DIAGNOSIS AND THERAPY PARTICULARITIES IN POST-CHOLECYSTECTOMY CHOLANGITIS AT PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Introduction. The objective of the present study is to assess the diagnosis and therapeutic particularities in post-cholecystectomy cholangitis at patients with type 2 diabetes mellitus. Patients suffering of diabetes frequently present other pathologies existing before cholecystectomy: cardio-vascular, neurological, renal; these conditions can negatively influence the therapeutic approach of the complex post-cholecystectomy pathology.

Material and method. The study was performed on 76 hospitalized patients. The main diagnosis of these patients was post-cholecystectomy cholangitis. 12 patients had type 2 diabetes mellitus as associated condition. A control batch was selected, 12 non-diabetes patients, having approximately the same age, mainly living in urban areas and having the same main hospitalization diagnosis.

Results. The etiology of post-cholecystectomy cholangitis in case of patients suffering of diabetes was represented by chronic pancreatitis (25%), choledochal lithiasis (33.33%), acute pancreatitis (8.33%), cholangiocarcinoma (16.66%), head pancreas tumor (8.33%).

Conclusions. As a particularity in the surgical approach in case of patients suffering of diabetes within the assessed group, a strict monitoring should be applied in regards with the metabolic status, especially in case of disbalanced diabetes mellitus with chronic complications.

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Keywords: *post-cholecystectomy cholangitis pancreatitis, cholangiocarcinoma, choledochal lithiasis.*

Rezumat

Introducere. *Obiectivul prezentului studiu îl reprezintă evaluarea particularităților diagnostice și terapeutice ale colangitei post-colecistectomie la pacienții cu diabet zaharat de tip 2. Pacienții diabetici prezintă adesea numeroase comorbidități: cardiovasculare, neurologice, renale; aceste afecțiuni pot influența negativ abordarea terapeutică a patologiei complexe post-colecistectomie.*

Material și metodă. *Studiul a fost realizat pe 76 de pacienți spitalizați. Principalul diagnostic al acestor pacienți a fost colangita post-colecistectomie. Un număr de 12 pacienți prezentau diabet zaharat de tip 2. A fost selectat un lot de control, format din 12 pacienți fără diabet, având aproximativ aceeași vârstă, domiciliați în principal în mediul urban și cu același diagnostic principal de spitalizare.*

Rezultate. *Factorul etiologic al colangitelor post-colecistectomie în cazul pacienților diabetici a fost reprezentat de pancreatită cronică (25%), litiază coledociană (33,33%), pancreatită acută (8,33%), colangiocarcinom (16,66%), tumoră de cap de pancreas (8,33%).*

Concluzii. *Ca o particularitate a abordării chirurgicale în cazul pacienților diabetici, ar trebui aplicată o monitorizare strictă în ceea ce privește starea metabolică, în special în caz de diabet zaharat dezechilibrat cu complicații cronice.*

Cuvinte cheie: *pancreatită colangitică post-colecistectomie, colangiocarcinom, litiază coledociană.*

Introduction

The objective of the present study is to assess the diagnosis and therapeutic particularities in post-cholecystectomy cholangitis in case of patients suffering of type 2 diabetes mellitus.

Diabetes mellitus can be an important risk factor in the prevalence of post-cholecystectomy's pathology, being similar with the lithiastic bile pathology present before cholecystectomy. Lithiastic bile pathology, with cholesterolithic calculi, has a higher prevalence in case of patients with metabolic disbalances: hyperinsulinemia, decreased tolerance to glucose, obesity, dyslipidemia^(1,2).

Patients with type 2 diabetes mellitus frequently suffer of other pathologies pre-existent to cholecystectomy in comparison with non-diabetic patients: cardio-vascular, neurological, renal. This aspect can have a negative impact over the therapeutic approach of post-cholecystectomy's complex pathology.

Material and method

This study was performed on a batch of 76 patients hospitalized between 2017 and 2018 in the Surgery I Department of the Emergency County Clinical Hospital of Oradea, their main diagnosis being post-cholecystectomy cholangitis. Of these, 12 patients (15.78%) had type 2 diabetes mellitus as associated condition.

For the purpose of having a head-to-head study, a second control batch of subjects was selected, 12 non-diabetes patients, having approximately the same age, mainly living in urban areas and having the same main hospitalization diagnosis, namely post-cholecystectomy cholangitis. The criteria for

selecting the patients for the two assessment batches were: gender, age, living area, main diagnosis, other associated conditions, anamnesis data, clinical investigations, radio-imagery and laboratory methods.

As laboratory methods, the following were used: serum glucose, glycosuria, glycated hemoglobin, bile retention samples; direct and total bilirubin; hepatic cytolysis tests - ASAT, ALAT, GGT; cellular hypofunction tests, coagulation tests: prothrombin, INR; CBC, reactive C protein, tests for renal performance; creatinine, urea; glomerular filtration rate, serum electrolytes;

For the bio-chemistry tests, the spectrophotometric method was used (Architect C4000 analyzer); reactive C protein was assessed through the turbidimetry method (Architect C4000 analyzer); glycated hemoglobin assessed through the enzyme method, from integral blood, with Architect c4000 analyzer; blood count - from integral blood, assessed through the photometric impedance method (Cell Dyn Ruby); erythrocyte sedimentation rate (VSH) - from integral blood, assessed through the capilar photometry method, with ALIFAX analyzer.

From the perspective of statistic analysis methodology, the information was processed in the SPSS 17.0 static program; descriptive analysis, Anova and Chi-Square statistic tests were used; the reliability threshold is 95%, meaning that there is a maximum 5% statistical error; P or P-value is seen as probability or Pearson value.

As treatment methods, pharmacology, interventional imagery (retrograde endoscopic cholangiopancreatography) and, with decreased frequency, surgery (invasive on bile ducts and mini-invasive) were used.

In case of patients suffering of diabetes who

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undergone surgery treatment methods, specific pre, intra and post-surgery specific measures were applied. These were used for the purpose of avoiding hypo-glycemic acute disbalances and also intra and post-surgery ketoacidosis and hyperglycemia disbalances. Post-surgery, high values of glycemia increase the risk of thrombotic accidents, prevent quick post-surgery recovery and favor the development of septic complications.

Results

From the total number of patients hospitalized with post-cholecystectomy cholangitis during 2017-2018, women had a percentage of 66.66%. Within the batch of patients with diabetes, 83.83% were living in urban areas. The patients belonged to the age group of over 65 years of age, the percentage being 91.66%. Within the 12 patients suffering of type 2 diabetes mellitus between 2017-2018 diagnosed with post-cholecystectomy cholangitis, 7 patients had type 2 diabetes mellitus with need for insulin. Out of these 6 cases, 3 were cases of type 2 diabetes mellitus with disbalanced need for insulin.

Other frequent associated pathologies within batch I of study were connected to diabetes complications: cardio-vascular (congestive heart failure, chronic arterial fibrillation, high

blood pressure, chronic coronary heart disease), renal (acute and chronic kidney failure), neurological (stroke) and ophthalmologic (cecidity). Other co-morbidities in the assessed batch were: hepatic steatosis, chronic hepatopathy, obesity.

At hospitalization, in case of patients suffering of diabetes, in 9 cases (75.00%) high glycemic values were present (150-406 mg/dl); in case of a patient with disbalanced insulin needing diabetes, hypoglycemia was present (38mg/dl).

The presence of a significantly statistic difference has been identified ($p=0.017$), at a reliability threshold of 95%, between the average of blood sugar in case of patients suffering of diabetes (183.40 mg/dl) and the average of blood sugar in case of patients not suffering of diabetes (108 mg/dl), thus in the case of patients diagnosed with diabetes, the blood sugar values highly outrun the normal values.

In case of two patients hospitalized with post-cholecystectomy cholangitis and type 2 disbalanced diabetes mellitus, severe hydro-electrolytic disbalances were present.

Bile-excretive syndrome associated with inflammation had a high percentage (58.33%). Cholestasis and hepatocytolysis syndrome had a significant percentage (66.66%).

There were high values of gamma glutamyl transferase with high specificity and

Chronic pancreatitis	3	25.00%
Acute pancreatitis	1	8.33%
Pancreatic cephalic tumor	1	8.33%
Choledochal lithiasis	4	33.33%
Inferior choledochal cholangio-carcinoma	2	16.66%
Klatskin tumor	1	8.33%

Table 1. Etiology of post-cholecystectomy cholangitis hospitalized patients with diabetes

Number of diabetes patients with post-cholecystectomy cholangitis (study batch)		12	100%
Pharmacological methods		6	50.00%
Endoscopic methods (ERCP)	Endoscopic sphincterectomy with extraction of residual calculi	3	25.00%
	Suppression of the stent placed on the main bile duct	1	8.33%
Invasive surgery methods	Choledochotomy + external bile drainage on Kehr tube	1	8.33%
	Exploration laparotomy	1	8.33%

Table 2. Prevalence of therapeutic approach methods in case of diabetes patients with post-cholecystectomy cholangitis

Residual choledochal lithiasis	6	33.33%
Stenosis of choledochal-duodenum anastomosis	1	8.33%
Stenosis of distal choledoch	1	8.33%
Acute pancreatitis	1	25.00%
Chronic pancreatitis	3	16.66%

Table 3. Etiology of post-cholecystectomy cholangitis in case on non-diabetes patients (control batch)

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Number of non-diabetes patients with post-cholecystectomy cholangitis (control batch)		12
Pharmacological methods		4
Endoscopic retrograde cholangiopancreatography -endoscopic sphincterectomy with extraction of residual calculi		6
Invasive surgery methods	Choledochotomy + choledoc-duodenum anastomosis	1
	Choledochotomy + external bile drainage on Kehr tube	1

Table 4. Prevalence of therapeutic approach methods in case of non-diabetes patients with post-cholecystectomy cholangitis

sensibility in the diagnosis of post-cholecystectomy main bile duct residual lithiasis.

Within the assessment batch, of patients suffering of diabetes, there is a significantly positive statistics and directly proportional connection at a reliability threshold of 95% between the etiology of post-cholecystectomy cholangitis and GGT type hepatic cytolysis syndrome ($p=0.027$), thus: the higher the value of gamma glutamil transferasis (GGT) is, the more severe the condition is, a low value of GGT variable is seen in acute pancreatitis, while a higher value of GGT variable lead to diagnosing the patient with a tumoral pathology. Within the control batch, there is a significantly positive

statistics and directly proportional connection at a reliability threshold of 95% between the etiology of post-cholecystectomy cholangitis and ALAT type hepatic cytolysis syndrome ($p=0.014$), thus a lower value of ALAT variable leads to lighter diagnosis (pancreatitis), and a higher value of the ALAT variable leads to a more severe diagnosis (benign or malign stenosis).

Surgery was performed in one case, a patient with type 2 diabetes mellitus without insulin need, associated with an acute post-cholecystectomy cholangitis of malign etiology (main bile duct tumor, without the ability to perform surgery). The patient had a mechanic icterus, with marked bile-excretory syndrome (direct bilirubin -

18,63mg/dl; total bilirubin 25,33 mg/dl), intrahepatic cholestasis and hepatic failure, with increased hepatocytolysis syndrome (very high values of gamma glutamyl transferase -2528 U/L). Also, the patient was suffering of associated chronic pancreatitis. Also, glycemic values were high at hospitalization - 269mg/dl. As palliative surgery treatment, choledochotomy with external Kehr tube drainage was performed. The second case where surgery was performed was the case of a female patient with diabetes mellitus with balanced need for insulin, hospitalized with post-cholecystectomy cholangitis through pancreatic cephalic tumor, with duodenum invasion; in her surgery medical history she had several interventions for bile obstructive pathology (cholecystectomy, anastomosis-choledochal-duodenum).

Exploration laparotomy was performed, without the possibility of tumoral excision due to adherence to the portal vein. Glycemia had values of 169mg/dl. There is a significant positive statistics correlation at a reliability threshold of 95% between the etiology of post-cholecystectomy cholangitis in case of patients with diabetes and the therapeutic approach ($p = 0.049$), thus, in acute cholangitis severe cases will be approached as precociously as possible for draining the bile ducts, with endoscopic or surgery methods; light or moderate chronic or acute cholangitis cases respond efficiently to specific anti-microbe therapy.

Of high importance in these surgery cases was the pre-surgery, intra-surgery and post-surgery monitoring of patients suffering of diabetes.

We have to take into account the negative impact of a surgical intervention in situations of blood sugar level disturbance. In 6 cases, the treatment of post-cholecystectomy

cholangitis has been performed with pharmacology methods similar to those used in case of patients without diabetes. In 3 cases, endoscopic sphincterectomy through retrograde endoscopic cholangiopancreatography has been performed, with extraction of calculi through choledochal lithiasis in case of patients with post-cholecystectomy cholangitis.

In one case it was necessary to endoscopically suppress a choledochal stent, in a specialized center, a post-cholecystectomy cholangitis patient with type 2 diabetes mellitus with need for insulin. The patient has shown post ERCP angiocholitis after placing a stent on the main bile duct for an inferior choledochal cholangio-carcinoma. At hospitalization, the patient had high blood sugar values (406mg/dl), an inflammatory, marked bile-excretory and hepatocytolytic syndrome.

In 6 cases, the treatment of post-cholecystectomy angiocholitis has been performed with pharmacology methods similar to those used in case of patients without diabetes. As a control batch, in the reference study, 12 non-diabetes patients were assessed who were hospitalized with post-cholecystectomy cholangitis

There is a significant statistics correlation at a reliability threshold of 95% between the etiology of post-cholecystectomy cholangitis and the therapeutic approach, namely that in choledochal lithiasis endoscopic sphincterotomy will be applied, with extraction of residual choledochal calculi, in case of acute and chronic disorders pharmaceutical methods will be used, in a limited number of cases surgery management will be chosen.

As pathologies in the control batch, other possible causes associated to the pathology of post-cholecystectomy were observed:

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duodenum-gastric bile reflux, corporeal edematous gastropathy, satellite hepatitis. Other pathologies were also reported, especially cardio-vascular pathology.

Discussions

Type 2 diabetes mellitus has an important role in the lithogenesis process; an over saturation of the bile with cholesterol is generated, especially in case of obese patients and with dyslipidemia and in case of patients with type 2 diabetes mellitus with insulin need, after the initiation of insulin therapy. The low level of HDL cholesterol will generate an increase of cholesterol hepatic secretion and a decrease of the concentration of bile salts and phospholipids. There will be an over-saturation of the bile, with the precipitation of cholesterol crystals and, over time, the development of cholesterol calculi^(1,2,3). The mechanism of this cholesterol lithogenesis is closely connected with type 2 diabetes mellitus, with obesity, dyslipidemia and hyper-hyperinsulinemia. As additional factors, the inflammation of the bile ducts and low intestine mobility were reported. Recent specialty studies highlight the role of nuclear receptors, of damaged intestinal flora and of genetic polymorphism^(2,3,4).

The patient with type 2 diabetes mellitus has a higher morbidity than the non-diabetic

patient in the incidence of post-cholecystectomy. The prevalence of females in the assessed batch of patients was higher than the prevalence of males, similar to the higher prevalence of females in the pathology of lithiastic bile pathology^(5,6,7). Patients with type 2 diabetes from urban areas were higher in number. Type 2 diabetes mellitus was higher in case of patients with age over 65, who were hospitalized with post-cholecystectomy pathology. In case of these patients, rigorous monitoring was needed for avoiding long term diabetes complications, for avoiding hypoglycemia and maintaining a suitable life quality standard.

In the study batch with diabetes patients, the most frequent causes of post-cholecystectomy cholangitis were chronic pancreatitis, choledochal lithiasis and malign pathology (cholangiocarcinoma, Klszskin tumor, pancreatic cephalic tumor).

Pancreatic and peripancreatic chronic inflammatory processes can determine exocrine and endocrine pancreatic insufficiency with hyperglycemia and type 2 diabetes mellitus (pancreatogenic diabetes)^(8,9,10,11,12). Pathologic situation with subsequent impact over the pancreas are: acute, chronic pancreatitis, malign pancreatic tumors, traumas, atherosclerosis. Chronic cephalic pancreatitis is usually accompanying choledochal lithiasis, being

the consequence of infection spread through means of canals and contiguity.

Also, the long-term evolution of a type 2 diabetes mellitus determines important pancreas changes which will be added to the post-cholecystectomy pancreatic changes. There are controversies in the specialty literature, in regards with type 2 diabetes mellitus favoring or not the development of chronic pancreatitis and of post-cholecystectomy pancreatic tumoral pathology⁽¹³⁾. This risk would be lower in case of patients with type 2 diabetes mellitus, non-insulin dependent, due to the administration of metformin, in comparison with the higher risk of developing pancreas cancer in case of patients with type 2 diabetes mellitus who need insulin^(14,15).

Also, it is not clear if diabetes mellitus is the cause or the effect of pancreatic cancer. Specialty studies show that, generally, in case of patients with malign pancreatic tumor, diabetes mellitus has been recently diagnosed, being the consequence of the destruction of the pancreas by the invasion of malign cells^(14,15).

A type 2 diabetes mellitus which has a long-term evolution (5-7 years) can represent a risk factor for developing a pancreatic tumor. To this we can also add as an increased risk potential the effects of anti-diabetes medication. When the diagnosis was established before the pancreas cancer diagnosis, diabetes mellitus was non-insulin dependent. The association between post-cholecystectomy pancreatic malign tumor and diabetes mellitus can be present, the prognosis being unfavorable. The information from different specialty studies are contradictory, more in-depth studies being needed for an exact understanding of the connection between chronic pancreatitis, pancreas cancer and type 2 diabetes

mellitus^(13,14,15). Also, there were patients with type 2 diabetes mellitus within the study batch hospitalized with post-cholecystectomy choledocholithiasis.

Specialty studies confirm the association between diabetes and residual lithiasis of bile ducts. The low level of high-density lipoproteins (HDL) is an important mediator of the effects of type 2 diabetes mellitus over the post-cholecystectomy residual bile calculi.

There is a possible connection between type 2 diabetes mellitus and cholangiocarcinoma in case of patients with intervention in the bile area. Recent specialty studies assess the potential risk of certain additional factors in the pathogenesis of cholangiocarcinoma: B or C hepatitis, type 2 diabetes mellitus, obesity, alcoholic hepatopathy, hepatic cirrhosis, smoking. Post-cholecystectomy, increased bile secretion can favor the process of carcinogenesis on the level of the bile ducts through a mechanism similar to the carcinogenetic process on the hepatocitary level^(16,17,18,19).

The results gathered in the study batch with patients with type 2 diabetes mellitus, hospitalized with post-cholecystectomy angiocholitis and who were also diagnosed with cholangiocarcinoma are similar with the ones shown by recent specialty studies.

The therapeutic attitude in post-cholecystectomy cholangitis in case of patients with diabetes has been mainly based on specific medication methods, interventional imagery methods and, in only on a very low number of cases, on invasive surgery methods.

The increased susceptibility of diabetes patients to infections, high glycemic serum levels, hyperinsulinemia, malnutrition, dehydration, association of different cardiovascular comorbidities can negatively

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influence the post-surgery evolution. In case of diabetes patients, there is a deficient immune response to the inflammatory process, an inefficient chemotactic neutrophilic phagocytosis activity and also an incorrect intracellular bacteria activity^(20,21).

Surgical intervention and anesthesia have an important impact over the metabolic balance of the body. The diabetes patient has a higher risk than the non-diabetes patient to show metabolic and hydro-electrolytic intra and post-surgery disbalances.

Complex therapeutic approach aims at avoiding acute hypoglycemia disbalances during the anesthesia, ceto-acidosis and hyperglycemia during the intra and post-surgery period.

Post-surgery, the increased serum values on glycemia increase the risk of thrombotic accidents, obstruct the surgical healing of wounds and foster the development of abdominal parietal abscesses. (30) The surgical activity involves a period of starvation and a hypersecretion of counter-regulating hormones as a metabolic response to the stress created by the surgery. Thus, the high levels of cortisol, catecholamines and glucagon will have a counter effect over the insulin^(22,23).

Disbalanced diabetes mellitus and diabetic cardio-vascular, renal or neurological complications create a potential risk within

the surgical approach of the post-cholecystectomy bile pathology, similar to general surgery approach.

As a first pre-surgery measure in case of a patient with diabetes, a complete re-assessment is performed by an interdisciplinary team (surgeon, diabetologist, cardiologist, nephrologist, anesthesiologist). The purpose is to assure a glycemia control and correcting hydro-electrolytic and metabolic disbalances in case of patients who also have multiple comorbidities and specific diabetes complications, especially cardio-vascular and renal^(24,25).

Another measure, before a major surgery intervention with general anesthesia, is replacing the oral anti-diabetes medication with the according insulin treatment. If there are metabolic and/or hydro-electrolytic disbalances, the surgical intervention will be postponed until these are corrected. Intra-surgery, 500 ml of glucoses 10%+ 25 u.i. insulin with quick effect will be administered. The optimum glycemic level was maintained in accordance with the international therapeutic protocols, keeping glycemic values between 125-200 mg/dl^(26,27).

Post-surgery, IV treatment was continued in accordance with the scheme presented by the diabetologist and anesthesiologist. Using IV treatment with glucose solution buffered with insulin has led to a constant monitoring of the blood sugar at intervals of 2 h.

Based on the hydro-electrolytic and metabolic status of the diabetic patient, the diabetologist has established the optimum timing for administering under-cutaneous quick insulin. The surgical prognostic of the diabetes patients from the study group was favorable. This aspect allowed returning to the previous hypo-glycemic treatment schemes.

Conclusions

In both batches, both in the diabetic patients batch, and in the control batch on non-diabetic patients, post-cholecystectomy residual choledochal lithiasis was the main etiology.

In both batches - diabetes patients versus non-diabetic patients - the therapeutic approach in similar: pharmaceutical methods, interventional imagery and invasive surgery.

As a particularity in the surgical approach in case of patients suffering of diabetes within the assessed group, a correct and careful monitoring should be applied in regards with the metabolic status, especially in case of disbalanced diabetes mellitus with chronic complications.

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