DOI: 10.14744/ejmo.2018.47965
EJMO 2018;2(4):203–208

Research Article

Alteration of Fatty Infiltration Grades of the Liver in Sonography as an Outcome of Cholecystectomy

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Abstract

Introduction: Recent studies have not only reported that non-alcoholic fatty liver disease may be associated with cholecystectomy but also emphasized that cholecystectomy may be a risk factor for the accumulation of fat in the liver. In light of this information in the literature, in the present study, we compared the sonographic fatty infiltration grades of patients who had undergone cholecystectomy using laboratory findings obtained before and after the operation.
Objective: Fifty-nine cases whose almost complete laboratory and sonographic data were available were included in the study. Patients were divided into three groups according to the preoperative period and postoperative follow-up periods as 3 months and 6-12 months.
Results: In both groups, there was a statistically significant difference between the preoperative and postoperative steatosis and ultrasound (US) fatty infiltration grades ($p<0.001$). However, there were no statistically significant differences between the preoperative and two postoperative follow-up periods of US fatty liver grades alteration ($p=0.650$). The hepatic steatosis index had a significant correlation with steatosis and US fatty infiltration grades (Spearman's correlation rho=0.319 and rho=0.361, respectively, $p<0.001$).
Conclusion: Cholecystectomy may lead to an increase in the level of fatty infiltration of the liver in the follow-up sonography, which may occur over a certain period of time through adaptive processes. Early postoperative US imaging for the purpose of hepatosteatosis follow-up is not necessary.
Keywords: Cholecystectomy, steatosis, sonography, US fatty grades
Cite This Article: *Koc U, Eken H. Alteration of fatty infiltration grades of the liver in sonography as an outcome of cholecystectomy. EJMO. 2018; 2(4): 203-208*

Non-alcoholic fatty liver disease (NAFLD) is a very common finding in the current ultrasound practice, with a sonographic presence of 30% in various series in adult populations, and as a component of the metabolic syndrome with increasing incidence, it constitutes one of today's epidemics.[1,2,3] It is one of the important indications of liver failure and currently the second most common cause of liver transplantation.[4,5] NAFLD cases are usually asymptomatic and incidentally detected. Liver biopsy is the gold standard for the diagnosis of NAFLD. However, ultrasonography is the first imaging modality to evaluate for fatty liver infiltration in daily practice. Despite the inter- and intra-observer differences in ultrasound findings, this method achieves high sensitivity and specificity in determining moderate-advanced NAFLD.[5,6] There has been reported that NAFLD is associated with obesity, type2 diabetes mellitus (DM), atherosclerosis, cholelithiasis, hyperlipidemia, and the metabolic syndrome.[3,7-9]

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Submitted Date: April 11, 2018 **Accepted Date:** May 20, 2018 **Available Online Date:** October 10, 2018

The relationship between NAFLD and cholecystectomy has already reported in the most recent literature, which is predominantly progression.[10,11] On the other hand, none of them compare the different follow-up periods after surgery related to hepatic steatosis via radiological methods. In this study, the sonographic preoperative and different follow-up periods of postoperative liver fatty infiltration grades of patients that had undergone cholecystectomy were retrospectively compared in light of laboratory findings.

Methods

Study protocol and patients

The most recent preoperative (within one month) and 3 and 6-12 month after cholecystectomy follow-up ultrasound reports of cholecystectomy cases in Erzincan University Mengucek Gazi Education and Research Hospital were retrospectively screened in the patient medical chart from September, 2016 to August, 2017. Fifty-nine patients were included into the study, all of whom were operated by one general surgeon who has 10 years of experience and the reason of the operations were cholelithiasis in all cases. The ultrasound examinations were performed by a radiologist with 6 years' experience. The radiologist didn't look at old medical records to remember preoperative steatosis grade when the patients were examined at follow-up time. The study was approved by the ethics committee of the Erzincan University and conducted in accordance with the principles of the Helsinki Declaration. Getting informed consents from the cases were waived according to the local Ethic Committee decision.

The exclusion criteria were alcohol use; any kind of acute or chronic hepatitis, chronic inflammatory diseases including autoimmune etiology; inflammatory diseases; anemia; hemochromatosis; Wilson's disease; autoimmune diseases; malignancy; long term medication including estrogen, amiadorone, steroid or tamoxifen, chemotherapy; pregnancy; and iron overload.[11]

The height, weight and body mass index (BMI) of the patients, platelet, white blood cell (WBC), serum albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, amylase, fasting glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were recorded.

Measurement of Hepatic Steatosis

The measurement data comprised hepatic steatosis index (HSI) and ultrasound reports. HSI was calculated using the formula 8xALT / AST+BMI+2 (if type 2 diabetes was present)+2 (if female).[12] The preoperative ultrasound data was compared with the values obtained from two follow-up groups: Month 3 and Month 6-12. The ultrasound scanner used were Toshiba Aplio 300 and 500 (Tokyo, Japan). The sonographic fatty liver infiltration was categorized as follows; Grade 0, normal echogenicity; Grade 1, slight increase in echogenicity with normal visualization of the diaphragm and the intrahepatic vessel borders; Grade 2, moderate increase in echogenicity, accompanied by reduced visualization of the diaphragm and intrahepatic vessel walls; Grade 3, severe increase in echogenicity with almost no visualization of the diaphragm and intrahepatic vessel walls, making it difficult to evaluate the image.[11,13] Hepatomegaly was reported if the liver size exceeds 160 mm in greatest craniocaudal dimension.

Statistical Analysis

The basic characteristics of three groups were assessed using the ANOVA and the Kruskal Wallis test depending on the normal or skewed distribution of the data, respectively. The Chi square or Fisher's exact tests were used for the categorical data. The independent t-test or the Mann Whitney U test were applied based on whether the groups had a normal distribution of characteristics in the intergroup comparisons, and the intragroup comparison between preoperative and follow-up data was undertaken using a paired t-test or wilcoxon test. To assess the correlation between HSI, US grade, steatosis status (absent or present via US) and liver size alteration, Spearman's correlation was used. The data was expressed as mean +/- standard deviation (SD) in cases where the distribution was normal, and the median and minimum-maximum were included for data that was not normally distributed. SPSS version 24.0 (SPSS IBM Inc., Chicago, IL) was used for the statistical analysis. $p<0.05$ was considered to be statistically significant.

Results

Table 1 presents the preoperative (within 1 month) and postoperative data obtained from the 59 patients.

Figure 1 presents the US fatty liver grades count in three groups. A significant difference was found between preoperative and both 3-month and 6/12-month postoperative US regarding to steatosis grading that pre-operative no steatosis, grade 1, 2, 3 steatosis were 49.2% (n=29), 35.6% (n=21), 13.6% (n=8); 1.7% (n=1), respectively, which were 4.8% (n=1); 52.4% (n=11); 38.1% (n=8); 4.8% (n=1) in 3-month

Table 1. It presents the preoperative and postoperative data obtained from the fifty-nine patients and divided into three groups

	Preoperative Group (n=59)	Postoperative-3 Month Follow up (n=21)	Postoperative-6/12 Month Follow up (n=38)	p
M/F	20/39 (%33.9/%66.1)	7/14 (%33.3/%66.7)	13/25 (%34.2/%65.8)	0.998
Age	47.73±12.05	49.24±12.71	46.89±11.76	0.805
BMI	29.74±5.46	29.55±6.25	29.84±5.05	0.993
Diabetes Mellitus Status (+)	6 (%10.2)	2 (%9.5)	4 (%10.5)	1.000
Additional Illness (+)	25 (%42.4)	9 (%42.9)	16 (%42.1)	0.998
Diet Status (+)	3 (%5.1)	2 (%9.5)	1 (%2.6)	0.472
Postsurgery Complaints (+)	12 (%20.3)	5 (%23.8)	7 (%18.4)	0.886
Steatosis Status (+)	30 (%50.8)	20 (%95.2)	28 (%73.7)	0.001
AST (U/L)	22.50 (11:42)	18.00 (9:40)	21.50 (12:54)	0.489
ALT(U/L)	24.00 (8:87)	19.00 (10:44)	20.50 (6:124)	0.806
ALP(U/L)	85.50 (48:118)	79.00 (58:132)	78.50 (41:164)	0.934
Albumin(g/dl)	4.23±0.26	4.07±0.17	4.13±0.26	0.001
Total bilirubin(mg/dl)	0.57 (0.13:1.43)	0.54 (0.25:0.96)	0.65 (0.31:1.77)	0.110
Amylase(U/L)	67.00 (32:94)	73.00 (47:159)	72.50 (34:134)	0.310
Fasting Glucose(mg/dl)	95.00 (75:144)	109.00 (79:123)	98.00 (70:164)	0.034
Total Cholesterol(mg/dl)	182.50 (146:355)	205.00 (73:289)	194.50 (129:328)	0.703
Triglyceride(mg/dl)	150.00 (44:252)	134.00 (58:256)	127.00 (45:327)	0.637
HDL-C(mg/dl)	44.98±8.77	48.18±10.67	48.59±8.61	0.419
LDL-C(mg/dl)	115.00 (75:268)	127.20 (55:200)	110.30 (51:228)	0.478
WBC(10^3/mm^3)	7.14±1.64	6.74±1.12	7.58±1.98	0.539
PLT(10^3/mm^3)	271.90±48.52	272.29±55.49	300.41±66.90	0.467
HSI	42.56±8.69	39.62±6.85	40.24±6.58	0.934

M/F: Male/Female; BMI: Body mass index; PLT: Platelet; WBC: White blood cell; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; HSI: Hepatic steatosis index.

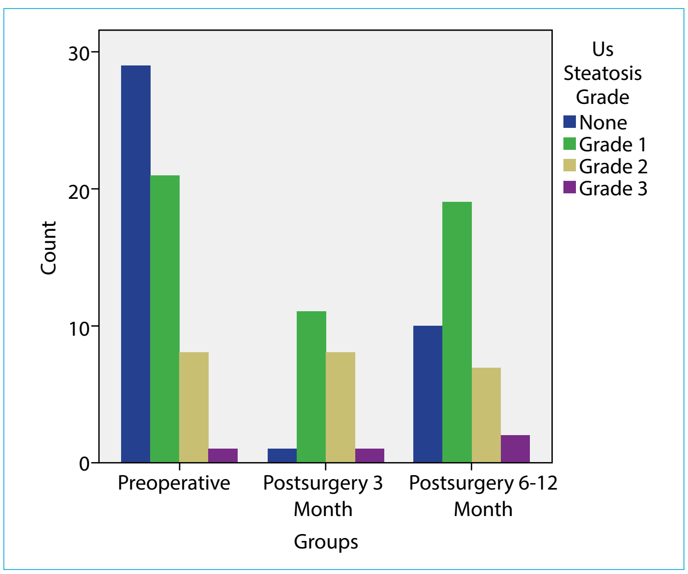

Figure 1. It presents the US fatty liver grades count in three groups.

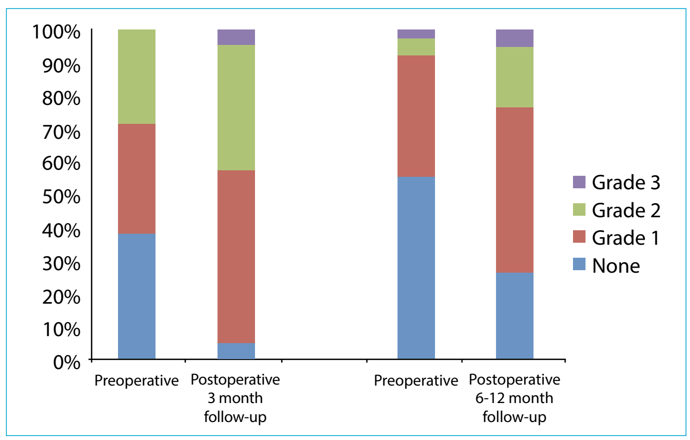

Figure 2. The preoperative and postoperative 3 month and postoperative 6-12 month follow up ultrasonographic liver steatosis grades were compared with each other. Preoperative 3 month postoperative follow up and preoperative 6/12 month postoperative follow up paired group comparison showed statistically significant differences according to US fatty liver grades alteration (p=0.001).

post-operative and 26.3% (n=10); 50%(n=19); 18.4% (n=7); 5.3% (n=2) in 6-12 month post operative groups (p=0.02). Furthermore, preoperative-3-month postoperative follow up and preoperative-6/12-month postoperative follow up paired group comparison showed statistically significant differences according to US fatty liver grades alteration (p=0.001) (Fig. 2). On the other hand, there was no significant difference between delta(∧ post-pre) in terms of change US fatty liver grades (3-month postoperative follow up-preoperative group) and (6/12-month postoperative follow up-preoperative group) (p=0.650).

Hepatic steatosis index were positively correlated with steatosis and US fatty infiltration grades (Spearman's correlation rho=0.319; rho=0.361, p<0.001 respectively).

Cholecystectomy had significant correlation with steatosis and US liver fatty infiltration grades (Spearman's correlation rho=0.322; rho=0.314, p<0.001 respectively). On the other hand, cholelithiasis had no statistically significant correlation with steatosis and US liver fatty infiltration grades (p>0.05).

Figure 3 presents the relation between liver size and steatosis. Liver size had significant correlation with steatosis and US fatty infiltration grades (Spearman's correlation rho=0.297; rho=0.373, p<0.001 respectively).

According to the preoperative ultrasound reports, 30 (50.8%) patients had fatty different grade of infiltration of the liver, and this number increased to 48 (81.4%) at the follow-up evaluation. Six of the cases (10.2%) had a diagnosis of controlled type2 diabetes. Furthermore, 25 cases (42.4%) had other accompanying conditions, such as hypertension, coronary artery disease, gastrointestinal complaints, and benign thyroid pathology. The two follow-up groups did not differ in this respect. None of the cases had experienced rapid weight loss. The number of cases with postoperative complaints was 12 (20.3%), with most complaints being related to gas and pricking pain in the right upper quadrant.

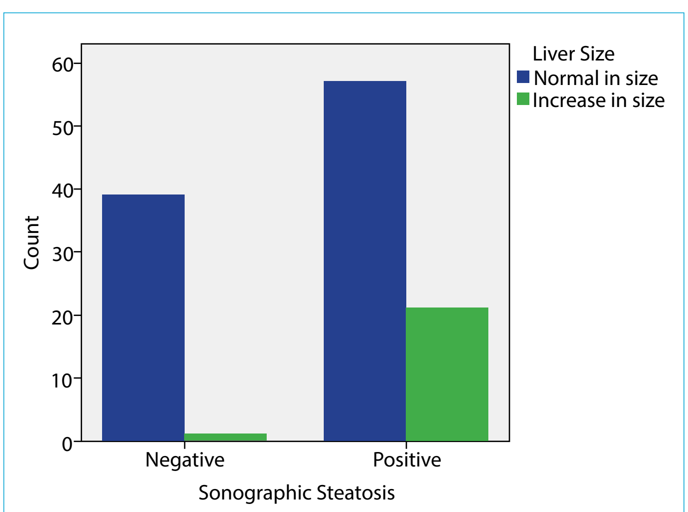

Figure 3. It presents the relationship between liver size and steatosis.

Discussion

Current prospective and retrospective studies suggest a strong association between cholecystectomy and NAFLD.[3,10-11] Cholecystectomy was emphasized as an independent risk factor for NAFLD.[10,14] Furthermore, Shen et al. presented the results of a multivariate logistic regression analysis, demonstrating that cholecystectomy significantly increased the risk of the development of the metabolic syndrome.[15] In addition to studies that reported cholelithiasis having an effect on or even being an independent risk factor for fatty liver, there are also large-scale multivariate logistic analyses in which cholelithiasis and cholecystectomy were evaluated together and the latter was found to be associated with NAFLD as an independent risk factor.[10,14-16] In the current study, following ultrasonography, 50.8% of the cases with cholelithiasis (n=30) were found to have fatty infiltration of the liver at various grades; however, no significant relationship was identified between cholelithiasis and steatosis (p>0.05). After cholecystectomy, fatty liver was present in the ultrasound of 81.4% of the cases (n=48). Compared to the preoperative values, there was a significant increase in the follow-up groups.

The increased risk of NAFLD after cholecystectomy is the result of possible metabolic effects. Excess cholesterol is eliminated by the bilioenteric route, and secreted cholesterol is absorbed back into the bowels; however, cholesterol crystals formed in the gall bladder are excreted through the feces without being absorbed. Interruption of elimination of excess cholesterol after cholecystectomy leads to an increase in cholesterol reabsorption.[17-20] Thus, bile acid circulation occurs more rapidly and the liver is exposed to more bile acid flux.[19-20] Fibroblast growth factor (FGF) is another important factor in bile acid synthesis and gall bladder motility, which is found more in gall bladder than in the blood and liver.[20-21] After cholecystectomy, the protective effect of FGF on the liver is significantly reduced.[21]

In a prospective study, it was emphasized that hepatic steatosis developed three months after cholecystectomy.[11] Similarly, in the present study, there was a significant difference in the grade of fatty infiltration of the liver between the groups of Month 3 and Month 6-12 (p<0.001). However, the comparison of the preoperative and postoperative fatty liver alteration grades between the two groups related to the follow up time did not show any significant difference. In literature, evaluation of different periods US fatty liver grades after operation has not been reported before. Our study demonstrated comparison between alteration of US steatosis grades preoperative-3 month follow up and preoperative- 6/12 month follow up periods, but no significant result was found. This may indicate that after cholecystectomy, a certain level of fat accumulation is expected, and this may occur over a certain period of time through adaptive processes.[11] Another adaptive process may be increase in liver size in a certain period of time. In current study, there was a positive correlation between liver size and steatosis (p<0.001). HSI values before and after surgery had a positive correlation with sonographic steatosis in accordance with literature.[11]

One of the limitations of the present study is that it did not have a prospective design. The other one, grade 1 steatosis is very subjective and the majority of the cases in the study were categorized into grade 1. Prospective studies via ultrasonography with at least two radiologist would be helpful to avoid from this selection bias. Another limitation is related to the lack of a comparison of the results with the gold standard method; i.e., liver biopsy. While biopsy is the golden standart for diagnosis, it is associated with sampling biases and a risk of complications. Future studies can be conducted with similar groups using magnetic resonance imaging techniques rather than biopsy at different periods. This would reduce the multiparametric, multivariate effects to a minimum.

Conclusion

Conclusion, cholecystectomy has effects on the fat accumulation in the liver, and this is associated with the possible deterioration of the bilioenteric bile flow and this may prolong at least 12 months after the surgery and early postoperative US imaging for the purpose of hepatosteatosis follow-up is not necessary. The contribution to the literature consists of the differences found in the fatty infiltration grades before and after cholecystectomy among patients with similar demographic characteristics and laboratory values; however, the preoperative and postoperative changes in the fatty infiltration grades did not statistically significantly differ between the different periods.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Funding: The author received no financial support and funding for this study.

Authorship Contributions: Concept – U.K.; Design – U.K., H.E.; Supervision – U.K., H.E.; Materials – U.K., H.E.; Data collection &/or processing – U.K., H.E.; Analysis and/or interpretation – U.K., H.E.; Literature search – U.K.; Writing – U.K.; Critical review – U.K., H.E.

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