Gdański Uniwersytet Medyczny
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Przebieg ostrego zapalenia pęcherzyka żółciowego u pacjentów obciążonych cukrzycą

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Dla Hani,
jesteś moim największym osiągnięciem.

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Spis treści

Słowa kluczowe

cholecystektomia, kamica żółciowa, cukrzyca, powikłania pooperacyjne, koszty hospitalizacji

Indeks skrótów

CRP, *C-reactive protein*, białko C-reaktywne
WBC, *white blood cells*, liczba białych krwinek
HGB, *hemoglobin*, hemoglobina
PRISMA, *preferred reporting items for systematic reviews and meta-analyses*, deklaracja zawierająca minimalny zestaw elementów niezbędnych do prawidłowego raportowania przeglądów systematycznych i meta-analiz
WHO, *World Health Organization*, Światowa Organizacja Zdrowia

Streszczenie

Wstęp

Według najnowszych danych Światowej Organizacji Zdrowia szacunkowa liczba osób cierpiących na cukrzycę na całym świecie wynosi 422 miliony[1]. Zapadalność na cukrzycę gwałtownie rośnie – przewiduje się, że do 2030 r. liczba chorych na cukrzycę zostanie podwojona[2]. Rocznie na świecie odnotowuje się 104 miliony przypadków patologii dotyczących pęcherzyka żółciowego i dróg żółciowych.

Cukrzyca zwiększa ryzyko wystąpienia ostrego zapalenia pęcherzyka żółciowego[3,4]. W grupie pacjentów obciążonych cukrzycą częściej występuje powikłany przebieg ostrego zapalenia pęcherzyka żółciowego. Dlatego też powyższe schorzenie stanowi istotny problem w populacji osób z cykrzycą[8]. W ciągu ostatnich 30 lat opublikowano niewiele badań na ten temat. Ponadto, neuropatia cukrzycowa może być czynnikiem opóźniającym i utrudniającym rozpoznanie objawów ostrego brzucha u chorych na cukrzycę[9]. Nie ma jednak badań wykazujących na większe miejscowe zaawansowanie ostrego zapalenia pęcherzyka żółciowego u pacjentów z cukrzycą.

Dodatkowo, cukrzyca ze względu na swoje powikłania powoduje ogromne koszty w publicznych systemach opieki zdrowotnej na całym świecie[10,11]. Ostre zapalenie pęcherzyka żółciowego u pacjentów z cukrzycą jest obarczone większym odsetkiem powikłań. Z tego powodu szacuje się, że koszty hospitalizacji chorych na cukrzycę są wyższe niż u osób bez cukrzycy. Literatura na ten temat jest jednak ograniczona.

Niniejszy przewód doktorski, składający się z dwóch prac oryginalnych oraz pracy będącej systematycznym przeglądem literatury, analizuje temat przebiegu ostrego zapalenia pęcherzyka żółciowego u pacjentów obciążonych cukrzycą.

Celem pracy było porównanie przebiegu ostrego zapalenia pęcherzyka żółciowego u pacjentów obciążonych cukrzycą oraz pacjentów bez cukrzycy.

Wstęp do rozprawy doktorskiej stanowi publikacja będąca systematycznym przeglądem dostępnej literatury na temat przebiegu ostrego zapalenia pęcherzyka żółciowego u pacjentów obciążonych cukrzycą pt „Acute cholecystitis in patients with diabetes mellitus-systematic review" (publikacja 1).

Część badawczą rozprawy doktorskiej stanowi praca oryginalna pt. - „Clinical presentation and outcomes of cholecystectomy for acute cholecystitis in patients with diabetes- A matched pair analysis. A pilot study"(publikacja 2). Retrospektywne badanie z dopasowaną pod względem wieku i płci grupą kontrolną pozwoliło wyciągnąć nowe wnioski na temat odmienności

przebiegu ostrego zapalenia pęcherzyka żółciowego u pacjentów chorych na cukrzycę. Trzecia praca oryginalna, zatytułowana „Cost of elective vs emergency cholecystectomy in diabetic patients", analizuje koszty hospitalizacji pacjentów obciążonych cukrzycą w porównaniu do pacjentów bez cukrzycy.

Cele

Publikacja 1

Celem pracy był systematyczny przegląd dostępnych danych naukowych dotyczących ostrego zapalenia pęcherzyka żółciowego u pacjentów chorych na cukrzycę.

Publikacja 2

Podstawowy cel badania stanowiło porównanie przebiegu klinicznego ostrego zapalenia pęcherzyka żółciowego u chorych na cukrzycę z osobami bez cukrzycy.

Celem drugorzędowym było porównanie wyników hospitalizacji powyższych pacjentów oraz odsetka powikłań w wymienionych grupach.

Publikacja 3

Celem badania było retrospektywne porównanie kosztów hospitalizacji związanej z wykonaniem cholecystektomii w trybie planowym oraz w trybie doraźnym u pacjentów chorych na cukrzycę oraz u pacjentów nieobciążonych cukrzycą.

Materiał i metody

Publikacja 1

Badanie zostało zaprojektowane zgodnie z wytycznymi deklaracji PRISMA (ang. Preferred reporting items for systematic reviews and meta-analyses). Przeprowadzono systematyczne przeszukiwanie baz danych PubMed i Web of Science w celu zidentyfikowania badań dotyczących ostrego zapalenia pęcherzyka żółciowego u pacjentów z cukrzycą, opublikowanych do dnia 1 września 2019 r. W celu wyszukiwania użyto następujących słów kluczowych: „(zapalenie pęcherzyka żółciowego LUB cholecystektomia) ORAZ (cukrzyca LUB pacjenci obciążeni cukrzycą)". W

przeglądzie uwzględniono jedynie publikacje pełnotekstowe opisujące przebieg hospitalizacji chorych na cukrzycę, którzy poddani zostali cholecystektomii z powodu ostrego zapalenia pęcherzyka żółciowego.
W kolejnym kroku porównano przebieg hospitalizacji u chorych na cukrzycę i bez cukrzycy, którzy zostali poddani cholecystektomii z powodu ostrego zapalenia pęcherzyka żółciowego. Wszystkie procedury związane z identyfikacją i oceną publikacji były wykonywane przez dwóch niezależnych badaczy.

Publikacja 2

Do retrospektywnego badania klinicznego włączono pacjentów, którzy poddani zostali cholecystektomii w trybie doraźnym w Klinice Chirurgii Ogólnej, Endokrynologicznej i Transplantacyjnej Uniwersyteckiego Centrum Klinicznego w Gdańsku w latach 2007–2017. Do badania włączono 267 pacjentów. Grupę badaną stanowiło 70 pacjentów obciążonych cukrzycą. Grupa kontrolna 197 pacjentów była dopasowana pod względem wieku i płci w stosunku 3:1. Identyfikację pacjenta w bazie danych oparto na obecności wszystkich następujących kryteriów: nieplanowane przyjęcie, cholecystektomia wykonana w ciągu 72 godzin od przyjęcia oraz dostępność wyników badań laboratoryjnych przy przyjęciu (CRP, WBC, HGB). Pacjentów przypisywano do grupy pacjentów z cukrzycą w przypadku stwierdzenia cukrzycy dowolnego typu podczas przyjęcia do szpitala lub w trakcie hospitalizacji. Z historii chorób pacjentów wyselekcjonowano następujące dane: objawy i wyniki badań laboratoryjnych odnotowane przy przyjęciu do szpitala, przebieg zabiegu operacyjnego, przebieg hospitalizacji, powikłania pooperacyjne, długość czasu hospitalizacji oraz zastosowanie antybiotykoterapii innej niż rutynowa profilaktyka okołooperacyjna.

Publikacja 3

Badanie to stanowi retrospektywną analizę, która objęła pacjentów, poddanych cholecystektomii w trybie doraźnym i planowym w Klinice Chirurgii Ogólnej, Endokrynologicznej i Transplantacyjnej Uniwersyteckiego Centrum Klinicznego w Gdańsku w latach 2016-2019. Spośród wszystkich zidentyfikowanych pacjentów, którzy poddani zostali cholecystektomii w trybie doraźnym, do badania włączono losową próbę 16 chorych na cukrzycę. Do powyższej grupy dopasowano grupę kontrolną skorygowaną względem wieku i płci. Następnie do badania włączono 20 chorych na cukrzycę, losowo wybranych spośród pacjentów, którzy przeszli planową cholecystektomię. Do

grupy dopasowano grupę kontrolną 80 pacjentów (dobraną pod względem wieku i płci) w stosunku 4: 1. Identyfikację pacjentów w bazie danych oparto na obecności wszystkich następujących kryteriów włączenia: przyjęcie nieplanowane lub planowane w zależności od grupy, cholecystektomia wykonana w ciągu 72 godzin od przyjęcia oraz dostępność pełnego raportu kosztów hospitalizacji w systemie elektronicznym. Pacjentów przypisywano do grupy pacjentów obciążonych cukrzycą w przypadku stwierdzenia cukrzycy dowolnego typu podczas przyjęcia do szpitala. Kalkulacja kosztów bezpośrednich oddziału ratunkowego obejmowała: obrazowanie medyczne, leki, konsultacje, badania laboratoryjne, wykonane zabiegi i sprzęt. Koszty brane pod uwagę przy obliczaniu kosztów bezpośrednich oddziału chirurgii ogólnej, w cholecystektomii doraźnej i planowej to: badania obrazowe, leki, konsultacje, badanie histopatologiczne, badania laboratoryjne, wykonane zabiegi, sprzęt, koszt sali operacyjnej oraz koszt pobytu. Całkowite koszty hospitalizacji brane pod uwagę przy planowej cholecystektomii to koszty oddziału chirurgii ogólnej. Całkowite koszty cholecystektomii w trybie doraźnym były sumą kosztów oddziału chirurgii ogólnej i oddziału ratunkowego.

Wyniki

Publikacja 1

Na podstawie analizowanej literatury uznano, że cukrzyca jest niezależnym czynnikiem ryzyka rozwoju zapalenia pęcherzyka żółciowego. Częstość występowania powikłań śródoperacyjnych i pooperacyjnych jest istotnie wyższa u chorych na cukrzycę. Pacjenci z cukrzycą, którzy z powodu ostrego zapalenia pęcherzyka żółciowego przeszli cholecystektomię w trybie doraźnym są narażeni na większe ryzyko powikłań infekcyjnych. W tej grupie pacjentów częściej obserwuje się zaburzenia ze strony układu oddechowego, układu krążenia, niewydolność nerek oraz większe ryzyko zgonu. Cukrzyca jest również czynnikiem ryzyka konwersji z cholecystektomii laparoskopowej do metody klasycznej.

Publikacja 2

Nie stwierdzono istotnej statystycznie różnicy w zakresie obserwowanych objawów przy przyjęciu do szpitala pomiędzy pacjentami obciążonymi cukrzycą oraz bez cukrzycy. Jednocześnie, częstość występowania powikłań śródoperacyjnych oraz pooperacyjnych jest istotnie wyższa u chorych na cukrzycę. U pacjentów z grupy badanej częściej obserwowano zakażenie

miejsca operowanego (p=0,04). Pacjenci obciążeni cukrzycą w okresie pooperacyjnym istotnie częściej wymagali leczenia w warunkach Oddziału Intensywnej Terapii (p=0,027). W trakcie hospitalizacji u pacjentów obciążonych cukrzycą istotnie częściej odnotowywano incydenty sercowe (p<0,001) oraz zapalenie płuc (p=0,009). Śmiertelność chorych w grupie chorych na cukrzycę była istotnie wyższa (p = 0,001). Czas operacji był dłuższy w grupie chorych na cukrzycę (p = 0,033). Długość hospitalizacji była istotnie dłuższa w grupie badanej (p <0,001). Nie stwierdzono istotnie wyższego współczynnika konwersji do metody klasycznej, ale istotnie częściej pacjentów obciążonych cukrzycą kwalifikowano pierwotnie do zabiegu metodą klasyczną (p=0.038) U pacjentów z cukrzycą, mimo mniej wyrażonych objawów, śródoperacyjnie stwierdzano bardziej miejscowo zaawansowaną chorobę.

Publikacja 3

Całkowity koszt hospitalizacji celem wykonania planowej cholecystektomii wyniósł 739,31 ± 423,07 USD dla pacjentów z cukrzycą i 797,14 ± 772,24 USD dla pacjentów bez cukrzycy (p = 0,51). Koszt cholecystektomii w trybie doraźnym wyniósł 3950,72 ± 2856,83 USD w przypadku chorych na cukrzycę i 2464,31 ± 1718,21 USD u pacjentów bez cukrzycy (p = 0,04). Różnica w całkowitych kosztach hospitalizacji między planową cholecystektomią, a zabiegiem w trybie doraźnym w obu badanych grupach (pacjenci z cukrzycą vs bez cukrzycy) była istotna statystycznie (odpowiednio p <0,01 vs p <0,05).

Wnioski

Przedstawione badania dostarczają nowych informacji dotyczących przebiegu ostrego zapalenia pęcherzyka żółciowego u pacjentów obciążonych cukrzycą.

Publikacja 1

Pacjenci obciążeni cukrzycą mają zwiększone ryzyko zachorowania na ostre zapalenie pęcherzyka żółciowego. Ponadto w tej grupie chorych istnieje zwiększone prawdopodobieństwo ciężkiego przebiegu ostrego zapalenia pęcherzyka żółciowego. Jednocześnie jakość danych uzyskanych z przeglądu systematycznego nie pozwala na metaanalizę.

Publikacja 2

Unikalną cechą pracy było stosowanie dopasowanej pod względem wieku i płci grupy kontrolnej. Pozwoliło to na ocenę wpływu cukrzycy jako niezależnej zmiennej. Udowodniono, że cukrzyca jest niezależnym czynnikiem ryzyka wystąpienia powikłanego przebiegu ostrego zapalenia pęcherzyka żółciowego. Badanie wykazało, że u pacjentów obciążonych cukrzycą, pomimo braku istotnych statystycznie różnic w wartościach wyników badań laboratoryjnych i nasilenia objawów podmiotowych, stwierdza się, zarówno śródoperacyjnie jak i w badaniach obrazowych, większe miejscowe zaawansowanie choroby.

Publikacja 3

W badaniu wykazano, że wykonanie cholecystektomii w trybie doraźnym wiąże się ze znacznym wzrostem kosztów leczenia chorych na cukrzycę w porównaniu z planową interwencją. Chociaż nie ma różnic w kosztach hospitalizacji w trybie planowym pomiędzy pacjentami z grupy badanej i kontrolnej, istnieje statystycznie istotna różnica w kosztach operacji w trybie doraźnym między chorymi na cukrzycę i bez cukrzycy.

Abstract

Introduction

According to the latest World Health Organization data, the estimated number of people suffering from diabetes worldwide is 422 million[1]. The incidence of diabetes is increasing rapidly and it is estimated that the number of people with diabetes will double by 2030[2].
Approximately 104 million new cases of gallbladder and bile duct pathologies are reported worldwide annually.

Diabetes increases the risk of developing acute cholecystitis[3,4]. In this group of patients, complications are more frequent[5,6]. Therefore, acute cholecystitis seems to be a serious problem in the diabetic population[8]. However, there were not many studies published in the last 30 years on this matter. Diabetic neuropathy may be a factor in the delayed and more difficult diagnosis of the acute abdomen in patients with diabetes[9]. There are no studies reporting a greater local advancement of acute cholecystitis in patients with diabetes. Because of its complications, diabetes mellitus impose huge costs in public healthcare systems around the globe[10-11]. Complications of acute cholecystitis in patients with diabetes are more frequent. For this reason diabetic patients hospitalization costs are estimated to be higher than non-diabetic. Literature on the topic is limited.

This doctoral thesis, consisting of two original papers and a paper that is a systematic literature review, explores the course of acute cholecystitis in diabetic patients.
The introduction to the doctoral dissertation is a publication that is a systematic review of the literature available on the course of acute cholecystitis in patients with diabetes, entitled "Acute cholecystitis in patients with diabetes mellitus - systematic review" (**publication 1**). The core of the doctoral dissertation is the original work entitled - "Clinical presentation and outcomes of cholecystectomy for acute cholecystitis in patients with diabetes- A matched pair analysis. A pilot study. "(**publication 2**). A retrospective study with age and sex-matched controls allowed for new conclusions to be drawn about the course of acute cholecystitis in patients with diabetes. The third original work, entitled "Cost of elective vs emergency cholecystectomy in diabetic patients" (**publication 3**), analyzes the costs of hospitalization of diabetic patients compared to non-diabetic patients.

Aims

Publication 1

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

Publication 2

The primary aim of this study was the comparison of the clinical course and laboratory parameters of acute cholecystitis in patients with diabetes vs. patients without diabetes. The secondary aim was to compare hospitalization results and the rate of complications between the above listed groups.

Publication 3

The aim of this study was to compare the costs of elective and emergency cholecystectomy of diabetic and non- diabetic patients.

Material and Methods

Publication 1

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We performed systematic search of the PubMed and Web of Science databases to identify studies on acute cholecystitis in patients with diabetes mellitus published until September 1st, 2019. Following search query was used: "(cholecystitis OR cholecystectomy) AND (diabetes OR diabetic)". 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. In the next step we compared the course of hospitalization of patients with and without diabetes who underwent cholecystectomy due to acute cholecystitis. All publications' selection and validation procedures were performed by two independent researchers.

Publication 2

The retrospective matched control study involved patients who underwent emergency cholecystectomy in the Department of General, Endocrine and Transplant Surgery of the University Clinical Center in Gdańsk, Poland in the years 2007–2017. There were 267 patients included in the study. The control group of 197 patients was age and sex matched at 3:1 ratio. Patient identification in the institution's registry was based on the presence of all of the following criteria: unplanned admission, cholecystectomy performed within 72 h of admission, and the availability of blood work at admission (CRP, WBC, HGB). Patients were assigned to the diabetic group whenever diabetes mellitus of any type was identified in the admission work-up.

The following data were identified in the patients' medical history: symptoms at admission, laboratory data at admission, course of surgery, postoperative course and complications, length of hospitalization and antibiotic therapy other than routine perioperative prophylaxis.

Publication 3

A retrospective analysis involved patients who underwent emergency and elective cholecystectomy in the Department of General, Endocrine and Transplant Surgery of University Clinical Center in Gdańsk, Poland between 2016-2019. A random sample of 16 diabetic patients who underwent emergency cholecystectomy were included to the study based on admission data criteria. Age and sex adjusted control group of non-diabetic patients was identified. Then, a random sample of 20 diabetic patients who underwent elective cholecystectomy were included to the study based on admission data criteria. The control group of 80 patients was age and sex matched in a 4:1 ratio.

Patients identification in the institution's registry was based on the presence of all of the following inclusion criteria: unplanned or planned admission depending on group, cholecystectomy performed within 72 h of admission, and the availability of complete report of hospitalization costs in the electronic system. Patients were assigned to the diabetic group whenever diabetes mellitus of any type was identified in the admission work-up.

Calculation of direct costs of emergency ward included: medical imaging, medicines, consultations, laboratory tests, procedures performed and equipment. Costs taken into account during calculating direct costs of general surgery ward, in emergency and elective cholecystectomy were: medical imaging, medicines, consultations, histopathology, laboratory works,

procedures performed, equipment, operating room cost, cost of stay. Total hospitalization costs taken into account for elective cholecystectomy were general surgery ward costs. Total costs of emergency cholecystectomy were a sum of costs of general surgery ward and costs of emergency ward.

Results

Publication 1

Diabetes is an independent risk factor for developing cholecystitis. Operative and postoperative complication rates were significantly higher in the diabetic patients. Patients with diabetes who had cholecystectomy due to acute cholecystitis have a higher risk of infectious complications, respiratory and circulatory disorders, renal failure and a higher risk of death. Diabetes is a risk factor for conversion from laparoscopic cholecystectomy to open method.

Publication 2

There was no significant difference between the diabetic and nondiabetic patients regarding symptoms at admission. Operative and postoperative complication rates were significantly higher in the diabetic patients.

Surgical site infection was observed more frequently in patients with diabetes ($p=0.04$). Hospitalization in the ICU was required significantly more often in study group ($p=0.027$). Patients with diabetes more frequently suffered from cardiac incidents ($p<0.001$) and pneumonia ($p=0.009$). Mortality rate in the patients with diabetes was higher ($p=0.001$).

The operative time was longer in the diabetic patients group ($p=0.033$). Length of hospitalization were significantly longer in the study group ($p <0.001$). The conversion rate was not higher in the study group, but open surgery was performed significantly more often ($p=0.038$). The diabetic patients had less pronounced symptoms with more locally advanced disease.

Publication 3

The total costs of an elective cholecystectomy were 739.31 ± 423.07 USD for diabetic patients and 797.14 ± 772.24 USD for non-diabetic patients ($p = 0.51$). Whereas emergency cholecystectomy total costs were 3950.72 ± 2856.83 USD (diabetic patients) and 2464.31 ± 1718.21 USD (non-diabetic patients) ($p = 0.04$). The difference in total costs between elective cholecystectomy vs

emergency cholecystectomy in both groups (diabetic vs non-diabetic patients) was statistically significant ($p<0.01$ vs $p< 0.05$ respectively).

Conclusions

Publication 1

Patients with diabetes have increased risk of developing acute cholecystitis. Furthermore, diabetic patients with acute cholecystitis tend to have more complicated course of the disease. However, the low quality of the data from the systematic review does not allow for performing a meta-analysis.

Publication 2

The presented studies provide new information on the course of acute cholecystitis in diabetic patients. The study shows that patients with diabetes have a significantly more eventful course of acute cholecystitis than patients without diabetes.
The study demonstrates that in patients with diabetes, despite the lack of statistically significant differences in the values of laboratory test results and the severity of symptoms, the disease is more locally advanced.

Publication 3

In this study we show that emergency cholecystectomy is associated with significant increase in costs in diabetic patients when compared to planned intervention. While there are no differences in the costs of elective hospitalizations, there is a statistically significant difference in the costs of emergency surgery between diabetic and non-diabetic patients.

Wstęp

Według najnowszych danych Światowej Organizacji Zdrowia szacunkowa liczba osób cierpiących na cukrzycę na całym świecie wynosi 422 miliony[1]. Zapadalność na cukrzycę gwałtownie rośnie – przewiduje się, że do 2030 r. liczba chorych na cukrzycę zostanie podwojona[2]. Rosnąca zapadalność na cukrzycę wynika z postępującej urbanizacji, zmian stylu życia, mniej wymagającej pracy fizycznej, coraz bardziej siedzącego trybu życia i spożywania wysokoenergetycznej żywności o niskiej wartości odżywczej.
Rocznie na świecie odnotowuje się 104 miliony przypadków patologii dotyczących pęcherzyka żółciowego i dróg żółciowych.

Cukrzyca zwiększa ryzyko wystąpienia ostrego zapalenia pęcherzyka żółciowego[3,4]. W grupie pacjentów obciążonych cukrzycą częściej występują powikłania, takie jak zgorzelinowe zapalenie pęcherzyka żółciowego i perforacja pęcherzyka żółciowego[5-7]. Dlatego też powyższe schorzenie stanowi istotny problemem w populacji pacjentów obciążonych cukrzycą [8]. Mimo to, w ciągu ostatnich 30 lat opublikowano niewiele badań na ten temat. Ponadto, neuropatia cukrzycowa może być czynnikiem opóźniającym i utrudniającym rozpoznanie objawów ostrego brzucha u chorych na cukrzycę[9]. Jest to związane m.in. z nietypowym obrazem klinicznym obserwowanym u chorych na cukrzycę. To opóźnia interwencję chirurgiczną, co z kolei może prowadzić do zwiększonej częstości powikłań. Nie ma badań wykazujących większe miejscowe zaawansowanie ostrego zapalenia pęcherzyka żółciowego u pacjentów z cukrzycą.

Cukrzyca ze względu na swoje powikłania powoduje ogromne koszty w publicznych systemach opieki zdrowotnej na całym świecie[10,11]. Ostre zapalenie pęcherzyka żółciowego u pacjentów z cukrzycą jest często powikłane zgorzelinowym zapaleniem pęcherzyka żółciowego, zapaleniem otrzewnej, perforacją pęcherzyka żółciowego, zaburzeniami gojenia się ran pooperacyjnych, zwiększonym ryzykiem incydentów sercowo-naczyniowych i niewydolnością nerek [12-19]. W związku z bardziej powikłanym przebiegiem hospitalizacji w grupie pacjentów obciążonych cukrzycą, szacuje się, że koszty hospitalizacji w tej grupie pacjentów są wyższe w porównaniu z chorymi bez cukrzycy. Literatura na ten temat jest ograniczona.
Celem pracy było porównanie przebiegu ostrego zapalenia pęcherzyka żółciowego u pacjentów obciążonych cukrzycą oraz pacjentów bez cukrzycy.

Niniejszy przewód doktorski, składający się z dwóch prac oryginalnych oraz pracy będącej systematycznym przeglądem literatury, analizuje temat przebiegu ostrego zapalenia pęcherzyka żółciowego u pacjentów obciążonych cukrzycą.

Wstęp do rozprawy doktorskiej stanowi publikacja będąca systematycznym przeglądem literatury dotyczącej przebiegu ostrego zapalenia pęcherzyka żółciowego u pacjentów obciążonych cukrzycą pt. - „Acute cholecystitis in patients with diabetes mellitus-systematic review"(**publikacja 1**). Główną część rozprawy doktorskiej stanowi praca oryginalna pt. - „Clinical presentation and outcomes of cholecystectomy for acute cholecystitis in patients with diabetes- A matched pair analysis. A pilot study."(**publikacja 2**) Retrospektywne badanie z dopasowaną pod względem wieku i płci grupą kontrolną pozwoliło wyciągnąć nowe wnioski na temat odmienności przebiegu ostrego zapalenia pęcherzyka żółciowego u pacjentów chorych na cukrzycę. Trzecia praca oryginalna przewodu, zatytułowana „Cost of elective vs emergency cholecystectomy in diabetic patients"(**publikacja 3**), analizuje koszty hospitalizacji pacjentów obciążonych cukrzycą w porównaniu do pacjentów zdrowych.

Cele prac

Publikacja 1

Acute cholecystitis in patients with diabetes mellitus-systematic review.
Celem pracy był systematyczny przegląd dostępnych danych naukowych dotyczących przebiegu ostrego zapalenia pęcherzyka żółciowego u pacjentów chorych na cukrzycę.

Publikacja 2

Clinical presentation and outcomes of cholecystectomy for acute cholecystitis in patients with diabetes- A matched pair analysis. A pilot study.
Główny cel badania stanowiło porównanie przebiegu klinicznego ostrego zapalenia pęcherzyka żółciowego u chorych na cukrzycę oraz u osób bez cukrzycy. Celem drugorzędnym było porównanie wyników hospitalizacji oraz odsetka powikłań w wymienionych grupach.

Publikacja 3

Costs of elective vs emergency cholecystectomy in diabetic patients
Celem badania było retrospektywne porównanie kosztów hospitalizacji związanej z wykonaniem cholecystektomii w trybie planowym oraz w trybie doraźnym u pacjentów chorych na cukrzycę oraz u pacjentów nieobciążonych cukrzycą.

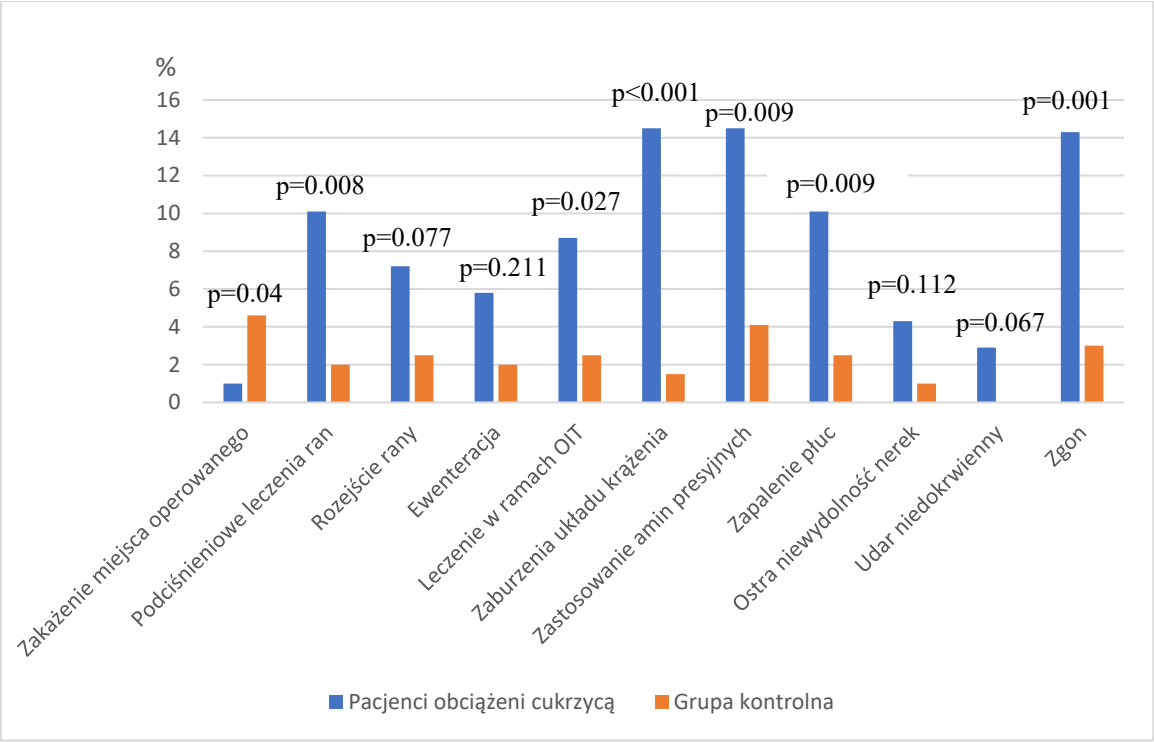
Wyniki

Publikacja 1

Na podstawie analizowanej literatury oceniono, że cukrzyca jest niezależnym czynnikiem ryzyka rozwoju zapalenia pęcherzyka żółciowego. Częstość występowania powikłań śródoperacyjnych i pooperacyjnych jest istotnie wyższa u chorych na cukrzycę. Pacjenci z cukrzycą, którzy z powodu ostrego zapalenia pęcherzyka żółciowego przeszli cholecystektomię w trybie doraźnym są narażeni na większe ryzyko powikłań infekcyjnych. W tej grupie pacjentów częściej obserwuje się zaburzenia ze strony układu oddechowego, układu krążenia, niewydolność nerek oraz większe ryzyko zgonu. Cukrzyca jest również czynnikiem ryzyka konwersji z cholecystektomii laparoskopowej do metody klasycznej.

Publikacja 2

Nie stwierdzono istotnej statystycznie różnicy w zakresie obserwowanych objawów przy przyjęciu do szpitala pomiędzy pacjentami obciążonymi cukrzycą oraz bez cukrzycy. Jednocześnie, częstość występowania powikłań śródoperacyjnych oraz pooperacyjnych jest istotnie wyższa u chorych na cukrzycę. U pacjentów z grupy badanej częściej obserwowano zakażenie miejsca operowanego 11,6% vs 4,6% (p=0,04). Pacjenci obciążeni cukrzycą w okresie pooperacyjnym istotnie częściej wymagali leczenia w warunkach Oddziału Intensywnej Terapii 8,7% vs 2,5% (p=0,027). W trakcie hospitalizacji u pacjentów obciążonych cukrzycą istotnie częściej odnotowywano incydenty sercowe 14,5% vs 1,5 % (p<0,001) oraz zapalenie płuc 10,1% vs 2,5% (p=0,009). Śmiertelność chorych w grupie chorych na cukrzycę była istotnie wyższa 14,3% vs 3% (p = 0,001). Czas operacji był dłuższy w grupie chorych na cukrzycę mediana (min-max) 97.5 min (22–448 min) vs 85 min (25–260 min) w grupie pacjentów bez cukrzycy (p = 0,033). Długość hospitalizacji była istotnie dłuższa w grupie badanej 6 dni (1–38) vs 4 dni (2–54) (mediana (min-max); (p <0,001). Nie stwierdzono istotnie wyższego współczynnika konwersji do metody klasycznej 15,7% vs 14,7% (p=0,841), ale istotnie częściej pacjentów obciążonych cukrzycą kwalifikowano pierwotnie do zabiegu metodą klasyczną 52,9% vs 38,6% (p=0.038) U pacjentów z cukrzycą, mimo mniej wyrażonych objawów, śródoperacyjnie stwierdzano bardziej miejscowo zaawansowaną chorobę 47,1% vs12,7% (p<0,001).



Tab.1. Powikłania przebiegu pooperacyjnego w grupie pacjentów obciążonych cukrzycą w porównaniu do pacjentów bez cukrzycy

Publikacja 3

Całkowity koszt hospitalizacji celem wykonania planowej cholecystektomii wyniósł 739,31 ± 423,07 USD dla pacjentów z cukrzycą i 797,14 ± 772,24 USD dla pacjentów bez cukrzycy (p = 0,51). Koszt cholecystektomii w trybie doraźnym wyniósł 3950,72 ± 2856,83 USD w przypadku chorych na cukrzycę i 2464,31 ± 1718,21 USD u pacjentów bez cukrzycy (p = 0,04). Różnica w całkowitych kosztach hospitalizacji między planową cholecystektomią, a zabiegiem w trybie doraźnym w obu badanych grupach (pacjenci z cukrzycą vs bez cukrzycy) była istotna statystycznie (odpowiednio p <0,01 vs p <0,05).

Koszt	Pacjenci obciążeni cukrzycą-tryb doraźny	Pacjenci bez cukrzycy-tryb doraźny	**p**	Pacjenci obciążeni cukrzycą-tryb planowy	Pacjenci bez cukrzycy-tryb planowy	**p**
Całkowity koszt hospitalizacji	3950,72 ± 2856,83	2464,31 ± 1718,21 USD	0,04	739,31 ± 423,07 USD	797,14 ± 772,24 USD	0,51

Tab.2. Całkowity koszt hospitalizacji w grupie operowanej w trybie doraźnym vs planowa cholecystektomia.

Wnioski

Publikacja 1

Pomimo ogromnej populacji pacjentów chorych na cukrzycę literatura na temat zapalenia pęcherzyka żółciowego w tej grupie chorych jest ograniczona. Aż 25% prac spełniających kryteria włączenia do przeglądu powstało ponad 20 lat temu.

Analizowana literatura nie pozwala na sformułowanie wysokiej jakości wniosków i stworzenie wytycznych dotyczących postępowania z pacjentami obciążonymi cukrzycą z ostrym zapaleniem pęcherzyka żółciowego. Jakość danych dostępnych do przeglądu systematycznego nie pozwala na przeprowadzenie metaanalizy.

Zdecydowana większość autorów jest zgodna, że cukrzyca jest niezależnym czynnikiem ryzyka wystąpienia ostrego zapalenia pęcherzyka żółciowego. Ponadto, ostre zapalenie pęcherzyka żółciowego u pacjentów obciążonych cukrzycą cechuje się znacznie bardziej powikłanym przebiegiem. Obserwowana zwiększona śmiertelność w tej grupie chorych może być związana z częściej występującymi powikłaniami. Nie można jednak wykluczyć, że wynika ona z bardziej zaawansowanego wieku pacjentów obciążonych cukrzycą w porównaniu z grupą kontrolną.

W analizowanej literaturze znajdują się rekomendacje dotyczące rutynowego badania przesiewowego w kierunku kamicy pęcherzyka żółciowego u pacjentów obciążonych cukrzycą. Zindywidualizowane podejście i badanie przesiewowe w wybranych przypadkach, a także planowa cholecystektomia po odpowiednim przygotowaniu chorego mogą poprawić wyniki leczenia.

Publikacja 2

Unikalną w tej tematyce cechą pracy było stosowanie dopasowanej pod względem wieku i płci grupy kontrolnej. Pozwoliło to na ocenę wpływu cukrzycy na przebieg ostrego zapalenia pęcherzyka żółciowego jako niezależnej zmiennej.

Na podstawie przeprowadzonych badań wykazano, że cukrzyca jest niezależnym czynnikiem ryzyka wystąpienia powikłanego przebiegu ostrego zapalenia pęcherzyka żółciowego. Stwierdzono, że przebieg kliniczny ostrego zapalenia pęcherzyka żółciowego u pacjentów obciążonych cukrzycą różni się istotnie od przebiegu tej choroby u pacjentów bez cukrzycy.

U chorych z grupy badanej częściej obserwowano zakażenie miejsca operowanego i cechy nieprawidłowego procesu gojenia. Upośledzone

gojenie ran jest udokumentowaną i dobrze znaną z codziennej praktyki klinicznej konsekwencją nieprawidłowej kontroli glikemii u pacjentów obciążonych cukrzycą. Ponadto w tej grupie pacjentów istotnie częściej decydowano się na klasyczną metodę przeprowadzenia zabiegu operacyjnego, co wiąże się z dużo większą raną operacyjną, a co za tym idzie większym urazem, utrudnionym gojeniem i większym ryzykiem zakażenia miejsca operowanego w porównaniu do ran powstałych w wyniku zabiegu laparoskopowego.

Czas trwania zabiegu operacyjnego był dłuższy w grupie chorych obciążonych cukrzycą, co stanowi naturalną konsekwencje bardziej miejscowo zaawansowanego procesu zapalnego. Dłuższy czas zabiegu operacyjnego jest czynnikiem ryzyka wystąpienia powikłań i dłuższego czasu hospitalizacji.

W trakcie hospitalizacji u pacjentów obciążonych cukrzycą istotnie częściej odnotowywano incydenty sercowe oraz zapalenie płuc. Osoby obciążone cukrzycą w okresie pooperacyjnym istotnie częściej wymagały leczenia w warunkach Oddziału Intensywnej Terapii, a śmiertelność pacjentów w tej grupie chorych była istotnie wyższa.

W badaniu nie wykazano istotnie większej ilości konwersji z metody laparoskopowej do metody klasycznej u pacjentów obciążonych cukrzycą. Stoi to w opozycji do wniosków uzyskanych z przeglądu systematycznego, gdzie większość autorów wskazywała cukrzycę jako czynnik ryzyka konwersji. Jednocześnie wykazano, że pacjenci obciążeni cukrzycą istotnie częściej byli kwalifikowani do operacji metodą klasyczną.

Badanie wykazało, że u pacjentów obciążonych cukrzycą, pomimo braku istotnych statystycznie różnic w wartościach wyników badań laboratoryjnych i nasilenia objawów podmiotowych w momencie przyjęcia, stwierdza się zarówno śródoperacyjnie, jak i w badaniach obrazowych, większe miejscowe zaawansowanie choroby. Prawdopodobnie jest to związane z neuropatią cukrzycową i ze zmniejszonym odczuwaniem bólu przez pacjentów obciążonych cukrzycą. Można podejrzewać, że bardziej zaawansowana miejscowo choroba u pacjentów obciążonych cukrzycą w porównaniu do grupy kontrolnej w momencie zgłoszenia się pacjenta do lekarza jest jednym z czynników wpływających na dalszy przebieg choroby i ostateczny wynik leczenia. Stanowi to istotny klinicznie wniosek i wymaga dalszych badań w zakresie ostrych schorzeń w obrębie jamy brzusznej w tej grupie chorych.

Publikacja 3

W badaniu wykazano, że u chorych na cukrzycę cholecystektomia wykonana w trybie doraźnym wiąże się ze znacznym wzrostem kosztów w porównaniu interwencją w trybie planowym. Zwiększone koszty hospitalizacji w trybie doraźnym wynikają ze zwiększonej częstości występowania powikłań, dłuższego okresu hospitalizacji oraz kosztów diagnostyki obrazowej.

Nie wykazano istotnej statystycznie różnicy w kosztach zabiegu planowego pomiędzy pacjentami z grupy badanej i kontrolnej. Świadczy to pośrednio o porównywalnym przebiegu hospitalizacji pod względem ilości odnotowanych powikłań i długości pobytu. Jest to kolejny wniosek przemawiający za potencjalną korzyścią, którą można uzyskać z wczesnej kwalifikacji pacjentów obciążonych cukrzycą i kamicą pęcherzyka żółciowego do planowej cholecystektomii.

Pomimo, że nie ma różnic w kosztach hospitalizacji w trybie planowym pomiędzy pacjentami z grupy badanej i kontrolnej, istnieje statystycznie istotna różnica w kosztach operacji w trybie doraźnym między pacjentami obciążonymi cukrzycą i bez cukrzycy. Jest to związane ze zwiększoną częstością występowania powikłań oraz dłuższą hospitalizacją w grupie pacjentów obciążonych cukrzycą. Powyższa obserwacja jest finansowym odzwierciedleniem danych uzyskanych w publikacji 2.

Podsumowanie

Zaprezentowane prace dostarczają nowych informacji dotyczących przebiegu ostrego zapalenia pęcherzyka żółciowego u pacjentów obciążonych cukrzycą.

Informacje dostarczone przez powyższe badanie pozwalają wyciągnąć wnioski, że pacjentów obciążonych cukrzycą powinno się wcześnie kwalifikować do zabiegu w trybie ostrodyżurowym, ale też należy być przygotowanym na bardziej powikłany przebieg pooperacyjny, a tym samym znacznie wyższe ryzyko związane z zabiegiem niż w przypadku pacjentów nieobciążonych cukrzycą.

Zindywidualizowane podejście i zwracanie szczególnej uwagi na zgłaszane przez pacjentów z cukrzycą objawy, a także planowa cholecystektomia po odpowiednim zakwalifikowaniu i przygotowaniu chorego, mogą poprawić wyniki leczenia w tej grupie chorych.

Lista publikacji i dane bibliometryczne

Publikacja 1
Acute cholecystitis in patients with diabetes mellitus – systematic review
Eur J Transl Clin Med. 2020;2(2):71-79
doi:10.31373/ejtcm/115402
Monika Łącka (autor korespondencyjny), Piotr Spychalski, Małgorzata Dobrzycka, Olga Rostkowska, Jarosław Kobiela
Bibliometria: MNiSW: 5.000

Publikacja 2
Clinical presentation and outcomes of cholecystectomy for acute cholecystitis in patients with diabetes - A matched pair analysis. A pilot study.
Adv Med Sci. 2020;65(2):409-414
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Monika Łącka (autor korespondencyjny), Paweł Obłój, Piotr Spychalski, Dariusz Łaski, Olga Rostkowska, Paulina Wieszczy, Jarosław Kobiela
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Publikacja 3
Costs of elective vs emergency cholecystectomy in diabetic patients.
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Monika Łącka (autor korespondencyjny), Piotr Spychalski, Paweł Obłój, Dariusz Łaski, Olga Rostkowska, Paulina Wieszczy, Jarosław Kobiela
Bibliometria: MNiSW: 5.000

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REVIEW ARTICLE

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

Citation

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DOI: 10.31373/ejtcm/115402

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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 (PRIMSA) 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 1st 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.

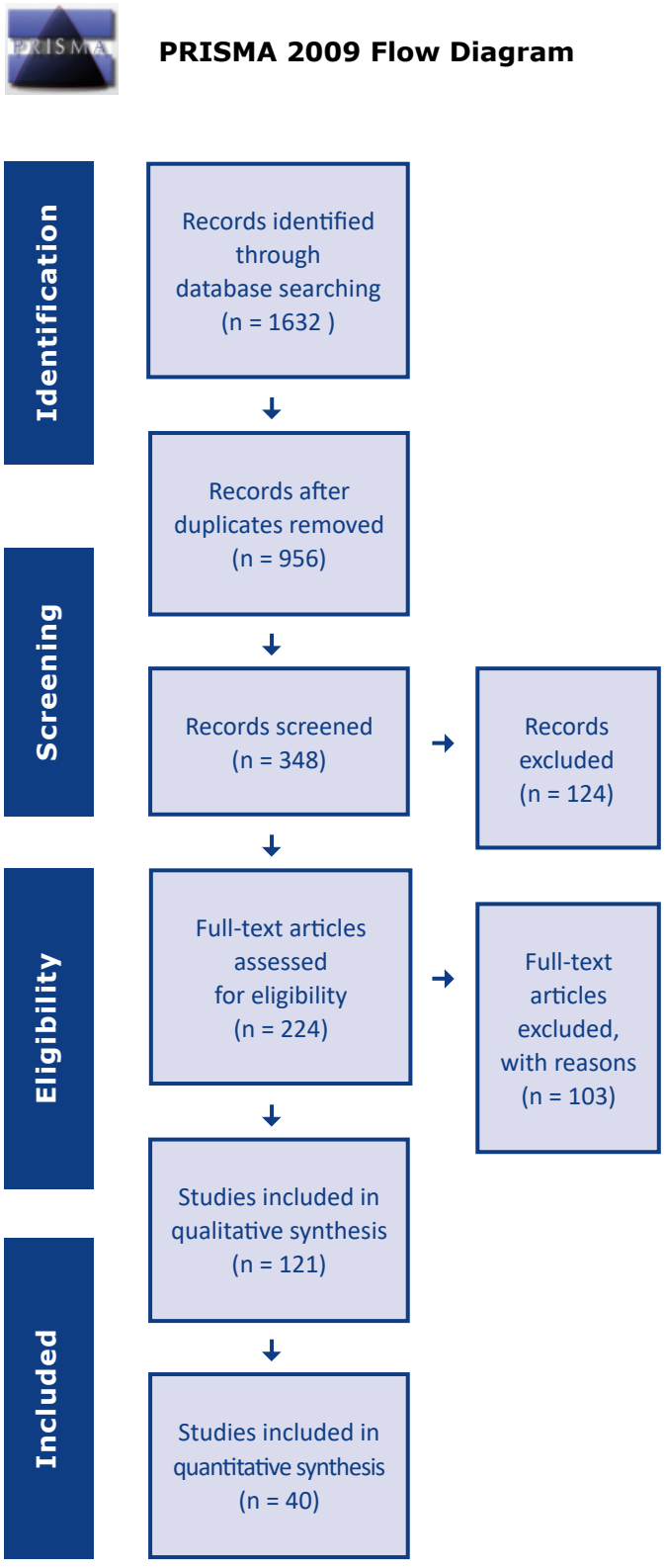

Figure 1. Flowchart illustrating the literature search

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.

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	
Cucchiaro 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)	

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 glycated 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 independent 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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Original research article

Clinical presentation and outcomes of cholecystectomy for acute cholecystitis in patients with diabetes - A matched pair analysis. A pilot study

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ABSTRACT

Purpose: The primary aim of this study is to compare the clinical course and laboratory parameters of acute cholecystitis in patients with diabetes *vs*. patients without diabetes.

Materials and methods: The study involved patients who underwent emergency cholecystectomy in the Department of General, Endocrine and Transplant Surgery of University Clinical Center in Gdansk (Poland) between 2007 and 2017.

There were 267 patients included in the study. The control group of 197 patients was age and sex matched at a 3:1 ratio.

The following was compared between the groups: symptoms at admission, course of surgery, postoperative course, length of hospitalization, total costs of hospitalization and antibiotic therapy, other than routine perioperative prophylaxis.

Results: There was no significant difference between the patients with and without diabetes regarding symptoms at admission. Operative and postoperative complication rates were significantly higher in the patients with diabetes. The operative time and length of hospitalization were significantly longer in the study group. The conversion rate was not higher in the study group, but classic surgery was performed significantly more often. The patients without diabetes had less pronounced symptoms with more locally advanced disease.

Conclusions: Our study demonstrates that patients with diabetes have a significantly more eventful course of acute cholecystitis than patients without diabetes. Patients with diabetes should therefore be qualified for cholecystectomy early in the course of acute cholecystitis.

1. Introduction

According to the latest World Health Organization data, the estimated number of people suffering from diabetes worldwide is 422 million [1], and the incidence of diabetes is increasing rapidly. It is estimated that the number of people with diabetes will double by 2030 [2]. The increasing incidence of diabetes results from progressive urbanization, lifestyle changes, less physically demanding work, increasingly sedentary lifestyles, and the consumption of high-energy food with low nutritional value.

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 [3–5]. People with diabetes, due to a functional deficit of unclear etiology, have a poorly emptying, larger gallbladder compared to the nondiabetic population. Moreover, the proportion of bile acids differs as well [6]. It has been proposed that diabetic neuropathy may play a role in the abovementioned differences [7]. Acute cholecystitis is, in more than 90% of cases, caused by a gallstone blocking the cystic duct [8]. Diabetes increases the risk of developing acute cholecystitis [9,10]. In this group of patients, complications of acute cholecystitis such as gangrenous cholecystitis, bacteriobila, perforation and

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emphysematous cholecystitis are more frequent [11–13]. Therefore, acute cholecystitis seems to be a serious problem in the diabetic population [14]. However, there were not many studies 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 an almost threefold increase in postoperative complications [15]. The literature in this regard is, however, limited.

Diabetic neuropathy may be a factor in the delayed and more difficult diagnosis of the acute abdomen in patients with diabetes [16]. This is related to, among others, the atypical presentation of symptoms in patients with diabetes. This postpones surgical intervention, which in turn may lead to the increased incidence of complications. There are no studies reporting a greater local advancement of acute cholecystitis in patients with diabetes.

The primary aim of this study is the comparison of the clinical course and laboratory parameters of acute cholecystitis in patients with diabetes *vs.* patients without diabetes. The secondary aim is to compare hospitalization results and the rate of complications between the above listed groups. The tertiary aim is to compare the costs of hospitalization between these groups.

2. Materials and Methods

2.1. Study design

The retrospective matched case control study involved patients who underwent emergency cholecystectomy at the Department of General, Endocrine and Transplant Surgery of the University Clinical Center in Gdansk (Poland) between 2007 and 2017. A total of 661 patients were identified in the institution's registries, of which there were 70 patients with diabetes - the study group - and 591 patients without diabetes. The latter group was used to select an age and sex adjusted control group.

Patient identification in the institution's registry was based on the presence of all of the following criteria: unplanned admission, cholecystectomy performed within 72 h of admission, and the availability of blood work at admission (C-reactive protein - CRP, white blood count - WBC and hemoglobin - HGB). Patients were assigned to the diabetic group whenever diabetes mellitus of any type was identified in the admission work-up. A control group of 197 patients was age and sex matched at a 3:1 ratio (Fig 1).

2.2. Data compared

The following data were identified in the patients' medical history: symptoms at admission, laboratory data at admission, surgery approach, postoperative course complications, antibiotic therapy, length of hospitalization, and cost of hospitalization.

2.2.1. Symptoms at admission

We verified the medical history to see if there was peritoneal reflex, Chełmoński's (Murphy's) sign, presence of peristalsis.

2.2.2. Laboratory data at admission

We checked the medical history to see the CRP, WBC and HGB values at admission (Table 2).

2.2.3. Surgery approach

We verified the medical history to see if there was open or laparoscopic approach, length of surgery, use of bile duct drainage or peritoneal drainage, changes in the morphological image of the gallbladder observed during surgery, empyema, presence of free fluid in the peritoneal cavity (Table 3).

2.2.4. Postoperative course complications

We checked the medical history to see if there was surgical site infection, use of negative pressure wound therapy (NPWT), wound dehiscence, eventration, cardiac event (myocardial infarction, atrial fibrillation, ventricular fibrillation), transfer to Intensive Care Unit (ICU), noradrenaline use, pneumonia, acute kidney injury (AKI), ischaemic stroke, death (Fig. 2).

Table 1
Demographic information.

	Diabetes n (%)	Non-diabetic n (%)
Females	27 (39%)	77 (39%)
< 35	3 (11.11%)	9 (11.69%)
35-64	11 (40.74%)	32 (41.56%)
65-80	8 (29.63%)	22 (28.57%)
> 80	5 (18.52%)	14 (18.18%)
Males	43 (61%)	120 (61%)
< 35	1 (2.33%)	3 (2.5%)
35-64	22 (51.16%)	66 (55%)
65-80	17 (39.54%)	42 (35%)
> 80	3 (6.97%)	9 (7.5%)

Table 2
Initial presentation.

Variable	Case n = 70	Control n = 197	p value
Chełmoński/Murphy sign, n (%)	39 (56.5%)	122 (64.9%)	0.219
Peritoneal reflexes, n (%)	11 (15.9%)	29 (15.3%)	0.906
Peristalsis, n (%)	63 (91.3%)	183 (96.8%)	0.062
CRP, median (min-max)	72.0 (4.8–363.9)	64.6 (0.2–337.7)	0.221
WBC, median (min-max)	9.5 (4.7–60.9)	8.9 (3.3–30.4)	0.589
HGB, median (min-max)	11.4 (6.9–15.6)	12.8 (6.8–17.8)	< 0.001

2.2.5. Antibiotic therapy

We verified the medical history to see if there was other than routine perioperative prophylaxis during hospitalization, antibiotic treatment continued after discharge. The frequencies of the abovementioned was compared between the study groups (Table 4).

2.2.6. Length of hospitalization

Length of hospitalization is presented in Table 4.

2.2.7. Cost of hospitalization

Total cost of emergency cholecystectomy was a sum of the costs of the general surgery ward and the costs of the emergency ward. Values were converted from PLN to USD using the exchange rates as of 11th September 2019 according to the National Bank of Poland (Table 4).

2.3. Ethical issues

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

2.4. Statistical Analysis

For descriptive analysis, the medians, means and standard deviations were used. The Chi-square test or the exact Fisher test (if the number of observations in the cells was < 5) was used to compare the categorical variables. Normality was tested with the Shapiro-Wilk test. For continuous variables that were not following the normal distribution, nonparametric Wilcoxon and Mann-Whitney U tests were used to make comparisons between the groups. For variables following the normal distribution Student's t-test was used. Statistical significance was accepted at $p < 0.05$. Statistical analyses were performed using Statistica 13.3 Polish language version (TIBCO Software, Stat Soft

Table 3
Surgery findings.

Variable	Case n = 70	Control n = 197	p value
Laparoscopic procedure, n (%)	33 (47.1%)	121 (61.4%)	0.038
Open procedure, n (%)	37 (52.9%)	76 (38.6%)	0.038
Conversion from laparoscopic to open cholecystectomy, n (%)	11 (15.7%)	29 (14.7%)	0.841
Length of surgery, median (min-max)	97.5 (22–448)	85 (25–260)	0.033
Bile ducts' drainage, n (%)	0 (0.0%)	6 (3.0%)	0.486
Peritoneal drainage, n (%)	69 (98.6%)	187 (94.9%)	0.298
Changes in the morphological intraoperative image of the gallbladder, n (%)	33 (47.1%)	25 (12.7%)	< 0.001
Empyema intraoperatively, n (%)	26 (37.1%)	61 (31.0%)	0.343
Free fluid in peritoneal cavity, n (%)	15 (21.4%)	12 (6.1%)	< 0.001

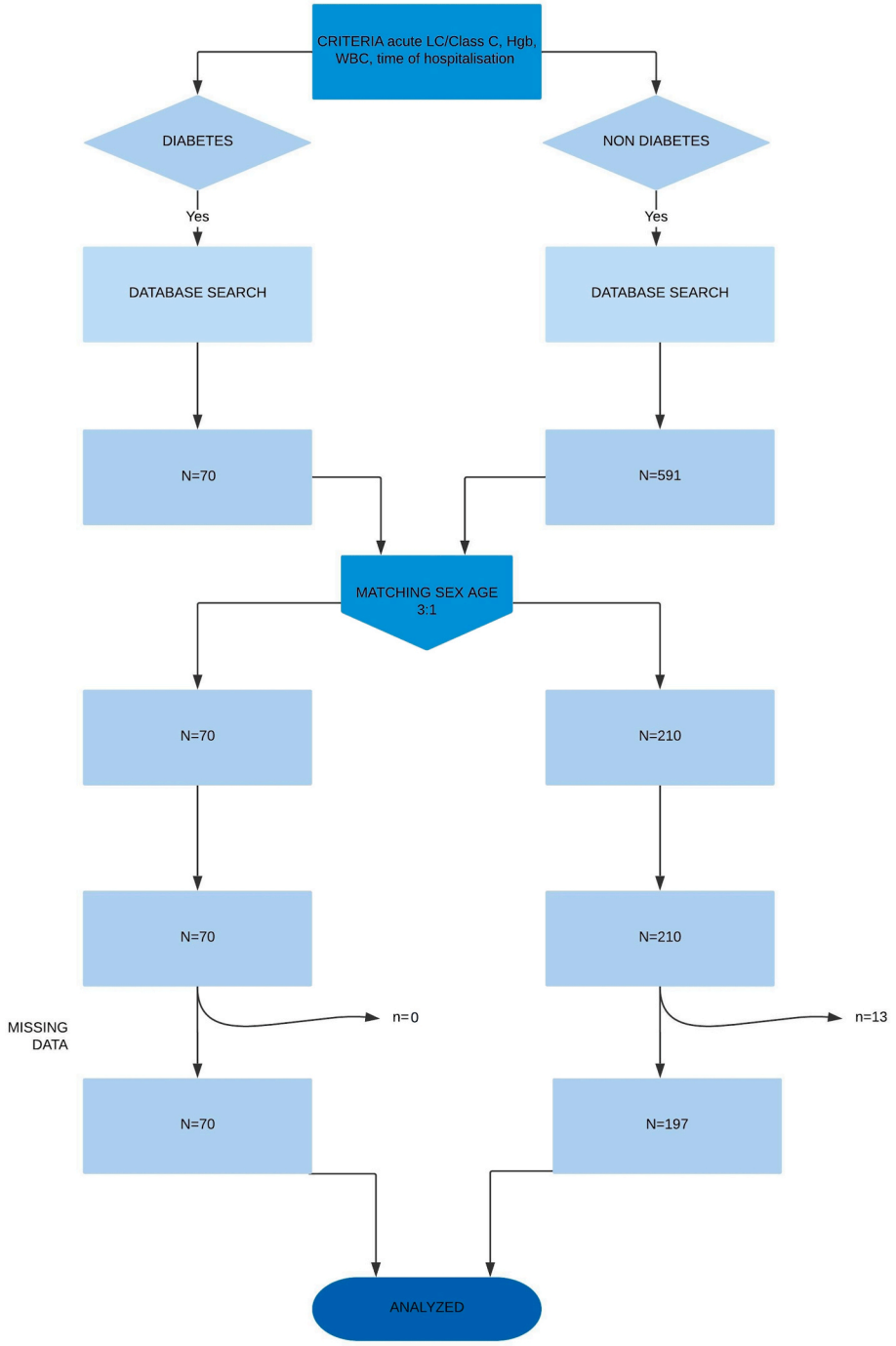

Fig. 1. Flowchart illustrating patient selection.

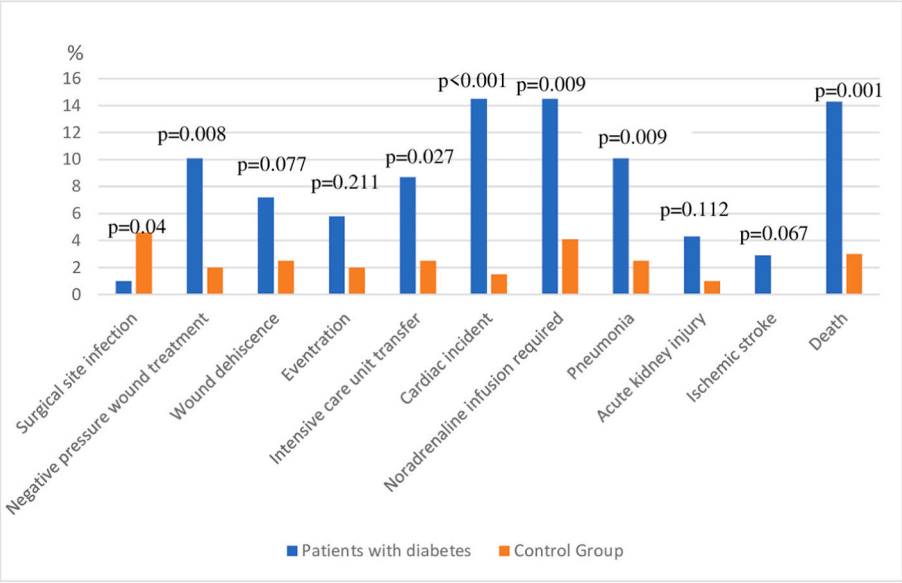

Fig. 2. Postoperative course – complications.

Krakow, Poland).

3. Results

3.1. Patients selection

A group of 280 patients was selected: 172 men and 108 women. Due to incomplete data, 13 patients were then excluded from the study, which resulted in a total of 267 patients being included in the study. There were 27 women and 43 men in the study group, and 77 women and 120 men in the control group.

The average age of patients in the study group was 54 years, and 52 years in the control group (Table 1).

3.2. Data compared

3.2.1. Symptoms at admission

Morphological changes typical for the course of acute cholecystitis were found in 47.1% of patients from the study group and 12.7% of patients from the control group ($p < 0.001$). Free fluid in the peritoneal cavity was found and collected for culture in 21.4% of the study group and 6.1% of the control group ($p < 0.001$) (Table 2).

3.2.2. Laboratory data at admission

CRP value at admission in the study group was median (min-max) 72.0 mg/l (4.8–363.9), and 64.6 mg/l (0.2–337.7) in the control group ($p = 0.221$) (Table 2).

3.2.3. Surgery

In the study group, cholecystectomy was performed using the open approach in 52.9% of patients, while 38.6% were operated on with the open technique in the control group ($p = 0.038$). Conversion from the laparoscopic method to the open method was necessary in 15.7% of cases in the study group, and 14.7% in the control group ($p = 0.841$). The duration of surgery in the study group was significantly longer ($p = 0.033$) with median (min-max) 97.5 min (22–448 min) in the study group, and 85 min (25–260 min) in the control group ($p = 0.033$) (Table 3).

3.2.4. Postoperative course — complications

Surgical site infection was observed in 11.6% of patients from the study group and 4.6% from the control group ($p = 0.04$). Negative pressure wound therapy was used in 10.1% of patients from the study group and 2.0% from the control group ($p = 0.008$). Wound dehiscence was observed in 7.2% of patients from the study group and 2.5% of patients from the control group ($p = 0.077$). Hospitalization in the ICU was required in 8.7% of patients from the study group and 2.5% from the control group ($p = 0.027$). Patients suffered from cardiac incidents in 14.5% of cases from the study group and 1.5% from the control group ($p < 0.001$). Types of cardiac incidents observed in the control group included acute circulatory failure, arrhythmias (atrial fibrillation, ventricular tachycardia) and cardiac arrest.

Acute circulatory failure was observed in 7% of patients from the study group and 1.02% of patients from the control group ($p = 0.0003$). Arrhythmias - atrial fibrillation or ventricular tachycardia - was observed in 5.71% of patients from the study group and 0.51% of patients from the control group ($p = 0.0058$). Cardiac arrest was observed in 7% of patients from the study group and 0.51% of patients from control group ($p = 0.0001$).

Patients required noradrenaline infusion in 14.5% of the time in the study group and 4.1% in the control group ($p = 0.009$). The course of hospitalization was complicated by pneumonia in the study group in 10.1% of cases and in the control group in 2.5% ($p = 0.009$). Mortality in the patients with diabetes was 14.3% and in the patients without diabetes 3% ($p = 0.001$) (Fig. 2).

Table 4
Postoperative course-antibiotics, length of hospitalization, total cost of hospitalization.

Variable	Case n = 70	Control n = 197	p value
Antibiotics during hospitalization, n (%)	46 (65.7%)	118 (59.9%)	0.391
Antibiotics on discharge, n (%)	24 (34.3%)	82 (42.1%)	0.255
Length of hospitalization in days, median (min-max)	6 (1–38)	4 (2–54)	< 0.001
Total hospitalization cost (USD)	3950.72 ± 2856.83	2464.31 ± 1718.21	0.04

3.2.5. Antibiotic therapy

In the study group, 65.7% of patients, and in the control group 59.9% (p = 0.391) required other than routine antibiotic therapy during hospitalization. In the study group, 34.3% of patients required antibiotics on discharge and in the control group it was 42.1% of patients (p = 0.255).

3.2.6. Length of hospitalization

Length of hospitalization in the study group was 6 days (1–38) and in the control group 4 days (2–54) (median (min-max); p < 0.001) (Table 4).

3.2.7. Total cost of hospitalization

In the group of patients who underwent emergency cholecystectomy, the total costs were 3950.72 ± 2856.83 USD for the patients with diabetes and 2464.31 ± 1718.21 USD for the patients without diabetes (p = 0.04) (Table 4).

4. Discussion

To the best of our knowledge, this is the first study with age and sex matched controls to comprehensively describe the differences between the course of acute cholecystitis of patients with diabetes and patients without diabetes treated surgically.

In our study, despite there being no differences in the CRP levels between the study and control groups, the patients with diabetes had a more locally advanced disease. It was previously described that in patients with diabetes, less pronounced symptoms were observed with simultaneously more locally advanced disease [16]. It was assumed that acute abdomen in patients with diabetes creates greater diagnostic difficulties because patients with neuropathy have less characteristic symptoms [17]. Further studies are required to elucidate whether patients with diabetes present later to the emergency department due to visceral neuropathy or whether cholelithiasis progresses faster due to metabolic disturbances caused by diabetes. Regardless of the mechanism, it was concluded that patients with diabetes should be qualified for cholecystectomy early in the course of acute cholecystitis [18].

In our study, there was no increased frequency of conversion from the laparoscopic to open approach in cholecystectomy in the group of patients with diabetes (p = 0.841). This is contrary to the results presented in many other reports [19–22]. Diabetes was identified among factors that can independently predict a higher risk of conversion [14,23,24]. This issue was not recently studied, with the majority of studies being published in the 1990s. The results of our study are however in accordance with a recently published study indicating that diabetes is not a risk factor for conversion [25,26]. This may be due to the increasing laparoscopic experience of surgical teams worldwide [27]. On the contrary, there is the possibility that the statistical tests were underpowered to detect a small but present difference. We do not routinely examine glycated hemoglobin in emergency cases, but there are studies that show that only values HbA1c > 6% in patients with diabetes were a risk factor of conversion [28]. In our study, the open approach was used significantly more often in the group of patients with diabetes. It can be assumed, however, that this was associated with a suspicion of locally more advanced disease based on the preoperative work-up. When analyzing the percentages of surgeries ultimately requiring open access (initially open and converted procedures) this percentage is significantly higher in the group of patients with diabetes. The length of surgery in the study group is also significantly longer than in the control group. This may evidence technical difficulties associated with a more locally advanced disease. The prolonged time of surgery is detrimental to the patient and is associated with an increased incidence of complications and length of hospitalization [29–31].

Complications observed in the course of hospitalization were significantly more frequent in patients from the study group. Surgical site infection was observed more frequently (p = 0.04) as was the use of negative pressure wound therapy (p = 0.008). Impaired wound healing is known to be a direct consequence of the level of glycemic control in patients with diabetes [10,32]. Patients in the study group also required norepinephrine infusions more frequently during hospitalization due to cardiac insufficiency (p = 0.009). Cardiac events were more frequently observed in the patients with diabetes group (p < 0.001). In our study, there was increased frequency of acute circulatory failure in the study group (p = 0.0003). Arrhythmias were more frequently observed in the patients with diabetes group (p = 0.0058) Cardiac arrest incidence was more often observed in the patients with diabetes group (p = 0.0001). In consequence, the patients with diabetes required transfer to the ICU significantly more often (p = 0.027). This is consistent with previous reports concluding that diabetes is an independent risk factor for ICU hospitalization regardless of the level of glycaemic control [33]. Pneumonia was also a more common complication among patients with diabetes (p = 0.009). Analysis of the frequency of AKI and ischaemic stroke was underpowered in our study and thus inconclusive.

Postoperative in-hospital mortality was significantly higher in the study group (p = 0.001). Patients with diabetes required significantly longer hospitalization (p < 0.001). This was probably due to an increased incidence of complications. No difference in the length of hospitalization was reported by some authors [12]. The costs of hospitalization are also significantly higher in patients with diabetes compared to the control group. This is due to a significantly greater number of complications and longer hospitalization times.

The strengths of our study are matching patients in terms of age and sex, and the large number of variables compared.

4.1. Limitations of the study

The main weakness of the study is the retrospective design. In consequence, the study is missing comparison of the blood glucose values between groups and HbA1 levels. These data were not available in our dataset. At our institution, glycated hemoglobin is not routinely measured in acute admissions. Another limitation of the study is the fact that diagnosis of diabetes in the study group was drawn from the database as a time independent parameter. Thus it is possible that in some cases patients were diagnosed with diabetes after cholecystectomy. This is a result of construction of the database. Patients could have had diabetes during the hospitalization not included in the diagnosis or diagnosed later. Another limitation is that the patients were not matched in terms of comorbidities.

5. Conclusions

To our knowledge, this is the first report comparing the course of acute cholecystitis in patients with and without diabetes. It is the only work in the recent years in which a matched control group was used. This shows that diabetes is an independent risk factor for complications in acute cholecystitis. Our study demonstrates that patients with diabetes report to the emergency department with cholecystitis with more locally advanced disease. Interestingly, the severity of local disease in patients with diabetes did not correlate with the CRP levels. Therefore, it seems that patients with diabetes not only subjectively experience fewer symptoms of the disease, but objective tests, despite the locally more advanced disease, also present the CRP values similar to those from the control group.

Complications occur more frequently in this group of patients. The length of hospitalization is significantly longer. This may confirm the previously suggested recommendation that due to the more locally advanced disease, diabetic patients with cholecystitis should be more willingly qualified for urgent surgery with minimal delay [18]. We demonstrated that the costs of hospitalization for acute cholecystitis in patients with diabetes are significantly higher than in healthy patients. Considering the significantly more frequent complications of acute surgery and increased costs of such hospitalization, elective

cholecystectomy may be beneficial in uncomplicated cholelithiasis. Although such an approach is not supported in current guidelines, it seems that patients with diabetes would benefit from it [34]. This might form the rationale to reconsider the validity of recommendations that do not recommend elective cholecystectomy in asymptomatic patients with diabetes.

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The author contribution

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Statistical Analysis: Monika Łącka, Paulina Wieszczy, Piotr Spychalski.

Data Interpretation: Monika Łącka, Paweł Obłój, Jarek Kobiela, Dariusz Łaski, Olga Rostkowska, Piotr Spychalski, Paulina Wieszczy.

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Literature Search: Monika Łącka, Piotr Spychalski, Paweł Obłój.

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Declaration of competing interest

The authors declare no conflict of interests.

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RESEARCH ARTICLE

Costs of elective vs emergency cholecystectomy in diabetic patients

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Abstract

Introduction: Hospitalization costs of diabetic patients are estimated to be higher than non-diabetic. Literature on the topic is however limited. The aim of this study was to compare the costs of elective and emergency cholecystectomy of diabetic and non-diabetic patients. **Material and methods:** A retrospective analysis involved diabetic versus non-diabetic age- and sex-matched patients who underwent emergency and elective cholecystectomy at a single center in Poland between 2016-2019. **Results:** The total costs of an elective cholecystectomy were 739.31 ± 423.07 USD for diabetic patients and 797.14 ± 772.24 USD for non-diabetic patients ($p = 0.51$). Whereas emergency cholecystectomy total costs were 3950.72 ± 2856.83 USD (diabetic patients) and 2464.31 ± 1718.21 USD (non-diabetic patients) ($p = 0.04$). The difference in total costs between elective cholecystectomy vs emergency cholecystectomy in both groups (diabetic vs non-diabetic patients) was statistically significant ($p < 0.01$ vs $p < 0.05$ respectively). **Conclusions:** In this study we demonstrated that emergency cholecystectomy is associated with a significant increase in hospitalization costs, particularly in diabetic patients. This suggests that early qualification of diabetic patients for an elective cholecystectomy could be beneficial for both diabetic patients and public health insurers.

Keywords: diabetes · elective cholecystectomy · emergency cholecystectomy · costs of hospitalization

Citation

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Introduction

According to the latest World Health Organization data, the estimated number of people suffering from diabetes worldwide is 422 million and the incidence of diabetes is increasing rapidly [1]. Because of its many complications, diabetes mellitus is associated with significant costs in public healthcare systems around the globe [2,3]. Acute cholecystitis in diabetic patients is often complicated by gangrenous cholecystitis [1], peritonitis, preoperative perforation, impaired wound healing, infections, increased risk of cardiovascular events and renal failure [4–11]. For this reason, diabetic patients hospitalisation costs are estimated to be higher than non-diabetic. Literature on the topic is limited and mostly concludes that immediate intervention leads to a decrease in costs and shortens the length of hospital stay [12–16]. The aim of this study was to compare the costs of elective and emergency cholecystectomy of diabetic and non-diabetic patients.

Materials and methods

A retrospective analysis involved patients who underwent emergency and elective cholecystectomy at the Department of General, Endocrine and Transplant Surgery of University Clinical Center in Gdańsk (Poland) between 2016 and 2019. Patients were assigned to diabetic group whenever diabetes mellitus of any type was identified in admission work-up. Using institutional registries we identified a total of 661 patients who underwent emergency cholecystectomy, of whom 70 patients had diabetes and 591 were non-diabetic. A random sample of 16 diabetic patients was included to the study depending on admission data criteria and was used to assign an age- and sex-adjusted control group.

A total of 1608 patients who underwent elective cholecystectomy where identified in institutional registries, of whom 135 had diabetes and 1473 were non-diabetic patients. A random sample of 20 diabetic patients were included to the study depending on admission data criteria. The control group of 80 patients was age- and sex-matched in a 4:1 ratio (Non-diabetic: Diabetic) (see Figure 1, Table 1).

The following were the criteria of inclusion into the study: unplanned or planned admission depending on group, cholecystectomy performed within 72 h of admission, and the availability of complete report of hospitalization costs in the electronic system. Patients were assigned to the diabetic group whenever diabetes mellitus of any type was identified in the admission work-up. The exclusion criteria included the lack of data on the costs of hospitalization, incomplete

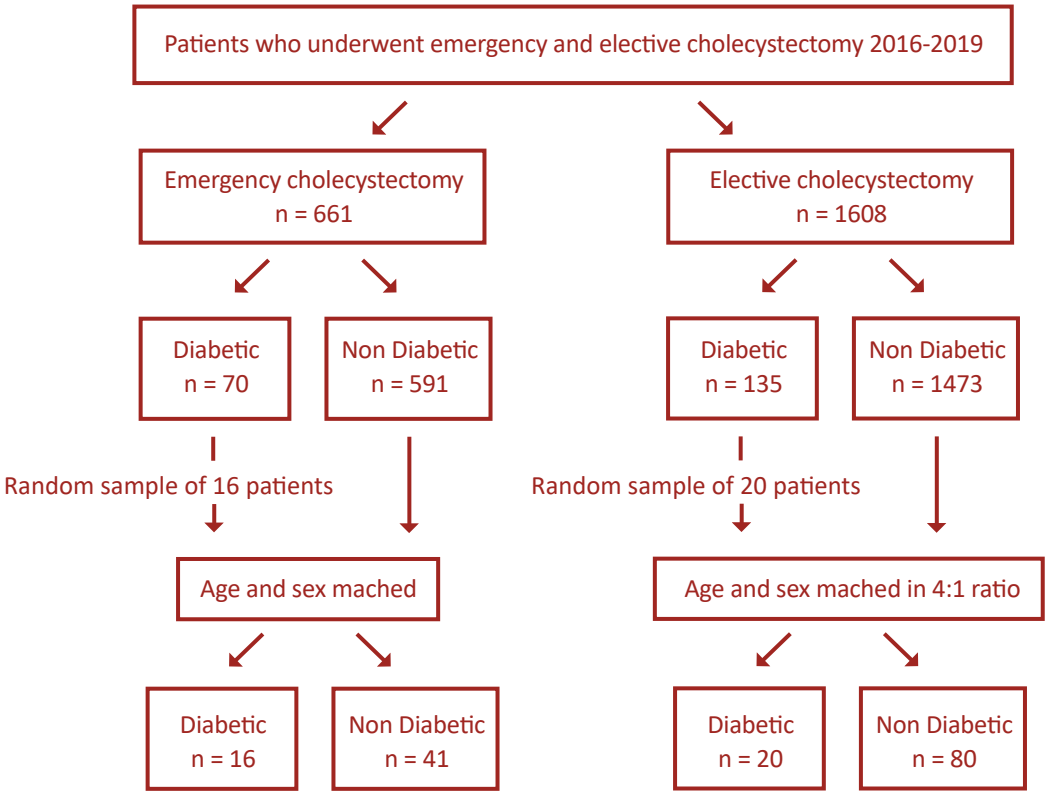

Figure 1. Flowchart illustrating patient selection

Table 1. Age distribution of patients in the emergency vs elective cholecystectomy group

Age	Diabetic	Non-diabetic	Diabetic	Non-diabetic
> 40	1	5	1	6
41-60	7	16	11	44
61-80	7	15	8	30
> 80	1	5	0	0

data on time or course of hospitalization, more than one surgery performed that was not related to cholecystectomy and its complications during the same hospitalization, cholecystectomy performed during hospitalization for a different reason.

Calculation of the direct costs of the Emergency Department included: medical imaging, medicines, consultations, laboratory tests, procedures performed and equipment. Whereas the General Surgery Department costs taken into account (in emergency and elective cholecystectomy) were: medical imaging, medicines, consultations, histopathology, laboratory works, procedures performed, equipment, operating room cost, cost of stay. Total costs of emergency cholecystectomy were a sum of costs incurred at the Emergency and General Surgery Departments. Total hospitalization costs taken into account for elective cholecystectomy were all generated at the General Surgery Department. Costs were converted from Polish Złoty (PLN) to US Dollars (USD) using the National Bank of Poland exchange rates from 11 September 2019. Descriptive analysis included medians, means and standard deviations. In comparative analysis U Mann-Whitney test, Student's t-test and the X^2 test were used. Distribution was tested using Shapiro-Wilk test. Statistical significance was accepted at $p < 0.05$. Statistical analyses were performed using Statistica 13.3 (TIBCO Software, Palo Alto, United States).

Results

A group of 57 patients (16 with diabetes and 41 non-diabetic) who underwent emergency cholecystectomy was analyzed. A total of 100 patients who underwent elective cholecystectomy were included to the study, 20 patients with diabetes and 80 patients without. Patients were matched in the group by age and sex. In the emergency group the access to viable data from the point of admission was limited, and therefore group size was limited as well. The downgrading of data quality was ruled out by the mean group size.

Total hospitalization cost

In a group of patients who underwent elective cholecystectomy, the total costs for diabetic patients were 739.31 ± 423.07 USD [median: 536.15 USD; range: 287.20 USD – 1606.67 USD] and for non-diabetic was 797.14 ± 772.24 USD ($p = 0.51$) [median: 651.47 USD; range: 281.75 – 6089.41 USD]. In a group of patients who underwent emergency cholecystectomy total costs for diabetic patients were 3950.72 ± 2856.83 USD [median: 3188.67 USD; range: 753.23 – 10760.15 USD] and 2464.31 ± 1718.21 USD ($p = 0.04$) [median: 2087.56 USD; range: 689.26 USD – 10950.16 USD] for non-diabetic patients. The difference in total costs between elective cholecystectomy and emergency cholecystectomy in both groups (diabetic and non-diabetic patients) was statistically significant ($p < 0.01$, $p < 0.05$ respectively) (see Table 2 and Table 3).

Table 2. Mean emergency ward costs in emergency cholecystectomy group

	Diabetic	Non-diabetic	p-value
Medical imaging	79.52 USD	50.29 USD	0.495
Consultations	31.13 USD	23.55 USD	0.356
Procedures	32.64 USD	35.33 USD	0.670
Laboratory tests	23.24 USD	20.91 USD	0.477
Medicines	3.47 USD	4.88USD	0.279
Equipment	8.35 USD	6.12 USD	0.657
Other	0 USD	0 USD	0.000
Total*	178.48 USD	141.20 USD	0.505

***Due to the applied approximations, individual costs cannot be summed up to a total cost.**

Table 3. Mean general surgery ward costs in emergency vs planned cholecystectomy group

	Diabetic	Non-diabetic	p-value	Diabetic	Non-diabetic	p-value
Cost of stay	1416.86 USD	758.01 USD	0.015	329.19 USD	424.29 USD	0.829
Operation room	628.81 USD	577.49 USD	0.676	605.53 USD	566.15 USD	0.113
Histopathology	31.56 USD	11.24 USD	0.901	9.40 USD	11.05 USD	0.595
Laboratory tests	73.86 USD	29.13 USD	0.012	11.96 USD	15.14 USD	0.510
Medicines	371.23 USD	178.93 USD	0.083	17.42 USD	34.10 USD	0.561
Medical imaging	87.28 USD	34.47 USD	0.066	0 USD	0 USD	0.000
Equipment	252.53 USD	98.09 USD	0.001	61.44 USD	63.59 USD	0.638
Consultations	26.36 USD	12.02 USD	0.050	0 USD	0 USD	0.000
Other	68.02 USD	18.50 USD	0.038	0 USD	0 USD	0.000
Total hospitalization*	3950.72 USD	2464.31 USD	0.040	739.31 USD	797.14 USD	0.515

***Due to the applied approximations, individual costs cannot be summed up to a total cost.**

Procedure-related costs

Procedure-related costs included General Surgery Department procedures plus costs of operating theatre (Table 3). Procedure costs in the emergency group were 724.60 ± 416.92 USD for diabetic patients and 625.26 ± 304.78 USD for non-diabetic patients (p = 0.613). Elective cholecystectomy group costs were 605.53 ± 246.04 USD for diabetic patients and 566.15 ± 325.37 USD for non-diabetic patients, p = 0.113. Differences in procedural costs between patients in diabetic and non-diabetic groups undergoing emergency cholecystectomy and those who underwent planned cholecystectomy were not statistically-significant, p = 0.824 and p = 0,992 respectively.

Other costs

Medical imaging costs were only applicable to the emergency cholecystectomy group and at the General Surgery Department they were 87.28 ± 152.21 USD for diabetic patients and 34.47 ± 70.87 USD for non-diabetic patients, p = 0,066. Whereas at the Emergency Department they were 79.52 ± 103.90 USD for diabetic patients and 50.29 ± 75.10 USD for non-diabetic, p = 0495. Other types of costs were not statistically significant with all p-values greater than 0.05 (see Table 2 and Table 3).

Length of stay

Mean length of stay counted in days for patients undergoing elective surgery was: 3.12 ± 2.96 for diabetic patients and 2.35 ± 0.87 for non-diabetic patients, (p = 0.555). Difference between elective and emergency cholecystectomy was statistically significant both for diabetic p < 0.001 and for non-diabetic patients p < 0.001. For emergency cholecystectomy mean length of stay was 10.62 ± 8.15 for diabetics and 5.49 ± 3.96 for non-diabetic patients p = 0.017).

Discussion

To our knowledge, this is the first report of specific hospitalization costs of diabetic and non-diabetic patients undergoing elective and emergency cholecystectomy. Our results suggest that emergent intervention in diabetic and non-diabetic group of patients leads to greater total costs of hospitalization,

costs of stay and procedure-related costs compared to planned cholecystectomy ($p < 0.05$). Furthermore, a significant difference between emergency hospitalization costs of diabetic and non-diabetic patients was found ($p = 0.04$), while there was no significant difference in cost between diabetic and non-diabetic patients in elective hospitalisation (see Table 3). This suggests that acute cholecystitis is not only burdened with higher risk of complications but also with a much higher cost. This may be another important factor underlining the need for diabetes patients to undergo elective surgery. However according to EASL guidelines, routine surgical treatment is not recommended for patients with asymptomatic gallbladder stones [17]. In our analysis the costs of hospitalisation were greater in emergency intervention both in diabetic and non-diabetic patients. It was reported numerous times, that elective surgery carries lower risk of complications [12,15,18,19]. Perhaps this is due to the fact that patients undergoing elective surgery not only do not have a fast progressing emergency condition but also are better prepared for surgery i.e. intentional weight loss, adequate glycemic control, appropriate treatment of possible arrhythmias and hypertension. [20]

Treatment of complications significantly prolong the hospital stay directly leading to increased costs of hospitalization. Costs of emergency surgery in diabetic patients are significantly higher ($p = 0.015$) than in non-diabetic. This is due to increased levels of complications intraoperatively and in postoperative period in diabetic patients with acute cholecystitis in comparison to-non diabetics [11,19,21–24].

Increase of procedure-related costs could be explained by frequently more advanced disease at admission of diabetic patients with acute cholecystitis. As reported previously, diabetics more often present with gangrenous cholecystitis, gall bladder perforation or emphysematous cholecystitis [1,7,25–28]. This leads to extended duration of surgery and increased use of materials during surgical interventions resulting in increased costs of surgery [29]. Increased rate of complications such as wound infections or impaired wound healing requires additional instrumental interventions during post-operative stay and thus generates further costs [30,31].

Imaging costs were a significant part of increased costs in emergency patients because in our study patients undergoing elective cholecystectomy obtained imaging prior to their admission Furthermore, medical imaging during hospital stay was required due to emerging complications. It can be considered one of the major cost-generating factors along with procedures and the length of stay.

In our study, the length of hospitalization is a measure of effectiveness. There is a statistically significant difference between the length of hospitalization of elective and emergency patients in both groups diabetic and non-diabetic ($p < 0.001$) and the emergency patients' length of stay was longer.

There is no significant difference between the length of stay of diabetic and non-diabetic patients undergoing elective surgery. This is in contrast to emergency procedures. The length of stay of patients with diabetes operated urgently was statistically significantly longer than in non-diabetic patients (10.62 ± 8.15 vs 5.49 ± 3.96, $p = 0.017$). This may be due to a more locally advanced disease and more common complications. Regardless of the reason above, our study clearly shows that diabetic patients may benefit from elective cholecystectomy.

Study limitations

First of all, this study is limited due to its retrospective nature. We performed a univariate analysis and did not involve potential cofactors such as glycaemia control, comorbidities and medications. Furthermore, the calculated costs might differ in other health care systems and crude values might vary substantially. However, we believe that the differences shown seem universal due to common cost-generating factors.

Conclusion

In this study we demonstrated that an emergency cholecystectomy in a diabetic patient is associated with greater costs when compared to a planned cholecystectomy. While there are no differences in the costs of elective hospitalizations, there is a statistically significant difference in the costs of emergency surgery between diabetic and non-diabetic patients. As cholelithiasis in diabetic patients can often be diagnosed at its asymptomatic stage, we suggest that qualifying these patients to an elective cholecystectomy early on may lead to fewer serious complications and a decrease in total costs of hospitalization. Although elective cholecystectomy is not supported in current guidelines, it seems that such approach could be beneficial for both diabetic patients and public health insurers. (European Association for the Study of the Liver (EASL), 2016)

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