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# Relationship Between Diabetes and Acalculose Cholestitis in the Elderly

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## Abstract

**Aim:** The clinical picture of acute stoneless cholecystitis can be seen in a wide range from mild lesions to the size that threatens the patient's life. In this study, we aimed to contribute to the literature by investigating the relationship between patients with acute stone-free cholecystitis and diabetes mellitus (DM).

**Materials and Methods:** Patients were analyzed for age, sex, and blood tests. Descriptive statistics for numerical variables are presented as mean, standard deviation, min-max values. Non-parametric test procedures were performed on non-normally distributed data. In this context, dependent and independent sample t-test and Mann-Whitney U test were used to determine the relationships between the parameters. Spearman's correlation analysis was used, and chi-square analysis was performed to evaluate the relationship between categorical data.

**Results:** The parameters measured by complete blood count and biochemistry were as follows: neutrophil: 56.72±23.17, C-reactive protein (CRP): 38.31±7.70, aspartate aminotransferase (AST): 78.86±25.80, alanine aminotransferase (ALT): 73.59±159.90, gamma glutamyl transferase (GGT): 142.99±236.08, urea: 37.14±24.41, creatinine: 0.90±0.50, glucose: 115.42±53.70, white blood cell: 8.49±6.66, percentage of neutrophils: 63.80±14.10, platelet: 245.63±84.62. There was a positive correlation between CRP and AST, CRP and ALT, CRP and GGT, and ALT and GGT in DM+ patients.

**Conclusion:** It can be said that advanced age and the presence of DM increase the risk of stoneless cholecystitis, and blood parameters are used to show the presence of infection. In addition, deterioration in liver function tests increases more in patients with DM.

**Keywords:** Acalculous cholecystitis, blood tests, chronic diseases, diabetes mellitus, inflammation

## Introduction

Acute cholecystitis is an inflammatory disease of the gallbladder. When patients with abdominal pain complaints are evaluated, it is seen that 3-10% of them have acute cholecystitis (1,2). Acute cholecystitis usually occurs because of obstruction of the cystic duct by gallstones. However, approximately 5% of patients do not have gallstones, and this is called acalculous cholecystitis (3,4). The clinical picture of acute cholecystitis can be seen in a wide range from mild lesions to the size that threatens the patient's life. The reason for this can be the degree of inflammation, presence of comorbid disease, and advanced age (5,6). Diabetes

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mellitus (DM) is a chronic disease that affects 150 million people worldwide and is still ongoing, manifested by impaired function of beta cells in the pancreas and development of resistance to the effects of insulin in the organs. increases rapidly (7,8). In DM examined in two subgroups, type 1 DM mostly occurs due to insulin deficiency, whereas type 2 DM is mostly associated with insulin resistance in tissues (9-11). In this study, we aimed to reveal whether there is a relationship between DM and acute stone-free cholecystitis and to contribute to the literature by investigating the relationship between patients with acute stone-free cholecystitis and DM and examining its correlation.

## Materials and Methods

This retrospective study was cross-sectional and observational. Demographic data and computed tomography of patients with and without DM who were diagnosed with acute stone-free cholecystitis and who applied to the Emergency Department and Internal Medicine Clinic of Kafkas University Health Research and Application Hospital between 01.10.2016 and 01.10.2019 were included. Ethical approval for our study was obtained from the Ethics Committee of Kafkas University, numbered 80576354-050-99/223 on 10.10.2019. Hemogram, biochemistry, such as C-reactive protein (CRP), creatinine, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), liver function test (LFT), kidney function test, and blood glucose of the patients were analyzed. Patients under the age of 18 years were not included in our study.

### Statistical Analysis

Age, sex, blood tests, and data were analyzed using the SPSS 20.0 (IBM, USA) program. Descriptive statistics for numerical variables are presented as mean, standard deviation, median, min-max values. In this context, the relations between parameters are presented. Mann-Whitney U test, which is a non-parametric alternative to the independent sample t-test, was used to determine Spearman correlation analysis in correlation analysis. Chi-square analysis was used to evaluate the relationship between categorical data. Results were evaluated at a 95% confidence level and $p<0.05$ was accepted as statistically significant. Because our study was retrospective, the voluntary consent form was waived and patient data were kept confidential.

## Results

### Descriptive Statistics

Of the patients, 53.67% were female (n=59) and 46.33% were male (n=51). The mean age of the patients in the study was found to be 69.96±4.128 years. The blood parameters of the patients were evaluated using the ABX Pentra DX 120 (Horiba, HORIBA ABX SAS, Japan) in our hospital according to sex and reference ranges. All diabetic patients participating in the study were diagnosed with type-2 DM. The parameters measured by complete blood count and biochemistry were determined to be as follows: neutrophil: 56.72±23.17, CRP: 38.31±7.70, AST: 78.86±25.80, ALT: 73.59±159.90, GGT: 142.99±236.08, urea: 37.14±24.41, creatinine: 0.90±0.50, glucose: 115.42±53.70, white blood cell (WBC): 8.49±6.66, neutrophil percentage: 63.80±14.10, hemoglobin: 13.80±4.60, hematocrit: 41.5±5.25,

**Table 1. Parameters measured by age, complete blood count and biochemistry parameters**

| n=110 | Mean | Deviation | Minimum | Maximum | Median |
|---|---|---|---|---|---|
| Age, years | 69.96 | 4.13 | 65.00 | 89.00 | 71.55 |
| Neutrophil, $x10^3$ | 56.72 | 23.17 | 0.29 | 60.00 | 54.02 |
| CRP, mg/dL | 38.31 | 7.70 | 1.10 | 38.90 | 34.95 |
| AST, U/L | 78.86 | 25.80 | 9.00 | 2592.00 | 77.03 |
| ALT, U/L | 73.59 | 159.90 | 2.00 | 1366.00 | 71.23 |
| GGT, U/L | 142.99 | 236.08 | 6.00 | 1044.00 | 82.32 |
| Urea, mg/dL | 37.14 | 24.41 | 11.00 | 187.00 | 36.54 |
| Creatinine, mg/dL | 0.90 | 0.50 | 0.60 | 3.80 | 0.70 |
| Glucose, mg/dL | 115.42 | 53.70 | 45.00 | 482.00 | 118.40 |
| WBC, $x10^3$ | 8.49 | 6.66 | 4.00 | 28.00 | 9.02 |
| Hb, g/L | 13.80 | 4.60 | 6.70 | 17.40 | 13.70 |
| Hct, % | 41.50 | 5.25 | 19.50 | 51.90 | 41.60 |
| Neutrophil percentage | 63.80 | 14.10 | 48.50 | 89.00 | 60.06 |
| Plt, fL | 245.63 | 84.62 | 210.00 | 639.00 | 252.00 |

CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, WBC: White blood cell, Hb: Hemoglobin, Htc: Hematocrit, Plt: Platelet count

platelet count: 245.63±84.62 (Table 1).

Acute stone-free cholecystitis was diagnosed together with DM at a rate of 31.81% in our study. When the patients' age, neutrophil, CRP, AST, ALT, GGT, urea, creatinine, glucose, WBC count, neutrophil percentage, hemoglobin, hematocrit, and platelet values were analyzed according to the presence of DM, age, CRP, AST, ALT, and glucose were determined to be statistically

**Table 2. Clinical characteristics and laboratory findings of patients according to the presence of DM**

| | **DM status** | **n** | **p value** |
|---|---|---|---|
| Age, years | DM (+) | 75 | 0.043* |
| | DM (-) | 35 | |
| | n | 110 | |
| Neutrophil, x10$^3$ | DM (+) | 75 | 0.372* |
| | DM (-) | 35 | |
| | n | 110 | |
| CRP, mg/dL | DM (+) | 75 | 0.002** |
| | DM (-) | 35 | |
| | n | 110 | |
| AST, U/L | DM (+) | 75 | 0.064** |
| | DM (-) | 35 | |
| | n | 110 | |
| ALT, U/L | DM (+) | 75 | 0.049** |
| | DM (-) | 35 | |
| | n | 110 | |
| GGT,U/L | DM (+) | 54 | 0.004* |
| | DM (-) | | |
| | n | 27 | |
| | Total | 81 | |
| Urea, mg/dL | DM (+) | 75 | 0.485* |
| | DM (-) | 35 | |
| | n | 110 | |
| Creatinine, mg/dL | DM (+) | 75 | 0.810* |
| | DM (-) | 35 | |
| | n | 110 | |
| Glucose, mg/dL | DM (+) | 75 | 0.001* |
| | DM (-) | 35 | |
| | n | 110 | |
| WBC, x10$^3$ | DM (+) | 75 | 0.264* |
| | DM (-) | 35 | |
| | n | 110 | |
| Neutrophil, % | DM (+) | 75 | 0.311* |
| | DM (-) | 35 | |
| | n | 110 | |
| Hb, g/L | DM (+) | 75 | 0.499* |
| | DM(-) | 35 | |
| | n | 110 | |
| Hct, % | DM (+) | 75 | 0.893* |
| | DM (-) | 35 | |
| | n | 110 | |
| Plt, fL | DM (+) | 75 | 0.793** |
| | DM (-) | 35 | |
| | n | 110 | |

*The Mann-Whitney U, **the independent sample t-test. CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, WBC: White blood cell, Hb: Hemoglobin, Htc: Hematocrit, Plt: Platelet count, DM: Diabetes mellitus

| Table 3. The relationship of blood paremeters of patients with diabetes and non-diabetes | | | | | |
|---|---|---|---|---|---|
| | | | **AST** | **ALT** | **GGT** |
| DM- patients | CRP, mg/dL | Correlation coefficient | 0.282* | 0.205 | 0.604** |
| | | Sig. (2-tailed) | **0.023** | 0.098 | **0.001** |
| | AST, U/L | Correlation coefficient | | 0.804** | 0.654** |
| | | Sig. (2-tailed) | | **0.001** | **0.001** |
| | ALT, U/L | Correlation coefficient | | | 0.586** |
| | | Sig. (2-tailed) | | | **0.001** |
| DM+ patients | CRP, mg/dL | Correlation coefficient | 0.533** | 0.405* | 0.437* |
| | | Sig. (2-tailed) | **0.001** | **0.016** | **0.023** |
| | AST, U/L | Correlation coefficient | | 0.894** | 0.673** |
| | | Sig. (2-tailed) | | **0.001** | **0.001** |
| | ALT, U/L | Correlation coefficient | | | 0.654** |
| | | Sig. (2-tailed) | | | **0.001** |

*Spearman's correlation analysis, p<0.05, **p<0.001
CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, DM: Diabetes mellitus

significant (Table 2).

The difference between gender and the presence of DM was not statistically significant (p=0.361).

While there was a moderate positive correlation between CRP and AST levels in DM+ patients, there was a low positive correlation between CRP and AST levels in DM patients. Although there was a moderate positive correlation between CRP and ALT in DM+ patients, no correlation was found in DM patients. While there was a moderate positive correlation between CRP and GGT in DM+ patients, a high positive correlation was observed in DM patients. Although there was a high positive correlation between ALT and GGT in DM+ patients there was a moderate positive correlation in DM patients (Table 3).

When the hospital stay times of the patients between the diabetic and non-diabetic groups were compared, the hospital stay time in the diabetic acute stone-free group was statistically longer. (p=0.002). Again, a strong positive correlation was detected between blood sugar and hospital stay duration.

## Discussion

Gallbladder inflammation may be acute, chronic, or acute-on-chronic. The mechanism of inflammation has not been understood well and is likely to be multifactorial; infection, chemical and mechanical irritation, and cystic duct obstruction contribute to this. The most common cause of acute cholecystitis is acute inflammation of the cystic duct caused by obstruction by a stone. The gallbladder mucosa, which is stretched because of obstruction, is damaged, and the first step of inflammation begins. Hydrolysis of lipids (lecithin) and reabsorption of bile salts play a role in the initiation of inflammation. Bacteria can be produced in 80% of acutely inflamed gall bladders. However, there are no bacteria in many cases, which makes it impossible to detect microbial invasion as a primary cause. Therefore, it is thought that supersaturation in bile-forming elements, such as the presence of excess bile salts or acids, causes an imbalance or chemical inflammation and thus secondarily facilitates bacterial invasion. Bacterial invasion can initiate the disease in cholecystitis that develops during the course of only one systemic bacterial infection. Indeed, most of these patients do not have gallstones (12). Apart from this, acute cholecystitis has emerged as an important acute pathology in elderly patients. In this study, we believe that the presence of additional chronic diseases in elderly patients increases metabolism compared with anabolism (13).

Biliary system contamination is thought to occur by three mechanisms:

- Microorganisms in the duodenum can reach the bile ducts via the ascending path.

- The bile can also be infected by portal venous bacteremia and lymphatic route.

- In the primary intestinal disease phase (such as typhoid and cholera), there may be biliary infection with arterial and portal venous bacteremia, particularly acute cholecystitis (14). The excess bile amount is the most important reason that the microorganism cannot hold here because the bile flows continuously from a narrow lumen (15).

Stone-free cholecystitis is more common in immunosuppressed

patients. Frequent gangrene and necrosis in acalculous cholecystitis suggest that ischemia is a factor (14). Although the symptoms are the same as those of acute stone cholecystitis, this situation can be masked. Pain can be masked by the use of analgesics and unconsciousness (16). Distension and a decrease in bowel sounds were observed in 25% of cases. Although 85-96% of the patients have an increase in white blood cells and 50% have an increased value of alkaline phosphatase, these tests are not helpful in diagnosis.

Recent evidence indicates that bacterial infections are common in diabetic individuals (17). Infection is more common in diabetic individuals than in healthy individuals (18). The reason for this is vascular and neuropathic complications related to the structure and dysfunction in organs that develop due to hyperglycemia (19). Hypotension and low blood flow are present in sepsis, trauma, and burns (20). We are of the conviction that this situation negatively affects the prognosis of the patients and explains their long-term stay in the hospital.

The gall bladders of diabetic individuals are often enlarged, which decreases motility and a significant impairment of gallbladder emptying (21).

Blood circulation in diabetes is insufficient. The lack of oxygen source in the gallbladder creates a suitable environment for the growth of bacteria, which is an important cause of emphysematous cholecystitis (22). We believe that our study is consistent with this mechanism and that acute stone-free cholecystitis is more common in the presence of DM.

Although infection is not the primary cause of acute cholecystitis, it develops in 50% of patients. The susceptibility of diabetic individuals to infection due to a weakened immune system increases the risk of cholecystitis (23). In our study, when the LFT of diabetic patients (AST, ALT, GGT) were evaluated by the correlation test compared with those with acalculous cholecystitis without diabetes, higher significant correlation data were found.

In a meta-analysis performed by Aune and Vatten (11), it was revealed that there was an increase in gallbladder diseases in patients with DM, and this situation was associated with insulin resistance and obesity. In another study, when patients with emphysematous cholecystitis were examined, it was found that 55% had DM (15). In our study, the association of DM with acute stone-free cholecystitis was determined at a rate of 31.81%. This rate is lower compared to the literature, and we believe that this is due to the eating habits in our region and low obesity rates.

Many clinical conditions that can cause or accompany the disease have been described. The theories suggested in the pathogenesis of acute stone-free cholecystitis can be categorized into three groups: biliary stasis, sepsis, and ischemia. Biliary stasis occurs when the gallbladder cannot contract. After stasis, the concentration of bile increases significantly, and a viscous substance known as bile sludge is formed. This viscous material prepares the ground for edema, venous and lymphatic obstruction, ischemia, and necrosis as a cause of functional obstruction in the gallbladder. Simultaneously, it plays a role in the invasion of bacteria into the gallbladder wall by increasing bacterial colonization. The high frequency of necrosis and gangrene in the gallbladder in acute stone-free cholecystitis suggests that ischemia also plays a role in the pathogenesis. A new distribution occurs in the mucosal blood flow in the kidney, stomach, gall bladder, and lungs due to hypotension or shock (15). Anoxia that occurs because of the new distribution disrupts the barrier function of the mucosa, which causes acute inflammation because of mucosal ulceration and secondary bacterial invasion. The lower incidence of gall bladder pathologies compared with other organ failures occurring in shock has been attributed to the less affected gallbladder microcirculation in hypotension or shock (24,25).

Although the WBC count may be normal in elderly, diabetic, and immunosuppressed patients, it usually increases (4). The WBC count is usually between 12.000 and 15.000/mm$^3$. The high WBC count supports the presence of complications such as gangrene and perforation. CRP, the serum level of which increases in inflammatory conditions and is reported to increase in correlation with disease severity, is used as a laboratory parameter in diagnosis (4-6).

In another study, Beliaev and Booth (26) determined that the average AST level was 29, the average ALT level was 33, the average ALP level was 88, the average GGT level was 65, and the average amylase level was. In our study, the liver AST, ALT, and GGT values were also increased in accordance with the findings in the literature.

While there was a moderate positive correlation between CRP and AST levels in DM+ patients, a low positive correlation was found between CRP and AST levels in DM patients. We believe that the reason for this is that infection parameters tend to increase in patients with DM (23). CRP is a positive acute phase reactant and is expected to increase in infective cases.

In our study, we found a high positive correlation between ALT and GGT levels in DM+ patients. In addition to the fact that GGT is more specific for biliary tract pathologies, in the study conducted by Elwood (21), they stated that the presence of DM increased the susceptibility to gallbladder pathologies. It is obvious that the precision of bile disorders is increased in diabetic patients

and that biochemical markers such as GGT and ALT are serious prognostic indicators in DM+.

### Study Limitations

This study has some important limitations. First, a small sample size. These limits are second, this study has affected the generalizability of the findings. Data obtained only from the Department of Emergency Medicine Kafkas University Application and Research Hospitals. Hospital. The data obtained from these hospitals may not fully reflect all patients.

## Conclusion

Therefore, we can say that the presence of DM increases the risk of acalculous cholecystitis and the blood parameters used to show infection. Furthermore, impairment in LFTs increases more in patients with DM.

### Ethics

**Ethics Committee Approval:** Ethical approval for our research was secured from the Ethics Committee of Kafkas University Faculty of Medicine Ethics Committee (ethics committee decision no: 80576354-050-99/223, date: 10.10.2019).

**Informed Consent:** Retrospective study.

### Authorship Contributions

Surgical and Medical Practices: T.D., L,Ş., HF.G., M.A., E.A., G.G.A., T.A., M.E., İ.A., H.C., Concept: T.D., HF.G., Design: T.D., HF.G., Data Collection or Processing: T.D., M.A., M.E., Analysis or Interpretation: T.D., L,Ş., HF.G., M.A., E.A., G.G.A., T.A., M.E., İ.A., H.C., Literature Search: T.D., L,Ş., HF.G., M.A., E.A., G.G.A., T.A., M.E., İ.A., H.C., Writing: T.D., L,Ş., HF.G., M.A., E.A., G.G.A., T.A., M.E., İ.A., H.C.

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