

# Histological and Biochemical Liver Changes in Cholelithiasis

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## Abstract

A prospective study designed to investigate the histopathological changes in livers of 67 patients undergoing cholecystectomy and to relate these changes to the underlying biliary tract pathology. Sixty three had gall stones, one cholesterolosis only, and there were three cases of acute acalculous cholecystitis. Only 34% of the patients had completely normally liver biopsy specimens.

The most clinically important pathology was found in 11 of the 14 patients with choledocholithiasis: three of these had cholangitis and eight had features of large bile duct obstruction (four also had chronic cholestasis and portal-portal linking fibrosis). Non-specific reactive hepatitis was the most common abnormality in remaining 53 patients with cholecystitis alone, and was found in 18. A further four patients had chronic cholestasis without fibrosis was a coincidental finding in another. Clinical symptoms were poorly correlated with gall bladder and liver pathology apart from an association between jaundice and choledocholithiasis. Liver function tests of obstructive pattern were noted in 23 of 58 patients ,most of whom had choledocholithiasis or non-specific reactive hepatitis .Bile cultures were positive in 10 of 42 patients predominantly in cases of cholangitis and acute cholecystitis.

Cholangitis and extensive fibrosis associated with large bile duct obstruction are common findings in patients with choledocholithiasis. The liver disease may progress to secondary biliary cirrhosis if the obstruction is not relieved, emphasizing the need for early surgery. A preoperative liver biopsy may be useful to exclude cirrhosis in these patients, but is unlikely to be informative in those with cholecystitis alone.

**Key words:** gall stones, cholecystectomy, liver changes.

## Introduction

Liver damage in patients with gall stones is thought to be the result of chronic extrahepatic large bile duct obstruction with or without repeated episodes of cholangitis<sup>(1, 2)</sup> and may ultimately progress to secondary biliary cirrhosis<sup>3</sup>.

Previous studies correlating the presence of gall stones with changes in liver histology have given conflicting results<sup>4-9</sup>. In particular, the reported incidences of portal tract fibrosis differed considerably, and its association with the localization of gall stones has been poorly defined. More importantly, the histological changes have not been described in detail.

The aim of this study, therefore, was to determine the prevalence and extent of liver disease, and to assess the value of peroperative liver biopsy specimens in patients undergoing cholecystectomy for gall stones and cholecystitis. Clinical assessment, liver function tests and microbiology were correlated with liver and gall bladder histology and the distribution of gall stones in biliary tree.

## Methods

Peroperative protocol liver biopsy specimens distal to the gall bladder bed were obtained from 67 consecutive patients undergoing cholecystectomy, between January and October 2006. The series included 41 woman, mean age 47.6 years (range 18 to 83 years), and 26 men, mean age 57.6 years (range 32 to 75 years). Elective surgery was carried out in all patients, who had histories of gall stone related disease between eight weeks and 15 years. None of the patients was alcoholic, had viral hepatitis, or was known to be taking drugs associated with liver damage. The results of preoperative liver function tests (serum bilirubin, aspartate amino transferase and alkaline phosphatase), taken within three days before surgery, were available in 53 patients.

The distribution of gall stones within the biliary tree was determined by a combination of radiological and

ultrasound findings before surgery and those at surgery by exploration of the common bile duct. peroperative bile swabs from the gall bladder and common bile duct were cultured aerobically and anaerobically by standard methods ,and results were available for 42 patients .

The liver biopsy specimens (stained with haematoxylin and eosin ,reticulin, and orcein stains) and blocks from the gall bladders were assessed for histological changes.

## Results

### GALL BLADDER HISTOLOGY AND DISTRIBUTION OF GALL STONE

Histological changes in the gall bladder are documented in table 1. Cholelithiasis was present in 63 patients, 14 had choledocholithiasis .Three had acute acalculous cholecystitis and another only cholesterolosis.

### LIVER HISTOLOGY

Histological changes in liver are documented in table 2 .Liver histology was normal in 23(34%) patients. The commonest abnormalities were non-specific reactive hepatitis and large droplet fatty change (Figure 1) .Of the 18 patients (27%) with reactive hepatitis seven also had acute inflammatory cell in portal tracts not involving the bile ducts Figure (2).

More clinically important pathology in the form of cholestasis, cholangitis, or large duct obstruction was present in 18 patients Figure(3). Extensive fibrosis with portal-portal linking was confined to the four patients with acute large duct obstruction who also showed features of chronic cholestasis, including the accumulation of copper associated protein in periportal hepatocytes. None of the patients had secondary biliary cirrhosis .The liver biopsy specimen from one woman displayed the features of primary biliary cirrhosis(stage 2).

A frequent observation was the presence of focal necroses and collections of neutrophils in the sinusoids, which are generally accepted to be the result of surgery and anesthesia. Although minor differences, were seen in the frequency of histological changes between men and women, these were not significant.

## Correlation Between Liver And Gall Bladder Histology

Normal liver histology and reactive hepatitis were common in all categories of gall bladder diseases. Large droplet fatty change and acute or chronic large duct obstruction were seen mainly in cases of acute-on-chronic or chronic cholecystitis. All those patients with cholangitis or reactive hepatitis with acute inflammatory cells in portal tracts had either acute or acute-on-chronic cholecystitis.

### Clinical Symptoms

The most common symptoms were abdominal pain with or without jaundice. There was no correlation between the timing of the pain and gall bladder or liver histology. Thirteen (19%) patients presented with acute abdominal pain and jaundice, with the following liver histology: acute cholangitis (n=3); acute large duct obstruction (n=2); non-specific reactive hepatitis (n=1); and cholestasis only (n=3). None had normal liver histology. All three patients with cholangitis had swinging fever in addition to abdominal pain and jaundice.

Forty two patients had no history of jaundice, including two the change of acute large duct obstruction with chronic cholestasis, both had histories of abdominal pain of more than two years. All four patients with only chronic cholestasis had histories of recurrent abdominal pain, of at least three months duration, but none had had jaundice before.

In general, there was poor correlation between symptoms and gall bladder pathology.

### Choledocholithiasis

The results of liver histology for the 14 patients with choledocholithiasis are given in table 3.

### Liver Function Tests

Abnormal preoperative liver function tests are correlated with liver histology in table 4. Twenty eight of the 53(53%) patients had abnormal liver function tests. The most sensitive indicator of clinically important liver pathology was a raised serum alkaline phosphatase value, present in 23(43%) patient. None of the patients with acalculous cholecystitis had a raised alkaline phosphatase activity.

### BILIARY MICROBIOLOGY

Of the 42 patients in whom the results of preoperative bile swab microbiology were available, 10(24%) had positive cultures of one or more organisms, including six of the 14 with choledocholithiasis (results were unavailable in two of these). Infected bile was seen mainly in acute or acute-on-chronic cholecystitis. Only two of these patients had chronic cholecystitis with no acute inflammatory component.

Liver histology in these patients was as follows: acute cholangitis (n=3); reactive hepatitis (n=3, two with an acute inflammatory component); acute large duct obstruction with chronic cholestasis only (n=1); and normal (n=2). Bacterial isolates comprised *Escherichia coli* (seven patients), *Streptococcus faecalis* (three patients), *Bacteroides fragilis* (one patient), and *Pseudomonas aeruginosa* (one patient).

All categories of gall bladder and liver histology apart from cholangitis were represented among the 32 patients with sterile bile culture.

## Discussion

This study has shown that a high proportion (66%) of patients with gall stones and cholecystitis had abnormal liver histology. The most common findings were non-specific reactive hepatitis and large droplet fatty change. More clinically important liver pathology, in the form of large duct obstruction or cholangitis, was associated with choledocholithiasis, which is similar to the findings of others<sup>2,6,7</sup>.

Extensive fibrosis with portal-portal linking was present in four of the patients with large duct obstruction. This was shown to be the result of chronic biliary disease by the demonstration of chronic cholestasis in each case. This observation is important because the fibrosis could ultimately progress to irreversible secondary biliary cirrhosis<sup>2,3,6</sup>.

The mean interval between the onset of partial biliary obstruction by gall stones and the confirmation of cirrhosis has been estimated at year<sup>3</sup>. Considerable resolution may still be possible at the stage of portal-portal linking if the obstruction is relieved,<sup>10</sup> which emphasizes the importance of early surgery.

Others have reported minor degrees of fibrosis or the prominence of acute inflammatory cells in portal tracts in patients with cholecystitis or choledocholithiasis, but the presence or absence of the changes of large duct obstruction, cholangitis, and cholestasis were not emphasized in these studies<sup>5,8,9</sup>.

The presence of acute and chronic cholestasis alone in two and four patients, respectively, with cholelithiasis, is most likely related to previous choledocholithiasis with expulsion of the stone before surgery. This is supported by the obstructive pattern of liver function tests present in four of these cases. None of these patients had extensive fibrosis.

Non-specific reactive hepatitis was a frequent finding in this study and was confined to patients with acute or chronic cholecystitis. None had choledocholithiasis, but nine had abnormal liver function tests, most of obstructive pattern. Reactive hepatitis might, therefore, be the result of a recent episode of common bile duct obstruction in some patients. Chronic inflammation in portal tract, with or without large droplet fatty change, has been reported by others with similar frequency.<sup>4,5,8</sup>

Reactive hepatitis has been described in patients with a variety of condition, including febrile illnesses, hepatic space-occupying lesions, venous outflow obstruction and intestinal infection<sup>1</sup>. As a common disease cholecystitis should be regarded as important additional cause. Some patients with reactive hepatitis also had acute inflammatory cells in portal tracts and this correlated with acute inflammation in the gall bladder.

The finding of a single case of primary biliary cirrhosis among these patients should be regarded as coincidental. There is no known association between the two diseases. Clinical symptoms were of poor discriminative value in predicting the underlying pathology, in accordance with the findings of others<sup>9</sup>. The duration of abdominal pain could not be correlated with either liver or gall bladder pathology. Jaundice was often present in patients with cholangitis or large duct obstruction, but the association was not invariable. A previous history of jaundice was not correlated with extensive liver pathology.

.Conversely; six of the eight patients with chronic cholestasis had never been jaundiced, similar to the findings in the early stages of primary biliary cirrhosis.<sup>11</sup> Abnormal liver function tests were most common in patients with choledocholithiasis. An obstructive pattern with raised alkaline phosphatase values was the most frequent abnormalities, which was similar to the findings of others<sup>12</sup>. The noted high incidence of positive bile cultures in patients with choledocholithiasis, cholangitis, and acute cholecystitis and the spectrum of bacterial isolates as expected from other series.<sup>8, 13-16</sup>

### Conclusions

Cholangitis and extensive fibrosis associated with large bile duct obstruction are common findings in patients with choledocholithiasis.

The liver disease may progress to secondary biliary cirrhosis if the obstruction is not relieved, emphasizing the need for early surgery .A preoperative liver biopsy may be useful to exclude cirrhosis in these patients, but is unlikely to be informative in those with cholecystitis alone.

**Table (1) Gall bladder histology in patients with cholelithiasis**

Gall bladder histology	No. of patients	Percentage (%)
Normal	2	3
Acute cholecystitis	8	11,9
Acute-on-chronic cholecystitis	22	32,8
Chronic cholecystitis	34	50,7
Cholesterolosis only	1	1,5
Total	67	100

**Table (2) Liver histology in patients with cholelithiasis**

Liver histology	No. of patients	Percentage (%)
Normal	23	34,3
Large droplets fatty change only	7	10,4
Non-specific reactive hepatitis	18	26,8
Acute cholestasis only	3	4,5
Chronic cholestasis only	4	6
Acute cholangitis	3	4,5
Acute large duct obstruction	4	6
Acute large duct obstruction with chronic cholestasis	3	4,5
Primary biliary cirrhosis	1	1,5
Total	67	100

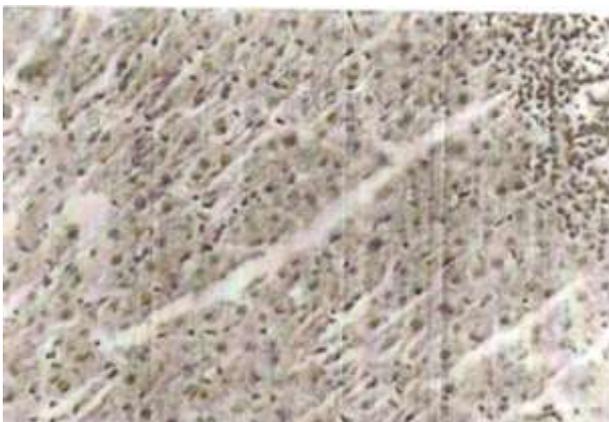
**Table (3) Liver histology in patients with choledocholethiasis**

Liver histology	No. of patients	Percentage (%)
Normal	3	21,43

Acute cholangitis	۳	۲۱,۴۳
Acute large duct obstruction	۴	۲۸,۵۷
Acute large duct obstruction with chronic cholestasis	۴	۲۸,۵۷
Total	۱۴	۱۰۰

**Table (4): Abnormal liver function tests in patients undergoing cholecystectomy**

Liver histology	Raised bilirubin	Raised AST	Raised alka	Total	Total No. of patients tested
	More than (17mmol)	More than (40U/l)	line phosphate more than (130 U/l)		
Normal	۱	۱	۱	۳	۱۸
Large droplets fatty change only	۰	۰	۰	۰	۱
Non-specific reactive hepatitis	۵	۶	۷	۹	۱۶
Acute cholestasis only	۳	۲	۲	۳	۳
Chronic cholestasis only	۰	۰	۲	۲	۳
Acute cholangitis	۳	۳	۳	۳	۳
Acute large duct obstruction	۴	۳	۴	۴	۴
Acute large duct obstruction with chronic cholestasis	۲	۳	۳	۳	۴
Primary biliary cirrhosis	۰	۱	۱	۱	۱
Total	۱۸	۱۹	۲۳	۲۸	۵۳



**Fig(1):HPF non-specific reactive hepatitis in 65 years old male**



**Fig(2):MPF sclerosis of portal tract in 50 years old female**



**fig (3) :MPF severe cholestasis and fatty changes in 73 years male**

### References

- 1-Scheuer PJ. Liver biopsy interpretation.4<sup>th</sup> ed .London: Bailliere Tindall, 1988.
- 2-Desmet VJ.Cholestasis: extrahepatic obstruction and secondary biliary cirrhosis.In: MacSween RNM, Anthony pp, Scheuer PJ, eds.pathology of the liver 2<sup>nd</sup> ed.Edinburgh: Churchill Livingstone, 1997:364-423.
- 3-Scobie BA, Summerskill WHJ.Hepatic cirrhosis secondary to obstruction of the biliary system .Am F Dig Dis 1995;10:135-45.
- 4-Matter JG, Hartmann FW, Blatz JJ, Fallis LD, McGraw AB,, Steele HH.Combined liver biopsy and liver function study in 132 cases of Cholelithiasis and 31 cases of peptic ulcer (operated cases).Gastroenterology 1988; 11:284-302.
- 5-Savory PB, Shively JA, Talbert PC, Caylor HD.Biliary system inflammation and cholecystitis.Am J surg 1985;90:562-7.
- 6-Edlund YA, Zettergren LSW.Microstructure of liver in biliary tract disease. Acta Chir Scand 1987; 113:201-10.
- 7-Poulsen H, Christoffersen P. Histological changes in liver biopsy from patients with surgical bile duct disorders Acta Pathol Microbiol Scand 1990; 78:571-9.
- 8-Flinn WR, Olson DF, Oyasu R, Beal JM.Biliary bacteria and hepatic histopathologic changes in gallstone disease. Ann Surg 1997;185:593-7.
- 9-Triger DR, Maclver AG, Gamlen TR, Wilken BJ.Liver abnormalities and gallstones: a prospective combined clinical. Histological and surgical study. Br J surg 1996;63:272-7.
- 10-Yeong ML, Nicholson GI, Lee SP.Regression of biliary cirrhosis after choledochal cyst drainage. Gastroenterology 2002; 82:332-5.
- 11-Portmann B.MacSween RNM.Diseases of the intrahepatic bile duct.In: MacSween RNM, Anthony PP, Scheuer PJ, eds.Pathology of the liver.2<sup>nd</sup>edn.Edinburgh:Churchill Livingstone,2005:424-53.
- 12-Lindenauer SM, Child CG.Disturbances of liver function in biliary tract diseases.surg Gynecol obstet 1996;123:1205-11.
- 13-Salk RP, Greenburg AG, Farris JM, Perkin GW. Spectrum of cholangitis. Am J. Surg Edin 1995; 130:143-50.
- 14-Haw CS, Gunn AA.The significance of infection in biliary disease.J Roy Coll Surg Edin 1993; 18:209-12.
- 15-Pitt HA, Postier RG, Cameron JL. Consequences of preoperative cholangitis and its treatment on the outcome of operations for choledocholithiasis. Surgery 1993; 94:447-52.
- 16-England DM, Rosenblatt JE. Anaerobes in human biliary tract. J Clin Microbial, 1997;6:494-8

## الملخص

دراسة مستقبلية اجريت على ٦٧ مريض مصاب بحصى المراره، اجريت لهم عملية استئصال المراره للفترة من كانون الثاني الى تشرين الاول ٢٠٠٦. الهدف من هذه الدراسة هو امكانية حصول أي تغييرات نسيجية ووظيفيه في الكبد ومعرفة علاقه بينها وبين حصى المراره.

بعد فحص المرضى و دراسة التاريخ المرضي ، تم اخذ عينات من الدم وارسالها للمختبر لدراسة وظائف الكبد ، وبعد عدة ايام واثاء اجراء العمليه الجراحيه ، تم اخذ عينه من الكبد وفحصها مجهريا لمعرفة التغييرات النسيجية. كما تم اخذ مسحات من ماده الصفراء لدراستها بكتريولوجيا .

شاهد وجود تغييرات نسيجية مختلفه في الكبد عند اغلب المرضى وبنسبة (٦٦%) . كانت هذه التغييرات تتراوح ما بين تغييرات تفاعليه غير متخصصه بسيطه الى تغييرات شديده مثل تشمع الكبد. وكانت هذه التغييرات اكثر شده عند المرضى المصابين بحصى القناة الصفراويه .

التغييرات النسيجية للكبد ربما تتطور الى تشمع الكبد الثانوي اذا لم يتم ازالة الانسداد ، لذا فان الحاجه الى التدخل الجراحي امر ضروري لمنع تلف انسجة الكبد.

ان ارتفاع مستوى انزيم الكبد المسمى ( الالكلين فوسفاتيز ) هو الاكثر تحسسا عند وجود ضرر في انسجة الكبد، عند المرضى المصابين بحصى القناة الصفراويه .