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Original Article

High incidence of non-alcoholic fatty liver disease in patients with Crohn's disease but not ulcerative colitis

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Abstract: Background: hepatic steatosis including nonalcoholic fatty liver disease (NAFLD) has several same pathogenesis with inflammatory bowel disease (IBD) and the parenteral complication about NAFLD was reported rare. The aim of this study was to study the NAFLD incidence of IBD patients and influence factors. Methods: we reviewed 137 patients with Crohn's disease (CD) and 69 patients with ulcerative colitis (UC). And 412 healthy controls with 2:1 ratio by gender, age, body mass index (BMI) were matched randomly to compare of nonalcoholic fatty liver disease (NAFLD) detective rate and analyzing other risk factors. Results: the detective rate of NAFLD in CD was higher (10.95% vs. 4.01%, *P*=0.006), while there was no difference in UC (10.14% vs. 9.42%, *P*=0.868). CD patients with female, BMI normal or underweight had higher NAFLD incidence, while no difference was found in UC. With the increase of CRP, NAFLD detective rate of CD patients had a rising trend. In addition, BMI (*P*=0.034), gender (*P*=0.047), triglyceride (*P*=0.026), LDL (*P*=0.01) were high risk factors of NAFLD in CD. And GGT (*P*=0.05), triglyceride (*P*=0.032), VLDL (*P*=0.043) were high risk factors in UC. Conclusions: the incidence of NAFLD was high in CD but not in UC. By multi-factor variable analysis, we found that pathogenesis of NAFLD was closely related to BMI and CRP. This phenomenon may explain that malnutrition, intestinal endotoxemia are likely to be the leading cause of NAFLD in CD.

Keywords: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, nonalcoholic fatty liver disease, detective rate

Introduction

Inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC), refers to a group of chronic gastrointestinal disorders characterized by dysregulated intestinal inflammation [1]. IBD is a common disease in North America and Europe. Recent decades, there is an upward trend of morbidity in eastern Europe, Asia, including China and other developing countries and regions [2-4]. IBD can cause a series of gastrointestinal symptoms including abdominal pain, diarrhea, hematochezia and so on. At the same time, parenteral complication of IBD can influence the whole system of body and the incidence can reach 21%-47% [5, 6].

As potential parenteral complication, hepatic steatosis including non-alcoholic fatty liver disease (NAFLD) was rarely reported. Incidence of NAFLD is as much as 30% in developed countries while it shows a fast increasing tendency in China [7]. The pathogenesis of NAFLD is unclear. Two-hit hypothesis is the most common pathogenesis [8]. Insulin resistance, mitochondria oxidative stress, endoplasmic reticulum stress and immune response are all important factors for the development of NAFLD. Kupffer cells (KCs), Natural killer T cells (NKTs), Natural killer cells (NKs), IL-17A also plays an important role in the development of NAFLD [9, 10].

In the development of IBD, immunoregulation is also a key factor. Pro-inflammatory cytokine released by Th1 cell-mediated immune response is an important mechanism in IBD especially in Crohn's disease (CD) [11]. It seems that development of IBD has some common mechanisms with NAFLD. However, malnutrition is common in IBD, while pathogenic factors such

Table 1. The basic characteristics of IBD patients and healthy controls

Group	N	Gender (male/female)	Age	BMI (kg/m^2)	Detective rate of NAFLD
CD	137	90/47	36.2±12.62	19.26±2.99	10.95% (15/137)
CD control	274	180/94	36.2±12.6	19.69±2.79	4.01% (11/274)
UC	69	43/26	48.94±15.26	20.42±3.54	10.14% (7/69)
UC control	138	86/52	48.94±15.21	20.78±3.2	9.42% (13/138)

as metabolic syndrome, obesity and other risk factors of NAFLD are extremely rare in IBD. In severe IBD patients, lose weight can reach 65-76% in CD and 18-62% in UC [12]. In active IBD patients, malnutrition ratio can reach 25.0-69.7% and severe malnutrition ratio can reach 1.3-31.6% [13].

Our retrospective study aimed to explore the incidence of hepatic steatosis in IBD patients compared to healthy controls group in order to provide more evidence about IBD and hepatic steatosis.

Materials and methods

Patients and diagnostic criteria

Medical records of patients undergoing evaluation and treatment for CD and UC at our tertiary care center between Jan. 1, 2012 and May. 1, 2016 were reviewed. This study was approved by our Institutional Review Board. We included 137 CD patients and 69 UC patients. The diagnoses of UC and CD were made based on a combined assessment of endoscopy, symptomatology, abdominal imaging, and histology. The pattern and distribution of UC and CD were obtained from endoscopic, radiological and histological findings [14]. At the same time, we selected 274 healthy cases and 138 healthy cases which were 2:1 radio matched by gender, age, Body Mass Index (BMI) from international medical center. Due to some results of BMI in IBD were so low, we selected the lowest BMI in the group of the same age and sex and then random matched with each other.

In our study, informed consent was signed from all subjects and their privacy was respected. Experimental protocol was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University and the Reference Number was 2016-458. In addition, all methods were performed in accordance with the relevant guidelines and regulations.

We excluded patients with: 1) age ≤18 years old; 2) history of alcohol intake and smoking-alcohol abuse; 3) alcoholic hepatitis, drug hepatitis, viral hepatitis, autoimmune liver disease, cirrhosis, liver cancer; 4) tuberculosis, cancer, cardiovascular and cerebrovascular diseases or other chronic diseases.

Data extraction

We extracted data of hepatic imaging, age, gender, BMI, albumin, globulin, gamma-glutamyltransferase (GGT), triglyceride (TG), cholesterol, high-density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), acidum uricum, c-reactive protein (CRP), cholinesterase, alkaline phosphatase (AKP). CRP was chosen to reflect the activity of disease [15]. All data were obtained when first diagnosed.

Statistical analysis

Univariate analysis was performed using Student's t test for the continuous variables. Student's t test was used to compare measurement data between IBD with NAFLD patients and IBD patients. And chi-square test was used to compare categorical variables such as detective rate of NAFLD. Then we conducted subgroup analysis according to gender, age, BMI respectively to compare the difference of NAFLD detective rate. Multivariate analysis was performed using logistic regression and coefficients of variables for multivariate model were estimated. The statistical significance was defined as $P \leq 0.05$. We used SPSS 21.0 (IBM, Chicago, IL, USA) to perform the statistical analysis. Another associated data was calculated and plotted using GraphPad Prism 5 (Graph Pad, San Diego, CA, USA).

Results

The difference of NAFLD detective rate between IBD patients and healthy controls

The basic characteristics of age, gender, BMI were listed in **Table 1**. The detective rate of

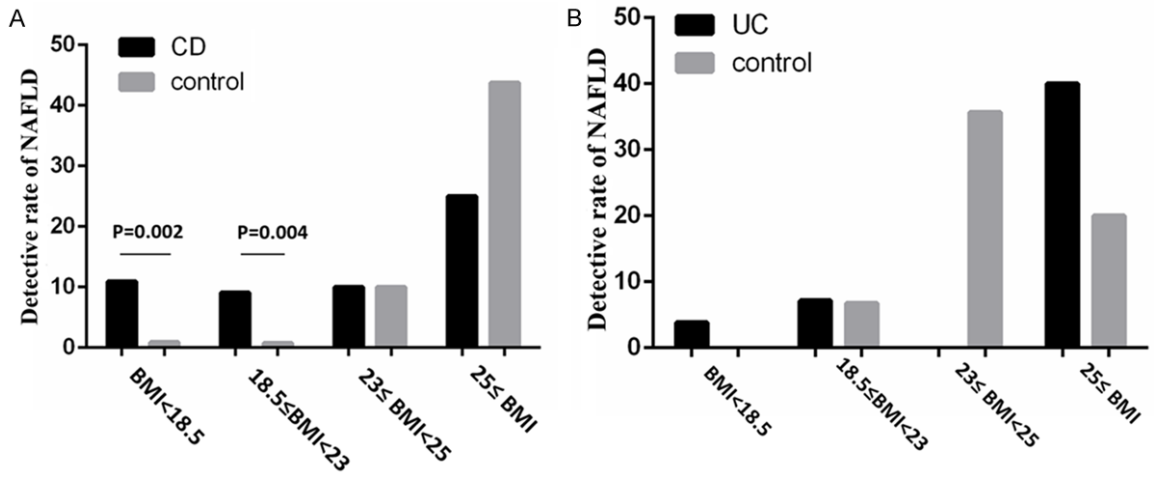

Figure 1. A: Comparison of detective rate of NAFLD under different BMI between CD patients and healthy controls; B: Comparison of detective rate of NAFLD under different BMI between UC patients and healthy controls.

NAFLD in CD patients was 10.95% (15/137), and 4.01% (11/274) in healthy controls. There were statistically significant differences between them (P=0.006). In addition, the detective rate of NAFLD in UC patients was 10.14% (7/69), while 9.42% (13/138) in healthy controls. There were no statistical differences (P=0.868).

Then, we conducted a subgroup analysis according to gender. In CD patients, the detective rate of NAFLD was 6.67% (6/90) in male and 19.15% (9/47) in female. While in healthy controls it was 6.11% (11/180) in male and 0 (0/94) in female. There was statistical difference between females (P<0.001), while there was no statistical difference between males (P=0.859). In UC patients, there was no statistical difference between males or females (P=0.854, 13.95% vs. 12.75%; P=0.21, 3.85% vs. 3.85%).

In addition, according to quartile of age, we conducted a subgroup analysis. We found detective rate of NAFLD was higher in every group in CD patients, but only group 44-79 years old had statistical difference (13.16% vs. 2.63%, P=0.027). In UC patients, there were no statistical differences between groups. Moreover, we found that in the peak age of CD, the detective rate of NAFLD in CD patients was higher than healthy controls.

According to BMI, we defined underweight group (BMI<18.5 kg/m^2), normal group (18.5≤BMI<23 kg/m^2), overweight group (23≤BMI<25 kg/m^2), obesity group (25≤BMI kg/m^2). In underweight and normal group, detective rate of NAFLD was Significantly higher than controls (P=0.002, P=0.004) (**Figure 1A**). In obesity group, healthy controls had a higher rate of NAFLD. In UC patients, we found no statistical differences between groups (**Figure 1B**).

In Jørgensen's article, they defined CRP<8 mg/L was in remission, 8≤CRP<16 mg/L was in activity, CRP≥16 mg/L was in severe activity [16]. We found that with the increase of CRP, detection rate of NAFLD in CD group had a rising trend (5.56%, 11.11%, 13.16%), but there were no statistical differences (P=0.479) (**Figure 2A**). This result suggested that development of NAFLD in CD patients is closely related to the degree of inflammatory activity. Moreover, in patients with severe activity, the detective rate of NAFLD was higher in underweight and normal group (14.28%, 13.33%). In patients with remission, the detective rate of NAFLD was higher in obesity group (33.33%) (**Figure 2B**). These results showed that in the different periods of CD, the cause of NAFLD development may be different. In remission, malnutrition or intestinal endotoxin disorders may be the main pathogenesis; in activity, inflammation and immune active controls are the dominant factors.

In addition, we found that there were no statistical differences between colon CD and intestinal CD (12.5 vs. 10.48%, P>0.05).

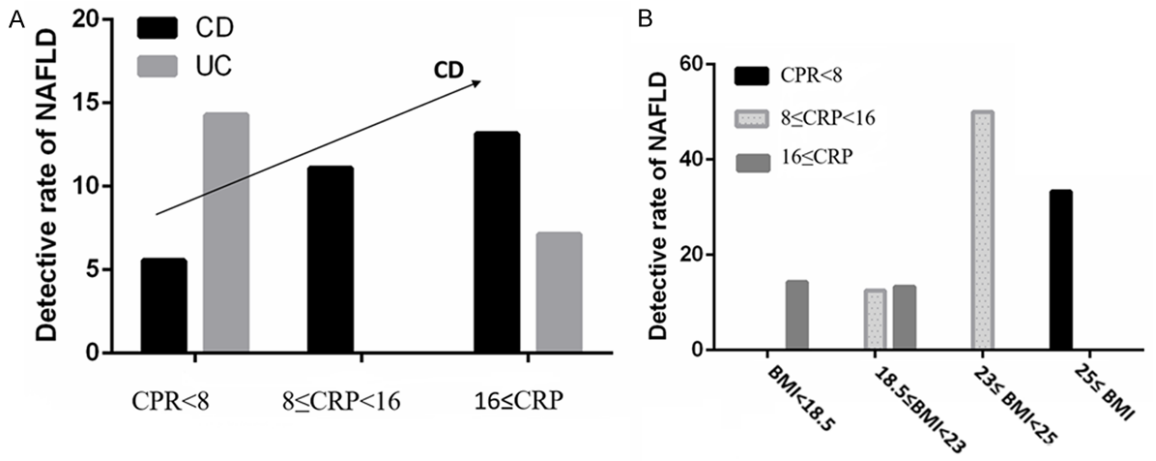

Figure 2. A: Comparison of detective rate of NAFLD under different CRP between CD patients and UC patients; B: Variation of detective rate of NAFLD under different BMI with the variation of CRP.

Table 2. Risk factors of NAFLD in CD patients

Variable	β	S.E.	Wald χ^2	*P*	OR
Gender	1.31	0.658	3.961	0.047	3.706
BMI	0.24	0.113	4.5	0.034	1.272
TG	1.435	0.644	4.965	0.026	4.201
LDL	-1.626	0.63	6.662	0.01	0.197

Table 3. Risk factors of NAFLD in UC patients

Variable	β	S.E.	Wald χ^2	*P*	OR
GGT	-0.015	0.008	3.857	0.05	0.985
TG	-10.757	5.022	4.587	0.032	<0.001
VLDL	17.672	8.731	4.097	0.043	>10

Differences between NAFLD in IBD patients and in healthy controls

Some indexes including BMI (*P*=0.003), gender (*P*=0.001), albumin (*P*<0.001), GGT (*P*=0.039), Uric Acid (*P*<0.001), TG (*P*=0.026), cholesterol (*P*<0.001), LDL (*P*<0.001), VLDL (*P*<0.001) all had significantly statistical differences between NAFLD in CD patients and NAFLD in healthy controls. While NAFLD in UC patients, only albumin (*P*=0.001) had statistical difference. These results suggested that development of NAFLD had more influence factors in CD.

Multivariate influences factors of NAFLD in IBD patients

By stepwise logistic regression, we found BMI (*P*=0.034, OR=3.70), gender (*P*=0.047, OR=1.272), TG (*P*=0.026, OR=4.20), LDL (*P*=0.01, OR=0.197) had significantly statistical differences between CD patients and NAFLD with CD patients (**Table 2**). While GGT (*P*=0.05, OR=0.985), TG (*P*=0.032, OR<0.001), VLDL (*P*=0.043, OR>10) had significantly statistical differences between UC patients and NAFLD with UC patients (**Table 3**).

Discussion

Previous IBD parenteral complication mainly focused on the joints, skin, mouth, eye which may be more easily to be involved. Parenteral complications were often associated with disease activity, while complication about liver was rarely reported. In 1873, Thomas *et al* reported the relationship between colonic ulcers and fatty liver for the first time. Bargiggia *et al* found that detective rate of NAFLD was 39.5% in CD and 35.5% in UC, which was higher than healthy controls (*P*<0.001) [17]. In our paper, we found that incidence of NAFLD in CD is higher than controls, while no statistical difference was found in UC. In CD group, female, 44-79 age group, underweight group and normal group had a higher rate than healthy controls, while no statistical difference was found in UC. In addition, NAFLD combined CD patients had lower BMI, albumin, globulin, GGT, TG, cholesterol, HDL, LDL than NAFLD patients. NAFLD combined UC patients only had lower albumin. By multivariable analyses, development of NAFLD in CD was related to BMI, TG, LDL, gender, while development of NAFLD in UC was related to GGT, TG, VLDL. Due to the lack of

large sample epidemiological evidence, our data can't be compared. The development of NAFLD caused by IBD is still unclear.

Malnutrition is likely to be a potential factor. Weight loss is one of important clinical characteristics of CD. Serious malnutrition was likely to be key role in the development of NAFLD in underweight BMI group and normal BMI group in CD. Mikolasevic *et al* reported that elderly hemodialysis patients occurred NAFLD is due to its malnutrition, low protein [18]. Sanada *et al* also reported a case about nonalcoholic fatty hepatitis caused by malnutrition after liver transplantation [19]. The potential mechanism is likely that decreased insulin sensitivity of peripheral tissue led to insulin resistance and peripheral fat decomposition. Hepatocyte lipid metabolic abnormalities and elevated inflammatory mediators such CRP, TNF led to activation of Kupffer cells (KCs), hepatic stellate cell (HSC). Finally, oxidative stress and aggravation of lipid metabolic abnormalities resulted in the development of NAFLD [20, 21].

In addition, the pathogenesis of IBD is closely related to immunoreaction. The activity of immunoreaction can be partly reflected by CRP. We found detective rate of NAFLD has a tendency to rise with increasing of CRP in CD patients. Th1/Th2 cell-mediated immune response plays an important role in the development of IBD, while it is also a key factor in development of NAFLD. Relative excess or deficiency of Th1 cytokines can affect the process of fatty liver [22]. Th1/Th2 cells mediated NKT cells and then release perforin and granzyme which can injure hepatic cells directly [23]. Th1 cytokines can also mediate TNF-α and IL-6, and their immune disorders is important factors to development of IBD [24]. In NAFLD, TNF-α can active KCs, which can release TNF-α, IL-12, IL-6 and reactive oxygen species (ROS) resulting in insulin resistance and lipid peroxidation [10]. Some papers had reported that TNF-α inhibitor- oxpentifylline can improve the prognosis of NAFLD [25-27]. In addition, infliximab has prominently curative effect in IBD, and it also has good curative effect in NAFLD [28]. So to speak, IBD patients have some abnormal immune adjustment, which also acts on liver immune cells lead to high detective rate of NAFLD in IBD patients.

Intestinal endotoxemia is also a potential mechanism. IBD patients often have intestinal microecological disorders. Gut bacteria and their products can promote swollen intestinal mucous and increased membrane permeability. Bacterial endotoxin (lipopolysaccharide) combine with lipopolysaccharide binding protein (LBP) into circulation. The complex transports to KCs surface membrane receptor CD14 and then combine to toll-like receptor 4 (TLR4). Next, activated KCs active transcription, expression, release of TNF-α, IL-6, ROS, TGF-β1 resulting in insulin resistance, lipid peroxidation and activation of HSC. Finally, it promotes the development of NAFLD even hepatic fibrosis [29].

Our study found that the incidence of NAFLD was higher in female CD patients while men was relatively little. Whether estrogen receptor in female is affected by the IBD related factors which play a role in NAFLD development. In IBD animal model, RNA expression level of estrogen receptor β (ERβ) had low expression along with increased intestinal permeability [30]. In IBD patients, low estrogen level is closely related to the severity of the disease [31, 32]. It may be related to the retroegulation between IL-6 and estrogen. We know the incidence of NAFLD of female is lower than male [33]. We thought that ERβ up-regulated the miR-125b, then down-regulated PPAR-γ, DGAT1/2, CD36, FAS. Finally, it prevented hepatocyte fatty-changed [34]. Therefore, elevated IL-6 in IBD patients may down- regulate ERβ and then influence the liver leading to the activation of pathway promoting the occurrence and development of NAFLD.

Our research still had many deficiencies. Firstly, ultrasound is widely used in physical examination instead of abdominal CT, MRI, liver biopsy. It was used as diagnostic criteria for the diagnose of NAFLD, which may exist missed diagnosis of NAFLD [35]. Ultrasonic diagnosis is overly dependent on instrument and doctor. Multiple examine may reduce the bias, while a practical perspective cannot reach such examine. Second, the difference of life-style, dietary, region of included people may affect the results of NAFLD detection. Our study is a single center study with small sample size, and multi-center large sample research is needed to support our results.

In conclusion, through our retrospective analysis, we found that the detective rate of NAFLD was significantly higher in CD patients than that of normal people, while there was no significant difference between UC patients and health controls. Furthermore, gender, age, BMI influence the development of NAFLD. In addition, with elevated of CRP, the detective rate of NAFLD had a rising trend in CD patients. By multi-factor variable analysis, we found that in CD patients, the detective rate of NAFLD is closely related to BMI, which indicated that malnutrition, intestinal endotoxemia could be the main cause of the development of NAFLD. In the later study, we need for basic research and more large sample prospective studies to provide more evidence of the relationship of IBD and liver fat.

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Informed consent was obtained from all patients for being included in the study.

Disclosure of conflict of interest

None.

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References

[1] Abraham C and Cho JH. Inflammatory bowel disease. N Engl J Med 2009; 361: 2066-2078.

[2] Bouma G and Strober W. The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol 2003; 3: 521-533.

[3] Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhart AH, Abraham C, Regueiro M, Griffiths A, Dassopoulos T, Bitton A, Yang H, Targan S, Datta LW, Kistner EO, Schumm LP, Lee AT, Gregersen PK, Barmada MM, Rotter JI, Nicolae DL and Cho JH. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 2006; 314: 1461-1463.

[4] Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology 2004; 126: 1504-1517.

[5] Bernstein CN, Blanchard JF, Rawsthorne P and Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol 2001; 96: 1116-1122.

[6] Bernstein CN, Wajda A and Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. Gastroenterology 2005; 129: 827-836.

[7] Li Z, Xue J, Chen P, Chen L, Yan S and Liu L. Prevalence of nonalcoholic fatty liver disease in mainland of China: a meta-analysis of published studies. J Gastroenterol Hepatol 2014; 29: 42-51.

[8] Cohen JC, Horton JD and Hobbs HH. Human fatty liver disease: old questions and new insights. Science 2011; 332: 1519-1523.

[9] Giles DA, Moreno-Fernandez ME, Stankiewicz TE, Cappelletti M, Huppert SS, Iwakura Y, Dong C, Shanmukhappa SK and Divanovic S. Regulation of inflammation by IL-17A and IL-17F modulates non-alcoholic fatty liver disease pathogenesis. PLoS One 2016; 11: e0149783.

[10] Zhan YT and An W. Roles of liver innate immune cells in nonalcoholic fatty liver disease. World J Gastroenterol 2010; 16: 4652-4660.

[11] MacDonald TT and Murch SH. Aetiology and pathogenesis of chronic inflammatory bowel disease. Baillieres Clin Gastroenterol 1994; 8: 1-34.

[12] Grivceva Stardelova K, Misevska P, Zdravkovska M, Trajkov D and Serafimoski V. Total parenteral nutrition in treatment of patients with inflammatory bowel disease. Prilozi 2008; 29: 21-43.

[13] Mijac DD, Jankovic GL, Jorga J and Krstic MN. Nutritional status in patients with active inflammatory bowel disease: prevalence of malnutrition and methods for routine nutritional assessment. Eur J Intern Med 2010; 21: 315-319.

[14] Bernstein CN, Fried M, Krabshuis JH, Cohen H, Eliakim R, Fedail S, Gearry R, Goh KL, Hamid S, Khan AG, LeMair AW, Malfertheiner, Ouyang Q, Rey JF, Sood A, Steinwurz F, Thomsen OO, Thomson A and Watermeyer G. World gastroenterology organization practice guidelines for the diagnosis and management of IBD in 2010. Inflamm Bowel Dis 2010; 16: 112-124.

[15] Iborra M, Beltran B and Nos P. Noninvasive testing for mucosal inflammation in inflammatory bowel disease. Gastrointest Endosc Clin N Am 2016; 26: 641-656.

[16] Jorgensen SP, Hvas CL, Agnholt J, Christensen LA, Heickendorff L and Dahlerup JF. Active Crohn's disease is associated with low vitamin D levels. J Crohns Colitis 2013; 7: e407-413.

[17] Bargiggia S, Maconi G, Elli M, Molteni P, Ardizzone S, Parente F, Todaro I, Greco S, Manzionna G and Bianchi Porro G. Sonographic prevalence of liver steatosis and biliary tract stones

in patients with inflammatory bowel disease: study of 511 subjects at a single center. J Clin Gastroenterol 2003; 36: 417-420.
[18] Mikolasevic I, Lukenda V, Racki S, Milic S, Sladoje-Martinovic B and Orlic L. Nonalcoholic fatty liver disease (NAFLD) - a new factor that interplays between inflammation, malnutrition, and atherosclerosis in elderly hemodialysis patients. Clin Interv Aging 2014; 9: 1295-1303.
[19] Sanada Y, Urahashi T, Wakiya T, Okada N, Hishikawa S, Kawano Y, Ushijima K, Otomo S, Sakamoto K and Mizuta K. Non-alcoholic steatohepatitis caused by malnutrition after pediatric liver transplantation. Pediatr Int 2011; 53: 1077-1081.
[20] Day CP and James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology 1998; 114: 842-845.
[21] Fan JG, Li F, Cai XB, Peng YD, Ao QH and Gao Y. Effects of nonalcoholic fatty liver disease on the development of metabolic disorders. J Gastroenterol Hepatol 2007; 22: 1086-1091.
[22] Maher JJ, Leon P and Ryan JC. Beyond insulin resistance: innate immunity in nonalcoholic steatohepatitis. Hepatology 2008; 48: 670-678.
[23] Swain MG. Hepatic NKT cells: friend or foe? Clin Sci (Lond) 2008; 114: 457-466.
[24] Plevy SE, Landers CJ, Prehn J, Carramanzana NM, Deem RL, Shealy D and Targan SR. A role for TNF-alpha and mucosal T helper-1 cytokines in the pathogenesis of Crohn's disease. J Immunol 1997; 159: 6276-6282.
[25] Adams LA, Zein CO, Angulo P and Lindor KD. A pilot trial of pentoxifylline in nonalcoholic steatohepatitis. Am J Gastroenterol 2004; 99: 2365-2368.
[26] Li W, Zheng L, Sheng C, Cheng X, Qing L and Qu S. Systematic review on the treatment of pentoxifylline in patients with non-alcoholic fatty liver disease. Lipids Health Dis 2011; 10: 49.
[27] Satapathy SK, Garg S, Chauhan R, Sakhuja P, Malhotra V, Sharma BC and Sarin SK. Beneficial effects of tumor necrosis factor-alpha inhibition by pentoxifylline on clinical, biochemical, and metabolic parameters of patients with nonalcoholic steatohepatitis. Am J Gastroenterol 2004; 99: 1946-1952.
[28] Coffin CS, Fraser HF, Panaccione R and Ghosh S. Liver diseases associated with anti-tumor necrosis factor-alpha (TNF-alpha) use for inflammatory bowel disease. Inflamm Bowel Dis 2011; 17: 479-484.
[29] Yarur AJ, Czul F and Levy C. Hepatobiliary manifestations of inflammatory bowel disease. Inflamm Bowel Dis 2014; 20: 1655-1667.
[30] Looijer-van Langen M, Hotte N, Dieleman LA, Albert E, Mulder C and Madsen KL. Estrogen receptor-beta signaling modulates epithelial barrier function. Am J Physiol Gastrointest Liver Physiol 2011; 300: G621-626.
[31] Kane SV and Reddy D. Hormonal replacement therapy after menopause is protective of disease activity in women with inflammatory bowel disease. Am J Gastroenterol 2008; 103: 1193-1196.
[32] Khalili H, Higuchi LM, Ananthakrishnan AN, Richter JM, Feskanich D, Fuchs CS and Chan AT. Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. Gut 2013; 62: 1153-1159.
[33] Yang JD, Abdelmalek MF, Pang H, Guy CD, Smith AD, Diehl AM and Suzuki A. Gender and menopause impact severity of fibrosis among patients with nonalcoholic steatohepatitis. Hepatology 2014; 59: 1406-1414.
[34] Zhang ZC, Liu Y, Xiao LL, Li SF, Jiang JH, Zhao Y, Qian SW, Tang QQ and Li X. Upregulation of miR-125b by estrogen protects against non-alcoholic fatty liver in female mice. J Hepatol 2015; 63: 1466-1475.
[35] Wieckowska A and Feldstein AE. Diagnosis of nonalcoholic fatty liver disease: invasive versus noninvasive. Semin Liver Dis 2008; 28: 386-395.