
Elevated liver enzymes in patients with cholecystitis

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Abstract: Aims: To investigate changes in liver function tests in calculous cholecystitis (acute and chronic) and to relate that changes to cholecystitis. Methods: A retrospective study including 389 patients with clinical and sonographic evidence of cholecystitis with exclusion of other causes of elevated liver function tests, which are done preoperatively and four weeks postoperatively. Results: Increased liver function tests observed in both acute and chronic cholecystitis. The only significant differences between both groups were a higher bilirubin level ($P=0.001$) and WBC ($P=0.018$). Pre and post-cholecystectomy levels of AST, ALK-P and GGT were significantly changed ($P=0.001$). Conclusion: Our study showed that the abnormal biochemical liver function tests resolved rapidly and spontaneously after cholecystectomy indicating transient hepatocellular injury with cholecystitis.

Keywords: Cholecystitis, Liver function tests, Leucocytosis

1. Introduction

Liver damage in patients with gallstones is thought to be the result of chronic extra hepatic large bile duct obstruction with or without repeated episodes of cholangitis and may ultimately progress to secondary biliary cirrhosis (11).

Hepatic viral infection is by no means the only cause of acute hepatitis (Chen et al, 2007). One sitting in which there may be an acute inflammation of the liver parenchyma is the presence of common bile duct stones and cholangitis, situations in which liver tests have been widely studied (15).

Hepatocellular injury is identified by increase in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The severity of such injury may be reflected in decreased hepatic production of certain products such as albumin and clotting factors. Inflammation or damage to the biliary tract is signaled by an increase in alkaline phosphatase (ALK-P) which is sometimes confirmed by measurement of gamma-glutamyl-traspeptidase (GGT). Serum bilirubin levels may be elevated in both biliary tract and hepatocellular diseases (5).

Non-specific reactive hepatitis was a frequent finding in patients with acute or chronic cholecystitis and some patients with reactive hepatitis also has acute inflammatory cells in portal tracts and this correlated with acute inflammation in the gallbladder (21).

2. Materials and Methods

This is a retrospective study. We reviewed the medical records of patients admitted to our Hospital, from January 2009 to April 2012 who underwent cholecystectomies for gallbladder stones associated with acute or chronic cholecystitis. Of 420 such records, we excluded those of patients who had undergone either preoperative endoscopic retrograde cholangiopancreatography(ERCP) or magnetic resonance cholangiopancreatography(MRCP), thus 389 patients were included in this study. Of total patients, 255 were women and 134 were men.

All patients were divided into two groups:

Group A: Which includes 158 patients with chronic cholecystitis, 40 males and 118 females with mean age 41.30 (range from 33 to 56 years).

Group B: Which includes 231 patients with acute cholecystitis, 94 males and 137 females with mean age 40.42 (range from 26 to 60 years).

The exclusion criteria for our patients include those who had undergone ERCP or MRCP, those with sonographic evidence of a common bile duct disorders, patients with viral hepatitis(hepatitis A, hepatitis B or, hepatitis C), alcoholic liver disease, drug related hepatitis, metabolic liver disease, autoimmune hepatitis and patients with pancreatitis.

All patients were subjected to liver function tests in the form of aspartate aminotransferase(AST),alanine aminotransferase(ALT), alkaline phosphatase(ALK-P), gammaglutamyl-transpeptidase(GGT), Total and direct bilirubin prior to and four weeks post-operatively. The peripheral leucocyte count was also recorded. All patients had stones in the gallbladder as demonstrated by abdominal sonography. All specimens were submitted for histopathological examinations and diagnosed as either simple or gangrenous cholecystitis.

3. Results

Of all 420 records, 389 patients (92.6%), (134 males and 255 females) met the study inclusion criteria.

Cholecystectomy was performed urgently in 231 patients and electively in 158. The method of Cholecystectomy was laparoscopic in all patients. In patients who underwent an urgent laparoscopic Cholecystectomy, acute right upper quadrant or epigastric pain had been present for no more than 3 days prior to surgery. Those undergoing elective surgery had had at least one recent episode of pain typical of biliary tract disease and has been deemed to have symptomatic cholelithiasis.

Of 389 patients, 182 (46.8 %) had an elevated AST levels

with the highest level was 900 IU/dl. A higher proportion of patients (87.4%) also had an elevated ALT with the highest level was 412 IU/dl.

Mild elevations of serum total bilirubin (40.61%), direct bilirubin (41.9%), GGT (51.1%), and alkaline phosphatase (38.6%) also noticed in those patients (table1). Among those 389 patients, 356 patients were seen for follow up four weeks after Cholecystectomy, by which time the mean values of liver function tests had almost returned to normal with the mean AST, ALT, GGT, still slightly elevated, but to a much lesser extents than the pre-operative levels.

There were 231 patients who had an acute calculous cholecystitis without evidence of common bile duct stones and who underwent urgent Cholecystectomy. The gallbladder histology revealed gangrenous cholecystitis in 47 patients (20.4%). The only significant differences between that group and the 184 patients with simple cholecystitis were a higher bilirubin level (P 0.001) and WBC (P 0.018). (table2).

At all, there were a significant differences between the levels of AST, ALK-P, GGT pre- and post-Cholecystectomy (P< 0.001), but the levels of ALT, Total and direct bilirubin showed no significant differences before and after Cholecystectomy (table 3).

Table (1). Age, sex, TLC, and Liver function tests in acute and chronic cholecystitis

	Acute cholecystitis		Chronic cholecystitis		P value
	Range	Mean \pm SD	Range	Mean \pm SD	
Age	26-60	40.42 \pm 8.85	33-56	41.31 \pm 5.8	0.269
AST	15-900	118 \pm 159.57	16-66	38.87 \pm 11.8	0.000
ALT	16-412	126.64 \pm 81.81	19-87	49.65 \pm 13.8	0.002
ALK-P	65-250	140.57 \pm 44.33	47-128	92.49 \pm 26.28	0.000
GGT	39-130	69.46 \pm 23.61	29-69	43.91 \pm 10.17	0.000
T. BILIRUBIN	0.8-2.7	1.55 \pm 0.5	0.8-1.4	1.05 \pm 0.19	0.000
D. BILIRUBIN	0.0-1.2	0.67 \pm 0.39	0.0-0.6	0.16 \pm 0.15	0.000
TLC	5.2-20.1	12.83 \pm 2.83	4-11.6	6.98 \pm 2.07	0.000
Sex M/F	94/137		40/118		

Table (2). Liver function tests and TLC in Patients with acute simple and acute gangrenous cholecystitis

	Acute simple cholecystitis (Mean \pm SD)	Acute gangrenous cholecystitis (Mean \pm SD)	P- value
AST	116.1 \pm 149.75	119.2 \pm 167.1	0.12
ALT	125.2 \pm 79.8	128.7 \pm 80.8	0.12
ALK-P	138.14 \pm 41.3	141.2 \pm 43.1	0.18
GGT	68.5 \pm 22.1	70.1 \pm 24.2	0.16
T. bilirubin	1.48 \pm 0.48	1.9 \pm 0.61	0.001
D. bilirubin	0.65 \pm 0.3	0.69 \pm 0.6	0.1
TLC	12.08 \pm 2.36	17.12 \pm 2.91	0.018

Table (3). Liver function tests before and 4 weeks after cholecystectomy

	Pre-operative (Mean \pm SD)	Post-operative (Mean \pm SD)	P- value
AST	85.85 \pm 99.55	33.14 \pm 16.95	0.001
ALT	95.36 \pm 54.18	76.12 \pm 47.2	0.23
ALK-P	121.04 \pm 36.9	72.7 \pm 26.1	0.001
GGT	59.08 \pm 18.15	29.26 \pm 18.2	0.001
T. bilirubin	1.35 \pm 0.37	1.02 \pm 0.1	0.1
D. bilirubin	0.46 \pm 0.29	0.3 \pm 0.08	0.1

4. Discussion

Cholecystitis is inflammation of the gallbladder that develops over hours, usually because a gallstone obstructs the cystic duct, if it develops slowly overtime it is called chronic cholecystitis. Symptoms include right upper quadrant pain and tenderness, sometimes accompanied by fever, chills nausea and vomiting (13, 17).

Acute cholecystitis is the most common complication of cholelithiasis. Conversely, about 95% of patients with acute cholecystitis have cholelithiasis. When a stone becomes impacted in the cystic duct and persistently obstructs it, acute inflammation results. Bile stasis triggers release of liver enzymes e.g., serum 5 NT, ALP, AST, ALT along with serum bilirubin level. The gallstones blocks fluid from passing out of the gallbladder. This results in an irritated and swollen gallbladder (2).

Liver function test has been used as a routine preoperative evaluation for the gallbladder surgery as a tool to check for functional status of the liver. In a study done by Geraghty and Goldin in 1994, he stated that there is a high proportion (66%) of patients with gallstones and cholecystitis had abnormal liver histology. The most common findings were non-specific reactive hepatitis and large droplet fatty change. Cholecystitis should be regarded as a cause of reactive hepatitis. Some patients with reactive hepatitis also had acute inflammatory cells in portal tracts and this correlates with acute inflammation in the gallbladder (11).

The origins of alkaline phosphatase are two, the liver and bone. If the serum alkaline phosphatase is persistently elevated for a long period of time, it suggests prolonged cholestasis (10). In our study, the serum alkaline phosphatase was significantly elevated in patients with acute calcular cholecystitis with the highest level up to 250 IU/L. This correlated with a study done by Thapa et al in 2010; he stated that, the serum level of ALK-P was raised in patients with acute cholecystitis by 1.69 ± 0.118 fold with significant statistical difference. But if serum level of ALK-P was more than 2.5 folds higher than normal value, we could predict common bile duct stones. However, ALK-P is a non-specific indicator of cholestatic liver disease because of its multiple sources like bone, placenta beside its production from the biliary canalicular membrane hence together with determination of more specific enzymes such as Gamma-glutamyl transpeptidase and 5' Nucleotidase had to be raised for inclusion criteria to minimize this error (20, 23).

In our patients, the serum levels of gammaglutamyl-transpeptidase (GGT) were significantly elevated in patients with acute and chronic calcular cholecystitis with the highest level was 130 IU/L. In a study done by Peng and his colleagues, the serum level of GGT was more than 90 IU/L is considered being high risk to have stone in common bile duct though not statistically significant and supported by many series.

The serum levels of AST and ALT were elevated in our patients, but the serum AST was significantly elevated if

compared to the serum level of ALT. This indicates that, there is some degree of hepatocellular injury in patients with cholecystitis especially of the acute form and this injury is transient and returned to normal after cholecystectomy by about 30 days as in our patients.

In a study done by Chen-Wang and his colleagues, he stated that hepatocellular injury (diagnosed clinically by elevation of aminotransferase and bilirubin levels) was common. The incidence was higher and the aminotransferase elevations were more marked in those with stones, but some patients without CBD stones also had a degree of hepatocellular injury. In most patients, the AST, ALT, and bilirubin levels had almost returned to normal within two weeks to one month after cholecystectomy. This hepatocellular injury, even showing relatively high serum levels of aminotransferases and bilirubin should not be an obstacle to preparation of these patients for surgical intervention. This injury is transient and mild and will resolve spontaneously as expected, provided that the diseased gallbladder is removed (5).

Jaundice is not a rare manifestation of gallbladder disease without evidence of CBD stones. Thus, in our patients the mean total bilirubin was 1.35 mg/dl with the highest level was 2.7mg/dl especially in patients with acute calcular cholecystitis. These results were correlated with the results done by Chang and his colleagues (3).

Twenty five percent of patients with acute calcular cholecystitis had a serum bilirubin level between 2 to 5 mg/dl with no CBD abnormality. Also, over one third of patients with acalculous cholecystitis had an elevated bilirubin level with a normal CBD (14). In some studies, there is a correlation between the bilirubin concentration and lipid peroxidation in cases of biliary tract diseases, with the presence of interaction between free radical reactions, gallbladder formation and the degree of cholecystitis (7, 21).

In our patients who had an acute calcular cholecystitis, the gallbladder histology revealed gangrenous cholecystitis (20.4%) and 79.6% had simple cholecystitis. There were a higher bilirubin level and high peripheral leukocyte count in gangrenous cholecystitis patients than simple cholecystitis patients, thus leucocytosis and hyperbilirubinemia were associated with more severe gangrenous cholecystitis (6).

There is a possibility that small stones passed through the duct during biliary colic resulting in biochemical liver function abnormalities. Our results are against this proposal. Firstly, ERCP is so far the most reliable and widely applicable imaging procedure to evaluate the common bile duct. Secondly, small stones less than 0.5 cm that can pass the duct may induce pancreatitis that is excluded in our patients to reduce this possible confounding factor. Finally, the mildly elevated to normal alkaline phosphatase levels argue against transient stone passage as a cause of the hepatocellular injury (8, 9, and 22).

It is likely that most bile duct stones pass spontaneously, especially after pancreatitis, biliary colic and cholecystitis but less commonly after jaundice (22).

Our study had some limitations. Firstly, it is a retrospective study in which we performed study only on patients with cholecystitis and it is better that we perform study on general population for better assessment of prediction of liver enzymes in calculi cholecystitis. Secondly, we performed our results in one clinical centre, thus multicenter study and analysis in separated age and sex group were recommended for next studies.

In conclusion, our study showed that the abnormal biochemical liver function test of almost all patients resolved rapidly and spontaneously after cholecystectomy and indicates that there is an acute hepatocellular injury in symptomatic gallstones with cholecystitis in the absence of common bile duct stones and this injury is mild and transient.

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