. Duplicated results were removed using Mendeley Software. Only full text papers describing the course of hospitalization in patients with diabetes who underwent cholecystectomy due to acute cholecystitis were included in the review (see Figure 1). In the next step we compared the course of hospitalization of patients with and without diabetes who underwent cholecystectomy due to acute cholecystitis.

All steps of the literature search were performed by two independent researchers. Decisions regarding final inclusion were resolved by a consensus.



## PRISMA 2009 Flow Diagram

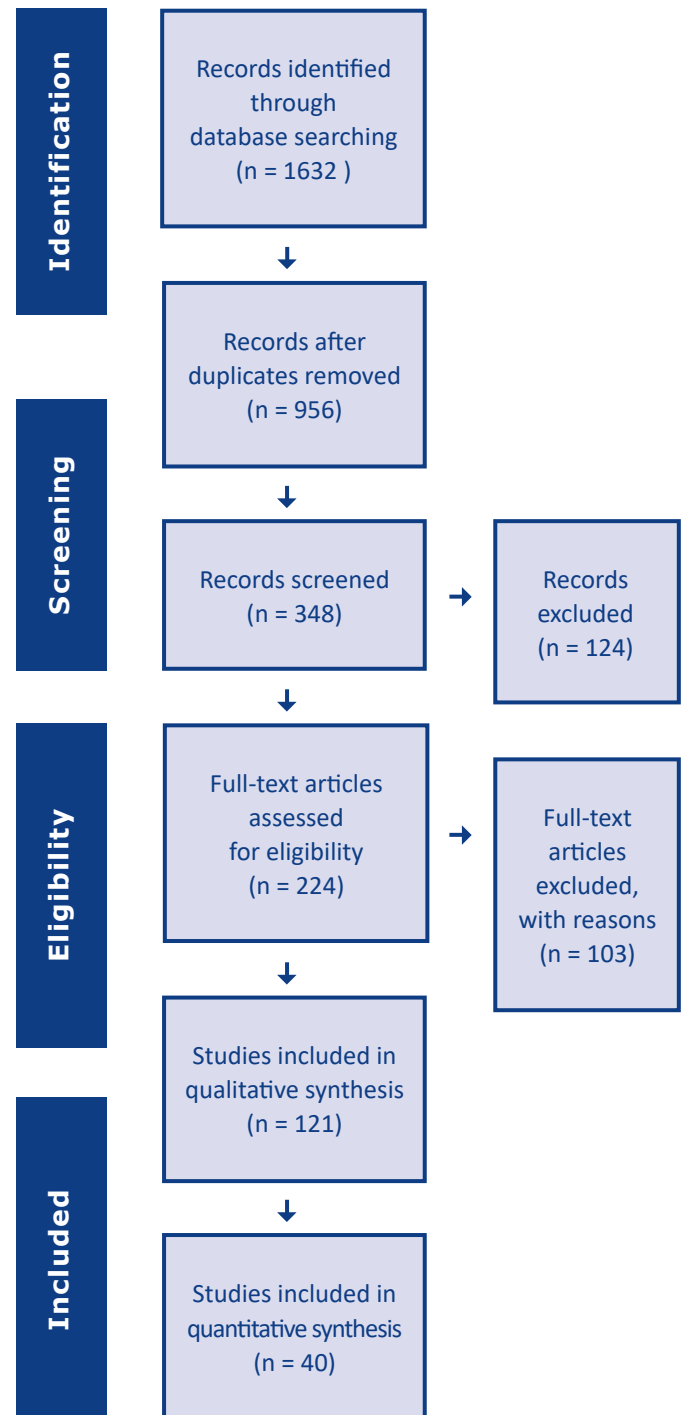


Figure 1. Flowchart illustrating the literature search

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

The following data was extracted from the original studies:

1. general study information: authors, publication year, country, institution,
2. demographics: number of patients, sex, age,
3. complications: septic shock, pneumonia, renal insufficiency, cardiovascular complications, (surgical site infection) SSI, wound dehiscence, infectious complications, conversion, preoperative perforation, bleeding, bile leakage, gangrenous cholecystitis, cholelithiasis, perioperative complications, postoperative complications, longer time of operation, anesthesia and total hospitalization time
4. recommendations for patients with diabetes: screening for gallstones, routine cholecystectomy before acute cholecystitis.

## Results

The initial search identified 1632 articles. After excluding articles that do not match the criteria described above, 221 articles were included in the abstract review. Finally, 121 abstracts were selected for full text appraisal of which 40 met all the inclusion criteria and were included in this review. This systematic review included 40 articles including over 1300000 patients. 8 articles did not contain information on the number of patients enrolled in the study. In only 10 articles the patients were grouped by sex. The age of patients enrolled in the study was given in 9 of 40 articles. 22 papers out of 40 were published before 2010, 11 of which contain data from before 2000. In effect, 25% of the analyzed literature contains data collected more than 20 years ago (see Table 1).

Table 1. Reviewed articles key data

Authors	Number of patients	Men %	Risk factor of AC	Mortality	Infectious complications during hospitalization	SSI	Conversion LC to open surgery	Postoperative complications
Cho JY et al. 2009 [4]	1059	46.36	YES, AOR 95% CI 1.802 (1.153-2.816)					
Bodmer M et al. 2011 [24]	22574	24.3	AOR for developing gallstone disease followed by cholecystectomy of 0.88, 95% CI 78-1.00, p = 0.05) that diabetes mellitus is not an independent risk factor for cholecystectomy.					
De Santis A et al. 1999 [11]	336	39.29	YES 11,6% vs. 4,8% respectively OR, 2.55; 95% CI, 1,39-4,67					

Karamanos E et al. 2013 [5]	5460	55.4	YES, NR	YES (AOR) (95% CI): 1.79 (1.09, 2.94), adjusted p = 0.022]	5.6 vs. 1.6%; AOR [95% CI]: 1.85 [1.53, 2.23]	On insulin vs. non-diabetics: 4.2 vs 1.6%; AOR [95% CI]: 1.80 [1.39, 2.34]		
Miguel-Yanes JM et al. 2016 [12]	611 533		YES, p < 0.001	After open cholecystectomy [OR = 0.82 (0.78-0.87)], but a higher IHM after laparoscopic cholecystectomy [OR = 1.18 (1.03-1.35)].				
Turrill FL et al. 1961 [36]	481			YES, NR	YES, NR	YES, NR		
Liu C-M et al. 2015 [22]	108850		YES, MALE p < 0.001	53,1 + D1:D31				
Bedirli A et al. 2001 [27]	862			YES, NR			YES, p = 0,012	YES, 0,0061
Terho PM et al. 2016 [9]	373						YES, OR 2.0 (1.2-3.6) p = 0.014	
Cucchiario G et al. 1989 [14]			YES, NR	YES, p = 0.002				
Lyass S et al. 2000 [15]	601	26.29	YES, NR	YES, NR			NO, NR	YES, p = 0.055
Jaafar G et al. 2017 [37]	94557				YES, complicated diabetes p < 0.001 OR 3.177 CI 2.153-4.689, uncomplicated diabetes p < 0.001 OR 2.943 CI 2.368-3.657	YES, complicated diabetes (OR 1.435, CI 1.205-1.708), uncomplicated diabetes (OR 1.391, CI 1.264-1.530)		

Lee S et al. 2011 [16]	611		YES, $p = 0,002$ OR (95% CI) 1,960 (1,262-3,044)					
Ransohoff DF et al. 1987 [17]	311	51.12	YES, NR	NO, $p = 0,55$				NO, NR
Pagliarulo M et al. 2004 [3]	1337	53.1	NO, BMI, AGE, FAMILY, NR					
de Siqueira Corradi MB et al. 2019 [18]	2520		YES, adjusted model $2.68 < 0.001$	53,1 + D1:D31				
Warren DK et al. 2017 [40]						Independent risk factors for SSI after cholecystectomy. Adjusted HR (95% CI) 1.53 (1.19–1.98)		
Paajanen H et al. 2011 [19]	2548		YES, $< 0.0001$	YES, $p < 0.01$	YES, NR		YES, $p < 0.0001$	YES, NR
Doran H et al. 2018 [20]			YES, NR	YES, NR	YES, NR	YES, NR	YES, NR	
Ismat U et al. 2016 [42]	120					Presence of diabetes mellitus did not significantly affect the onset of surgical site infection in patients undergoing laparoscopic cholecystectomy; $p = 0.07$		
Ibrahim S et al. 2006 [34]	1000						NO, but diabetic patients who had conversion had a significantly higher Hba1c (8.9% +/- 0.6%; $p < 0.038$ )	
Philip Rothman J et al. 2016 [35]	460995						None of the studies were eligible for meta-analysis.	

Lipman JM et al. 2012 [31]							YES, p = 0,002 OR (95% CI) 1,960 (1,262- 3,044)	
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Abbreviations: AC – acute cholecystitis, AOR – adjusted odds ratio, CI – confidence interval, Hba1c - glycosylated hemoglobin, HR – hazards ratio, IHM – in-hospital mortality, NR – not recorded, SSI – surgical site infection, LC – laparoscopic cholecystectomy, OR – odds ratio.

## Complications

In 19 of the analyzed articles, diabetes was discussed as an independent risk factor for acute cholecystitis and in 14 of them diabetes was confirmed as an independent risk factor for developing this disease [1, 8-19]. Two studies analyzed this correlation in detail and in one it was significant only for women ( $p < 0,001$ ), while in another it was significant only for men ( $p < 0,001$ ) [20-21]. On the contrary, in 3 studies diabetes was not confirmed as an independent risk factor for acute cholecystitis [22-24].

A total of 15 articles analyzed diabetes as a risk factor for conversion from laparoscopic to open surgery. In 10 studies diabetes was found to increase this conversion rate [6, 10, 25-32]. On the contrary, in 5 studies did not show that diabetes significantly affected the risk of conversion [16, 33-36]. However, in one of these studies it was noted that diabetic patients with higher levels of glycosylated hemoglobin had a significantly higher risk of conversion [35].

The problem of the number of postoperative complications in patients with diabetes was analyzed in 6 papers [6, 15-16, 18, 22, 32]. Authors of 4 articles noted that complications significantly more frequently affect this group of patients [6, 15-16, 32]. In all 6 papers pointed out systemic infectious complications after surgery [10, 13, 27, 32, 37-38] and 5 of them concluded that patients with diabetes are more at risk of systemic infectious complications [10, 27, 32, 37-38]. Septic shock as a separately listed postoperative complication appears in one study and its incidence is reported to be significantly higher for patients with diabetes [39].

Surgical site infection (SSI) in patients with diabetes has been discussed by the authors of 8 papers. In 6 articles it was reported that diabetes is a risk factor for SSI [13, 37-38, 40-42]. In one paper diabetes did not affect significantly the incidence of SSI [33]. In another paper, the authors summarized that diabetes did not increase significantly the incidence of SSI during laparoscopic cholecystectomy [43]. Authors of 4 articles analyzed the problem of postoperative wound dehiscence [10, 27, 37, 39]. Three of them reported that it significantly more frequently affected patients with

diabetes [10, 27, 37]. According to one study, respiratory complications were significantly more frequent in the group of patients with diabetes [33]. Cardiovascular events significantly more often affected patients suffering from diabetes according to 4 articles [10, 13, 37, 43]. The authors of all 3 papers which distinguished renal failure as a postoperative complication reported that the above problem significantly more often affects patients with diabetes [10, 39, 43].

In 9 studies, increased postoperative mortality in diabetics was analyzed. The authors of 7 of them reported that it is significantly higher in patients with diabetes [10, 15-16, 32, 37, 39, 43]. In one paper it was noticed that the mortality was increased only in patients who underwent laparoscopic surgery [13]. The authors of one paper did not observe the correlation between diabetes and increased mortality [18].

## Surgical complications

Just 2 papers examined the problem of intraoperative complications and only one of them confirmed the association between diabetes and the increased incidence of intraoperative complications [27, 32]. Two studies did not find the link between diabetes and increased intraoperative bleeding [26, 33]. On the other hand, one paper reported that diabetes increases the frequency of bleeding during surgery [27]. The authors of 3 papers reported that pre-operative gallbladder perforation occurs substantially more frequently to patients with diabetes [9, 27, 32]. In 3 studies no difference in the duration of surgery in patients with diabetes was noted, however in one of these studies it was demonstrated that the duration of anesthesia in patients with diabetes is significantly longer [26-27, 32].

## The course of hospitalization

Five studies analyzed the effect of diabetes on prolonged hospitalization after cholecystectomy. Two of those confirm that patients with diabetes require longer hospitalization [10, 26]. Whereas in the remaining 3 studies, no such correlation was observed [6, 27, 33].

## Recommendations

Elective surgery before the onset of symptoms of acute cholecystitis is recommended in 3 papers [15, 44, 45]. Whereas in 3 other articles such recommendation is not made [18, 22, 48]. Three authors discuss routine screening for cholelithiasis [15, 22, 45], and two of those recommend it [15, 45]. In one paper, the authors point out that patients with diabetes should be operated by laparoscopy because it improves postoperative outcomes [32].

## Discussion

The analyzed studies were very heterogeneous in terms of data quality and data reporting. Surprisingly many articles did not contain basic patient demographics, detailed methodology (e.g. patient inclusion/exclusion criteria) or full results presented in quantitative data. For these reasons it was impossible to perform a meta-analysis in addition to the systematic review and therefore to draw strong conclusions.

Most authors of the analyzed articles confirm that diabetes is a risk factor for acute cholecystitis, although some authors disagree [22-24]. Based on the literature reviewed, it seems that diabetes is an independent risk factor for acute cholecystitis. Most of the available literature suggests that diabetes is a risk factor for conversion from laparoscopic cholecystectomy to the open approach. Conversion was significantly more common in diabetics with higher HbA1c levels. The effectiveness of the patient's diabetes treatment affects the severity of biliary disease and can increase the risk of conversion. Postoperative complications seem to affect patients with diabetes more often. According to most authors diabetes is a risk factor for systemic infection, such as pneumonia or UTI. Diabetic patients significantly more often suffer from SSI, wound dehiscence and septic shock. Diabetes is an inde-

pendent risk factor for impaired wound healing, which is therefore in agreement with the general view.

The results of the analyzed articles also support the well-known fact that cardiovascular events and renal failure significantly more often affect patients with diabetes. It is noteworthy that the authors also noted a significantly increased postoperative mortality among diabetic patients. This may be directly related to the more frequent development of the above-mentioned complications. Another explanation for the above phenomenon is the more advanced age and more associated diseases discussed by the authors.

Regarding the recommendations for the management of patients with diabetes, the authors disagree whether elective cholecystectomy should be routinely performed in patients with diabetes. Although the EASL 2016 guidelines do not recommend routine cholecystectomy, the higher number of complications and mortality suggests that diabetic patients could benefit from such management [46]. Despite the large population of diabetic patients worldwide, at this time there is not enough high-quality evidence on this topic to formulate the necessary guidelines. An individualized approach, cholelithiasis screening and elective surgery could benefit not only patients but also the healthcare system.

## Conclusion

Patients with diabetes have an increased risk of developing acute cholecystitis. Furthermore, diabetic patients with acute cholecystitis tend to have more complicated course of the disease. An individualized approach and screening in selected cases, as well as elective cholecystectomy after proper preparation of the patient could have a positive effect on the outcome. However, the low quality of the data from the systematic review does not allow for meta-analysis, which is why we cannot draw strong conclusions.

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