The Correlation Between Liver Fat Content and Ulcerative Colitis Disease Severity

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Abstract- To evaluate the association between disease severity and hepatic steatosis in patients with ulcerative colitis (UC) and non-alcoholic steatohepatitis (NASH). Consecutively selected UC patients admitted to the gastroenterology clinic were enrolled in the study. UC severity was assessed by Truelove and Witts classification. Patients with severe UC were excluded from the study. NASH was determined based on persistently elevated serum aminotransferase levels and detection of fatty liver ultrasound. Patients with other etiologies for elevated aminotransferase levels were excluded. Liver fat content (LFC) was assessed by measuring liver fat score (LFS). One hundred patients (42% male) were included in the study. According to liver ultrasound examination, 62 (%) patients were identified with grade 1 fatty liver disease, and 38 (%) patients were classified as advanced (grade 2 and 3) fatty liver disease. Sixty-one patients had left-sided UC and (46%) had mild UC disease severity index. LFS was significantly higher in UC patients with the moderate disease than patients with mild disease (3.53±2.68 vs. 5.89±2.85, respectively; $P<0.01$). Nevertheless, no significant difference was observed in LFS regarding UC extension. There was no significant difference between NASH ultrasound grades in view of UC severity and extension. LFC might be associated with UC severity.

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Keywords: Ulcerative colitis; Non-alcoholic fatty liver disease; Severity; Ultrasound; Fatty liver

Introduction

Inflammatory Bowel Disease (IBD) is an immune-mediated gastrointestinal disorder including Crohn's disease and Ulcerative colitis (UC) with annual incidence of up to 6.3 per 100000 in Asia and the Middle East (1). Non-alcoholic fatty liver disease (NAFLD) entails a spectrum of hepatic disorders from simple steatosis, steatohepatitis (NASH) and cirrhosis (2,3). It is estimated that 10-24 percent of people have NAFLD which is much more common in the obese population (4-6). NAFLD is now considered as the liver manifestation of insulin resistance syndrome (7-11). The metabolic syndrome is associated with more severe IBD and longer hospitalization periods (12).

NAFLD is the most common hepatic morbidity in UC (13,14). The impaired liver-gut axis, corticosteroid consumption, and excess lipid intake are the proposed etiologies for the development of NASH in UC (15-19). It was shown that UC patients taking anti-inflammatory medications (such as anti-TNF antibodies) are less likely to develop NASH (13,20). Hepatic involvement in UC might have an impact on the therapeutic strategies and treatment options. Nevertheless, there is still paucity of the literature on the impact of the gut-liver axis impairment in the management of UC subjects.

The study aim was to evaluate the association between gut mucosal damage severity with liver fat content (LFC) in patients with UC and concomitant NASH.

Materials and Methods

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Ethical considerations

This study was performed according to the ethical principles of the Declaration of Helsinki. After explaining the aim and method of study, written informed consent was taken from all participants. The research committee of Tehran University of Medical Sciences approved the study protocol (Registration Number: 9211160020).

Patient enrolment

Patients older than 14 years with diagnosed UC admitted to a general hospital gastroenterology clinic and two private gastroenterology clinics during October 2013 to March 2016 were consecutively enrolled in the study. A board certified gastroenterologist confirmed UC diagnosis by implementing physical examination, endoscopic and laboratory evaluations (21) (Step 1).

Patients with the following characteristics were excluded from the study: 1) recent hospitalization due to UC flare-up during the past three months, 2) severe UC (more than six bowel movements per day plus any of the following features: fever more than 37.8 degrees centigrade, erythrocyte sedimentation rate more than 30, hemoglobin less than 10 grams per deciliter, and heart rate more than 90 beat per minute), and 3) taking corticosteroid medications (Step 2).

Next, patients were assessed for the presence of NASH. Therefore, serum aminotransferase levels were evaluated as previously reported (3,6) and only patients with persistently elevated aminotransferase levels of more than 40 U/L were considered for the study (22). Further, patients with viral hepatitis, autoimmune hepatitis, Wilson disease, hemochromatosis or any other known liver diseases, and history of alcohol consumption or hepatotoxic medication were excluded (Step 3).

One radiologist who was unaware of the clinical data performed the liver ultrasound (Hitachi EUB 405 apparatus equipped with a convex 3.5 MHz probe). The diagnosis of the fatty liver by ultrasound examination was based on the criteria mentioned in the previous studies (23,24). At this step, the patients with persistent elevated aminotransferase level and existence of fatty liver at ultrasound were presumed to have NASH. Considering the drawbacks of liver biopsy for determination of NASH, we applied the following formula for appropriate selection of NASH subjects (25).

"Liver fat score (LFS)=(-2.89)+1.18 * metabolic syndrome (yes=1 / no = 0) + 0.45 * type 2 diabetes (yes =2/no=0)+0.15 * fasting serum insulin (mU/L)+0.04 * fasting serum AST (U/L)–0.94 * (AST/ALT)".

According to the result of the previous study, the score values greater than -0.64 showed a sensitivity of 86% and specificity of 71% for the prediction of NASH (25). Therefore, we included participants with score values of more than -0.64 in the study (Step 4).

Finally, magnetic resonance cholangiopancreatography (MRCP) was performed for the evaluation of biliary tract diseases including primary sclerosing cholangitis (PSC). At this step, all the participants with the mentioned diseases were excluded from the study (Step 5).

MRCP protocol

MRCP (thin slice) was performed with three plane localizer using balanced SSFP protocol. (MRI, 1.5 Tesla, Siemens, Germany)

UC severity measurement

UC severity was measured using Truelove and Witts severity index (26). The index assigns two points for the number of bowel habits per day and amounts of the blood in the stool, four points for pyrexia, pulse rate, anemia and erythrocyte sedimentation rate. Any patient passing more than five bloody stools with any of the four systemic features was classified as severe UC and excluded from the study. Mild disease severity is defined as less than four bowel movements per day without the presence of systemic features. Patients with the score between four and six were classified as moderate severity.

UC extension

The subjects with mucosal involvement up to splenic flexure at colonoscopy were labeled as left-sided colitis group. Patients with mucosal involvement beyond the splenic flexure were categorized as extensive colitis group.

LFC measurement

Considering the drawbacks of the liver biopsy to evaluate LFC, a reliable formula was applied in this study. The formula quantifies LFC in percentages by taking into account the presence of metabolic syndrome, type 2 diabetes, fasting serum insulin level, fasting serum AST level and AST/ALT ratio (25).

"Liver fat content (%)=10(-0.805+0.282 * metabolic syndrome (yes=1/no=0)+0.078 * type 2 diabetes (yes=2/no=0)+0.525 * log fasting serum insulin (mU/L)+

0.521 * log fasting serum AST (U/L)–0.454 * log

(AST/ALT)".

Liver steatosis grading based on liver ultrasound

In grade one liver steatosis based on the ultrasound, the liver echogenicity is slightly increased compared to the adjacent kidney with normal appearing diaphragm and intrahepatic vessels. In grade two, the liver echogenicity is apparently increased with impaired visualization of the diaphragm or intrahepatic vessel borders. In grade three, liver echogenicity is dramatically increased with very poor visualization of the diaphragm and intrahepatic vessels (6).

Laboratory investigations

Fasting blood samples (5cc) were taken. Serum was separated and stored in -80• C until further evaluation. Fasting blood glucose, insulin, lipid profiles and liver function tests were measured as previously described (3,6). All laboratory measurements were performed twice in the standard environment according to the manufacturers' instructions. The calculated coefficient of variation was less than five percent in the current experimentations.

Sample size calculation

Using statistical power analysis and taking the mean prevalence of NASH in UC (28%) according to the previous studies (27,28), assumption of α=0.05 and d=0.12, the sample size was calculated as 94 patients.

Statistical analysis

Distribution of the data was assessed by Kolmogorov-Smirnov test. Continuous variables were reported as mean±standard deviation. Comparison of mean age, clinical data, liver function tests, metabolic profile, UC duration, UC severity indices, and LFC between mild and moderate UC groups was performed by independent t-test. The correlation between UC severity and extension with LFC was defined by "General Linear Model" using univariate analysis. To adjust for the effect of potentially confounding factors regarding LFC, we considered the BMI, FBS, insulin, and lipid profile as covariates.

Receiver operating characteristic (ROC) analysis was performed to determine the cut-off values of LFS for discriminating UC disease activity groups. The best cut-off value was measured in order that the sum of sensitivity and specificity was the highest. The area under the curve (AUC) with 95% confidence interval was reported.

The comparison of ultrasound grade of NASH with UC extension and disease severity group was performed by chi-square test. For the latter analyses, we combined the patients with grade 2 or 3 of fatty liver as a single group and labeled them as "advanced group." The rationale for this merging is explained in discussion part. The patients with grade one fatty liver were labeled as "mild group." A two-sided *P* of 0.05 or less was considered statistically significant in all analyses. Statistical calculations were performed by a medical statistician using SPSS software version 21 (IBM Corporation, Somers, NY, USA).

Results

A total of one hundred UC patients with concomitant NASH were enrolled. The median age of patients was 40 years (range 18-77) and 42% were male. Table 1 shows patients' characteristics and laboratory data. The distribution of LFS was normal (Z score=1.3; $P>0.05$). LFS was significantly higher in UC patients with moderate disease severity than patients with mild disease severity (mean difference: -2.3, 95%CI: -3.5 to -1.2; $P<0.01$). However, there was no significant difference in LFS regarding UC extension (Table 2). There was no significant difference between NASH ultrasound grades in view of UC severity and extension (Table 2). The ROC curve with calculated AUC (±95% CI) for determining the cut-off values of LFS for differentiating UC mild disease activity from moderate disease activity is demonstrated in Figure 1. LFS value of 3.33% demonstrated a sensitivity of 83% and specificity of 70% for discriminating mild group from the moderate group.

Table 1. The clinic-demographic and laboratory (mean±standard deviation) data of studied population

Characteristics	Ulcerative colitis severity		Total
	Mild	Moderate	
Age (year)	41.50 ± 11.22	40.88 ± 9.65	41.2 ± 10.3
Height (cm)	165.57 ± 8.57	170.63 ± 8.74	168.30 ± 8.99
Weight (kg)	78.82 ± 11.07	84.05 ± 11.23	81.65 ± 11.41
Body mass index (kg/m^2)	28.80 ± 3.88	28.97 ± 4.05	28.9 ± 4
Aspartate aminotransferase (U/L)	68.60 ± 15.47	70.27 ± 11.04	69.5 ± 13.2
Alanine aminotransferase (U/L)	65.06 ± 23.37	71.82 ± 20.20*	68.7 ± 11.8
Alkaline phosphatase (U/L)	170.50 ± 44.91	181.69 ± 55.42*	176.54 ± 50.91
Fasting blood sugar (mg/dl)	85.65 ± 7.89	101.35 ± 11.47*	94.13 ± 12.67
Triglyceride (mg/dl)	184.95 ± 72.12	164.67 ± 60.01*	173.95 ± 66.29
Cholesterol (mg/dl)	185.57 ± 8.54	193.13 ± 12.40*	189.65 ± 11.4
Low density lipoprotein (mg/dl)	102.87 ± 22.12	118.07 ± 22.00*	111.08 ± 23.24
High density lipoprotein (mg/dl)	42.41 ± 10.85	42.96 ± 8.37	42.71 ± 9.55
Insulin (mU/L)	5.28 ± 1.36	12.64 ± 3.63*	9.26 ± 4.63
Disease duration (week)	83.52 ± 78.31	51.88 ± 38.75*	66.44 ± 61.99
Temperature (degree centigrade)	36.22 ± 5.46	36.82 ± 0.51	36.54 ± 3.71
Pulse rate (beat per minute)	74.50 ± 13.59	74.81 ± 6.18	74.67 ± 10.22
Hemoglobin (g/dl)	12.31 ±1.97	11.74 ±1.10*	12.00 ±1.58
Erythrocyte sedimentation rate	5.28 ± 2.54	14.33 ± 9.32*	10.17 ± 8.37
Liver fat score	3.53 ± 2.68	5.89 ± 2.85*	4.8 ± 3

Abbreviations: Kg, Kilogram; cm, centimeter; M, meter; U, Unit; L, Liter; mg, milligram; dl, deciliter; g, gram.

Table 2. The correlation between ulcerative colitis severity and extension with liver fat content based on liver fat score and liver ultrasound grades

	Ulcerative colitis severity			Ulcerative colitis extension		
	Mild (n=46)	Moderate (n=54)	*P*	Left-sided (n=61)	Extensive (n=39)	*P*
Liver fat score	3.53 ± 2.68	5.89 ± 2.85	<0.01	4.5 ± 3.2	5.0 ± 2.9	0.3
Ultrasound mild group	30	32	0.5	37	25	0.7
Ultrasound advanced group	16	22	--	24	14	--

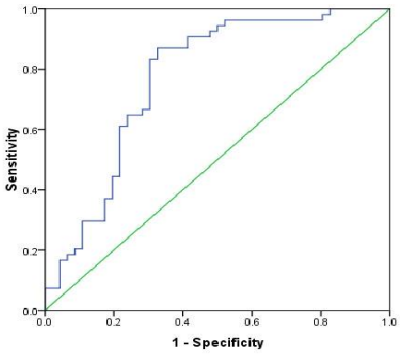

Figure 1. Receiver operating characteristic (ROC) analysis for defining the best cut-off value of liver fat score for differentiating ulcerative colitis mild disease activity from moderate disease activity. [Area under curve (AUC): 0.77 (95% confidence interval: 0.67-0.87)]

Discussion

Although many studies declared NASH as the common hepatic manifestation of UC, there is paucity of literature regarding the association of LFC and UC severity. The current research revealed this association in a sample of UC patients with mild to moderate disease severity. According to the results of this study, UC patients with more severe disease had a higher LFS. This finding is in line with some former studies that showed the high prevalence of NASH in severe and active UC (28-32). However, recent researches did not

find such a difference (20,29,33). The heterogeneity of the studied groups with regard to UC severity, extension, and medications used for the management could explain the differences in the mentioned studies results.

Truelove and Witts severity index that includes clinical and laboratory parameters have been often applied as a reliable tool for the determination of disease severity in UC. According to the correlation of LFS and disease severity in this study and its computation accuracy, we introduced LFS as an alternative for Truelove and Witts severity index. Besides, we calculated the best threshold value of LFS for determination of mild from moderate UC severity group.

One of the strengths of this study was evaluating a homogenous group of UC subjects with NASH. We adjusted for the metabolic factors associated with NASH when evaluating the correlation of LFC between UC activity groups. To reduce the bias in NASH selection, MRCP was performed in all of the included subjects to exclude PSC and other biliary tract disease causing elevated aminotransferase levels. One of the possible mechanisms for the development of fatty liver in UC is the consumption of steroids. They are necessary for the induction of remission in severe active UC. To omit the effect of steroids in the induction of fatty liver, we excluded patients with severe active disease (who required steroid) or those who needed to take steroids for their treatment in this study. Considering the limitations of liver biopsy, LFS was used for detection of NASH in this project. This score had a high sensitivity and specificity for NASH diagnosis (25). For accurate estimation of LFC, a valid formula was applied in this study. Previous research showed an appropriate correlation between LFC identified by proton magnetic resonance spectroscopy (PMRS) and LFC calculated by the mentioned formula ($r=0.7$, $P<0.001$) (25).

The mean serum concentrations of fasting blood glucose and insulin levels in this study were significantly lower than their values in the studies that evaluated pure NASH patients (3,23). This remarkable finding could indicate that the role of insulin resistance in the development of NASH in UC is not as strong as its role in pure NASH patients. Liver steatosis could be a result of malnutrition and hypoproteinemia in severe UC patients (13). The gut mucosal barrier is severely damaged by disease progression. Consequently, the increased permeability of gut mucosa facilitates the flow of hepatotoxic substances including bacterial endotoxins via the portal vein to the liver (17). The over ride of these antigens would trigger the inflammatory response in liver parenchyma. This theory could explain the possible mechanism that is responsible for the development of NASH in UC patients.

The extension of bowel involvement in UC patients was not related to the degree of LFC in this study. This finding is in line with the previous research that did not find IBD extension as a risk factor for fatty liver disease (28). It is noteworthy that disease extension is not a measure of severity for IBD. The dissimilar association of LFS with UC severity and extension in this study acknowledge the potential role for the load of inflammatory cytokines rather just the length of the involved gut in the development of fatty liver.

We merged the patients with grade 2 or 3 of fatty liver detected by ultrasound as a single group labeled as "advanced grade." Then we compared this group with subjects with grade 1 disease. The rationale for this integration was that distinguishing grade 2 and 3 fatty liver by ultrasound was challenging (27,34). The present study did not show any correlation between fatty liver grade in ultrasound and UC severity or extension which is similar to previous research (28) but in contrast to another one (35). This shows that ultrasound may not be a good instrument for distinguishing fatty liver severity due to inter-observer and intra-observer variability bias (27,34).

According to the results of this study, evaluating the correlation of disease severity in UC patients with liver histology findings (including liver inflammation and fibrosis) in concomitant biopsy-proven NASH patients is recommended. Meanwhile, clarifying the association of disease severity in UC patients with concomitant NASH would help the clinician to choose the appropriate medication. It seems to be a reasonable approach to limit the application of hepatotoxic medications (including steroids) in severe UC patients with concomitant NASH.

One limitation of the current study is the cross-sectional design. Therefore, no causal relationship can be drawn. Another limitation of the study was not performing liver biopsy for defining NASH. This modality is now considered as the gold standard method for the diagnosis and evaluation of LFC in NASH. Finally, we only evaluated LFC as a marker of NASH severity in this research. The extent of hepatic inflammation and fibrosis that has a great impact in the course of NASH was not determined in this study.

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