Correlation of liver function with intestinal flora, vitamin deficiency and IL-17A in patients with liver cirrhosis

HAIJUAN MOU1*, FENGYING YANG2*, JIANQIN ZHOU3 and CUIXIA BAO4

1Department of Public Health, 2Outpatient Department and 3Medical Department, Yantai Infectious Disease Hospital, Yantai, Shandong 264001; 4Department of Laboratory, The Affiliated Yantai Yuhuangding Hospital of Qingdao, University Medical College, Yantai, Shandong 264000, P.R. China

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Abstract. The aim of this study was to investigate the correlation of liver function, intestinal flora, vitamin D and interleukin-17A (IL-17A) levels in patients with liver cirrhosis. A total of 52 patients diagnosed with posthepatitic cirrhosis and admitted into Yantai Infectious Disease Hospital (Yantai, China) from January to December in 2012 (liver cirrhosis group), and 52 patients with chronic hepatitis B (hepatitis group), and 40 healthy volunteers receiving physical examination in the hospital (normal control group) were selected into the study. The liver function, hepatitis B virus (HBV) deoxyribonucleic acid (DNA) level, intestinal flora distribution, vitamin D and IL-17A levels of all patients were detected, and the correlation among them was analyzed via Pearson’s analysis. The number of Enterobacteriaceae, Enterococcus, Staphylococcus aureus and Saccharomyces in hepatatis and liver cirrhosis groups was significantly greater than in the normal control group (P<0.05), but the number of Lactobacillus, Bacteroides, Bifidobacterium and Clostridium was significantly decreased (P<0.05); the serum IL-17A levels in hepatatis and liver cirrhosis were obviously higher than that in the normal control group (P<0.05), but the serum vitamin D 25(OH)D and 1,25(OH)2D levels were obviously lower than that in the normal control group (P>0.05). In patients with liver cirrhosis, Enterobacteriaceae was positively correlated with prothrombin time (PT), Enterococcus was positively correlated with alanine aminotransferase and aspartate aminotransferase (AST) levels, Bifidobacterium was negatively correlated with AST, alkaline phosphatase (AKP) and HBV DNA levels, and Bacteroides was negatively correlated with AST level and PT.

There was a significant negative correlation between serum IL-17A and total bilirubin in patients with liver cirrhosis, and 25(OH) D was negatively correlated with AST, AKP and HBV DNA levels. In patients with liver cirrhosis, there was significant positive correlation between Enterococcus and IL-17A, and between Lactobacillus and 25(OH)D, but other bacteria were not obviously associated with IL-17A and vitamin D. Intestinal flora imbalance, vitamin D deficiency and IL-17A imbalance play an important role in the evolution of liver cirrhosis.

Introduction

Under normal circumstances, the intestinal flora is relatively constant in adults, and is disturbed and disordered only in case of illness or medication. Liver cirrhosis has various causes, and studies have shown that patients with liver cirrhosis suffer from varying degrees of intestinal flora imbalance, which is manifested as significantly decreased contents of Bifidobacterium, Lactobacillus and Bacteroides, and significantly increased contents of Enterobacteriaceae and Enterococcus (1-3). Such an imbalance is particularly prominent in patients with liver cirrhosis complications, so the concept of ‘gut-liver axis’ was proposed (4), providing a basis for clarifying the intestinal flora changes (mainly the changes in the number and proportion of bacteria or bacterial positioning) (5), and it is related to the progression of liver cirrhosis. Although the mechanism of cirrhosis remains unclear, studies have found that the cellular immunity is closely related to liver cirrhosis and injury and virus removal, among which the cytokines play important roles (6). Interleukin-17A (IL-17A) is a newly-discovered factor secreted by helper T lymphocyte (Th) 17, which is associated with the occurrence and development of various liver diseases (7). Another study has shown that vitamin D deficiency is closely related to the severe liver fibrosis (8). There are few studies on the roles of intestinal floras, vitamin D deficiency and IL-17A in posthepatitic cirrhosis and their correlations. This study investigated the correlations of liver function with intestinal flora, vitamin deficiency and IL-17A in patients with liver cirrhosis.

Patients and methods

Clinical materials. A total of 52 patients diagnosed with posthepatitic cirrhosis and admitted into Yantai Infectious...
Table I. Comparison of general conditions of patients in the three groups.

| Items                      | Control (n=40) | Hepatitis (n=52) | Liver cirrhosis (n=52) |
|----------------------------|----------------|------------------|------------------------|
| Sex (male/female)          | 13/27          | 17/35            | 16/36                  |
| Age (years)                | 36.7±10.1      | 40.6±14.8        | 53.1±11.4              |
| TBIL (µmol/l)              | 12.6±3.3       | 46.2±43.0        | 102.5±160.1            |
| ALT (U/l)                  | 22.5±6.4       | 679.8±670.1      | 120.2±225.3           |
| AST (U/l)                  | 20.7±4.2       | 542.7±610.5      | 115.8±176.4           |
| ALB (g/l)                  | 48.1±2.5       | 39.6±4.1         | 30.9±8.2              |
| GGT (U/l)                  | 24.4±7.8       | 130.3±75.8       | 115.8±142.4           |
| AKP (U/l)                  | 59.9±9.6       | 115.1±57.4       | 153.4±97.2            |
| PT time (sec)              | 12.2±0.6       | 14.0±2.3         | 17.5±14.2             |
| HBV DNA level              | -              | 6.8±13.2         | 6.7±14.3              |

*P<0.05 vs. the control group; †P<0.05 vs. the hepatitis group. TBIL, total bilirubin; ALT, alanine transaminase; AST, aspartate aminotransferase; ALB, albumin; GGT, glutamyltransferase; AKP, alkaline phosphatase; PT, prothrombin time; HBV, hepatitis B virus; DNA, deoxyribonucleic.

Disease Hospital (Yantai, China) from January to December in 2012 were collected, including 16 males and 36 females with an average age of 53.1±11.4 years. A total of 52 patients admitted due to chronic hepatitis B during the same period were selected, including 17 males and 35 females with an average age of 40.6±14.8 years. The diagnostic criteria were based on the Guidelines on Prevention and Control of Chronic Hepatitis B in 2011. Inclusion criteria were: i) Patients with serum hepatitis B surface antigen (+) ≥6 months; ii) with a history of abnormal liver function and iii) without taking any liver-protective or -antiviral drugs, micro-ecological agents or antibiotics. Another 40 healthy volunteers from the physical examination center of the hospital were enrolled as the normal control group, including 13 males and 27 females with an average age of 36.7±10.1 years. This study was approved by the Ethics Committee of Yantai Infectious Disease Hospital (Yantai, China), and the patients signed the informed consent. The comparison of general conditions of patients in the three groups is shown in Table I.

Methods
Detection of intestinal flora. The fresh stool specimens were collected from all patients within 2 h after defecation, stored in a closed stool box and placed in a refrigerator at -80˚C. The fresh stool specimens were cultured for 48 and 72 h, respectively, and identified using the VITEK-AMS full-automatic microbiological identification system (bioMérieux, Marcy-l’Étoile, France). The colony forming unit (CFU) per gram of wet dung was observed and recorded, and the logarithmic value was taken to indicate the result (namely immunoglobulin (Ig) CFU/g wet dung).

Detection of biochemical indexes. Fasting elbow venous blood (5 ml) was collected from all patients the next day after admission, and centrifuged at 8000 x g for 15 min to separate the serum. The serum was placed in a refrigerator at -80˚C. The laboratory reports of serum total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), prothrombin time (PT) and hepatitis B virus (HBV) DNA were from the Department of Laboratory of the hospital. The serum IL-17 and vitamin D in patients were detected via enzyme-linked immunosorbent assay (ELISA) in strict accordance with the instructions. Each specimen was detected 3 times, and the average was taken.

Statistical analysis. SPSS 18.0 (SPSS Inc., Chicago, IL, USA) software was used for analysis. Measurement data in normal distribution are presented as mean ± SD, and t-test or analysis of variance was used for the intergroup comparison and the Least Significant Difference test was used as the post hoc test. Pearson's correlation analysis was used. P<0.05 was considered to indicate a statistically significant analysis.

Results
Comparison of intestinal flora among the three groups. The number of Enterobacteriaceae, Enterococcus, Staphylococcus aureus and Saccharomyces in the hepatitis and liver cirrhosis groups was significantly greater than those in the normal control group (P<0.05), but the number of Lactobacillus, Bacteroides, Bifidobacterium and Clostridium was significantly decreased (P<0.05). There was no significant difference in other bacteria. In addition, the number of Lactobacillus in the liver cirrhosis group was obviously smaller than that in the hepatitis group (P<0.05). Although the change trends of other bacteria were more significant in the liver cirrhosis group than...
those in the hepatitis group, there were no statistically significant differences between the two groups (P>0.05) (Table II).

Comparison of serum IL-17A and vitamin D levels among the three groups. The serum IL-17A levels in the hepatitis and liver cirrhosis groups were obviously higher than that in the normal control group (P<0.05), but the serum vitamin D 25(OH)D and 1,25(OH)2D levels were obviously lower than that in the normal control group (P<0.05). The change trends of serum IL-17A and vitamin D levels were far more significant in the liver cirrhosis group than those in the hepatitis group, but there were no statistically significant differences between the two groups (P>0.05) (Table III).

Analyses of correlations of intestinal flora with liver function and HBV DNA level by Pearson's correlation analysis. In patients with liver cirrhosis, Enterobacteriaceae was positively correlated with PT (r=0.30, P=0.04), Enterococcus was positively correlated with ALT and AST levels (r=0.32, P=0.03; r=0.28, P=0.04), Bifidobacterium was negatively correlated with AST, AKP and HBV DNA levels (r=-0.36, P=0.02; r=-0.35, P=0.02; r=-0.29, P=0.04), and Bacteroides was negatively correlated with AST level and PT (r=-0.48, P=0.01; r=-0.38, P=0.01) (Table IV).

Analyses of correlations of serum IL-17A and vitamin D with liver function and HBV DNA level in patients with liver cirrhosis by Pearson's correlation analysis. There was a significant negative correlation between serum IL-17A and TBIL in patients with liver cirrhosis (r=-0.45, P<0.05), but had no obvious correlation with other indexes (P>0.05). In addition, 25(OH)D was negatively correlated with AST, AKP and HBV DNA levels (P<0.05), but 1,25(OH)2D had no obvious correlation with liver function indexes and HBV DNA level (P>0.05) (Table V).

Analyses of correlation of intestinal flora with serum IL-17A and vitamin D. Pearson's correlation analysis showed that in patients with liver cirrhosis, there was a significant positive correlation between Enterococcus and IL-17A (r=0.59, P<0.05), and between Lactobacillus and 25(OH)D (r=-0.36, P=0.02), but other bacteria were not obviously associated with IL-17A and vitamin D (P>0.05) (Table VI).

Discussion

Liver cirrhosis and intestinal flora. Hundreds of millions of micro-organisms sojourn in the human intestine, which is necessary and useful for the host under normal circumstances (9). Once the stability between host and intestinal microflora is broken, the alteration of intestinal flora will be caused, leading to diseases, such as obesity, inflammatory bowel disease and intestinal tumors (10-13). With the development of medical molecular biology, there have been more studies on the pathogenesis of intestinal flora involved in the liver cirrhosis. In the present study, it was found that the numbers of Enterobacteriaceae, Enterococcus, Staphylococcus aureus and Saccharomyces in the hepatitis and liver cirrhosis groups were significantly larger than those in the normal control group (P<0.05), but the numbers of Lactobacillus, Bacteroides, Bifidobacterium and Clostridium were significantly decreased (P<0.05), indicating that there are varying degrees of flora imbalance in patients with chronic hepatitis B and liver cirrhosis, which was consistent
with literature report (1-3). Studies have shown that the bacteria content in sigmoid colon and anal canal can be up to 1,011 g wet weight, accounting for 20% of the stool weight. In healthy people, the Bacteroides and Bifidobacterium in intestinal tract account for about 50% of the total bacteria, but Escherichia coli and Enterococci are no more than 1% (14). Bifidobacterium and Lactobacillus are the intestinal symbiotic dominant bacterial communities, which form the bacterial flora, acidify the intestinal tract, inhibit the spoilage and pathogens, constitute the intestinal barrier, reduce toxins into the blood, produce the organic acids, stimulate the peristalsis, prevent constipation, synthesize the vitamins and amino acids, stimulate the body’s immune system, decompose carcinogenic substances and reduce the occurrence of colon cancer (15,16). Moreover, Enterobacteriaceae belongs to the intestinal non-dominant flora, as well as the potential conditioned pathogen. Studies have shown that Enterobacteriaceae in patients with liver cirrhosis is increased significantly, a large amount of plasma endotoxin is released, and the intestinal epithelial protein synthesis is inhibited, leading to intestinal barrier damage, causing bacterial translocation and intestinal flora imbalance. Furthermore, the flora imbalance aggravates the excessive breeding of Enterobacteriaceae, repeating in endless cycles (17). Studies have also shown that Bacteroides have an inhibitory effect on the growth of translocation potential bacteria, and the reduction in its number promotes the bacterial translocation (18). Thus, it can be seen that the reduced Bifidobacteria and Lactobacilli in patients with chronic hepatitis B and liver cirrhosis weaken the intestinal barrier protection, thus leading to bacterial translocation, flora imbalance end endotoxemia. Therefore, promoting the intestinal bacteria (such as Bifidobacterium and Lactobacillus) growth and inhibiting the intestinal potential pathogens (such as Enterobacteriaceae) reproduction are of great significance in improving the intestinal flora imbalance as well as delaying and preventing liver cirrhosis.

Liver cirrhosis and IL-17A. IL-17 is both a pre-inflammatory cytokine and a fine-tuning factor for inflammatory responses. Besides, IL-17A is a major member of IL-17 (19). After IL-17A and receptor IL-17R bind and activate, the production of IL-8 and other chemokines can be stimulated, and the neutrophils and other inflammatory cells can be collected to reach the inflammatory site. Besides, IL-17A can stimulate the expression of IL-6 and other pro-inflammatory factors, thus exacerbating the local inflammatory response (20). Studies have shown that the growth of Enterococcus is rapid in hepatitis B patients, and the excessive reproduction of Enterococcus produces a lot of endotoxin, which, on the one hand, directly causes liver damage, and on the other hand, expands and aggravates the damage of inflammatory factors to liver cells by stimulating and activating inflammatory factors. The inactivation capacity of damaged liver against endotoxin is significantly reduced (21,22). This study showed that the serum IL-17A levels in the hepatitis and liver cirrhosis groups were obviously higher than that in the normal control group (P<0.05), and there was a significant positive correlation between Enterococcus and IL-17A in patients with liver cirrhosis, suggesting that IL-17A is widely involved in the pathogenesis of chronic liver disease and anti-viral immune response, and

### Table IV: Analyses of correlation of intestinal flora with liver function and HBV DNA level.

| Intestinal flora | HBV-DNA | ALT | AST | ALB | GGT | AKP | PT | DNA level | r | P-value | r | P-value | r | P-value | r | P-value | r | P-value | r | P-value | r | P-value |
|------------------|---------|-----|-----|-----|-----|-----|----|---------|---|---------|---|---------|---|---------|---|---------|---|---------|---|---------|---|---------|
| Enterobacteriaceae | -0.20   | 0.17 | 0.21 | 0.32 | 0.28 | -0.26 | 0.04* | 0.03* | -0.14 | 0.95 | -0.11 | 0.97 | -0.22 | 0.02* | -0.33 | 0.04* | -0.22 | 0.02* | -0.33 | 0.04* |
| Enterococcus      | 0.09    | 0.90 | 0.26 | 0.08 | 0.06 | 0.14   | 0.51 | 0.28   | 0.12 | 0.20 | -0.19 | 0.18 | 0.08  | 0.72  | -0.24 | 0.08  | 0.12 | 0.20 | -0.19 | 0.18 |
| Bacteroides       | -0.27   | 0.07 | 0.34 | 0.13 | 0.32 | 0.08 | 0.73 | 0.04   | 0.25 | 0.25 | -0.11 | 0.46 | -0.25 | 0.19 | -0.24 | 0.08  | -0.11 | 0.46 | -0.25 | 0.19 |
| Clostridium       | 0.07    | 0.90 | 0.13 | 0.21 | 0.10 | 0.24 | 0.92 | 0.05   | 0.46 | 0.06 | 0.82  | 0.05 | 0.46 | 0.05  | 0.46 | 0.05  | 0.46 | 0.05 | 0.46 |
| Peptostreptococcus | -0.22  | 0.07 | 0.87 | 0.09 | 0.09 | 0.10 | 0.73 | 0.03   | 0.08 | 0.25 | 0.06 | 0.25 | 0.03 | 0.08 | 0.25 | 0.06 | 0.25 | 0.03 | 0.08 |

IL-17A is both a pre-inflammatory cytokine and a fine-tuning factor for inflammatory responses. Besides, IL-17A is a major member of IL-17 (19). After IL-17A and receptor IL-17R bind and activate, the production of IL-8 and other chemokines can be stimulated, and the neutrophils and other inflammatory cells can be collected to reach the inflammatory site. Besides, IL-17A can stimulate the expression of IL-6 and other pro-inflammatory factors, thus exacerbating the local inflammatory response (20). Studies have shown that the growth of Enterococcus is rapid in hepatitis B patients, and the excessive reproduction of Enterococcus produces a lot of endotoxin, which, on the one hand, directly causes liver damage, and on the other hand, expands and aggravates the damage of inflammatory factors to liver cells by stimulating and activating inflammatory factors. The inactivation capacity of damaged liver against endotoxin is significantly reduced (21,22). This study showed that the serum IL-17A levels in the hepatitis and liver cirrhosis groups were obviously higher than that in the normal control group (P<0.05), and there was a significant positive correlation between Enterococcus and IL-17A in patients with liver cirrhosis, suggesting that IL-17A is widely involved in the pathogenesis of chronic liver disease and anti-viral immune response, and...
the increased IL-17A in patients with liver cirrhosis is involved in liver inflammatory response process through cooperation with Enterococcus, aggravating liver damage. It was also found in this study that the serum IL-17A in patients with liver cirrhosis was also negatively correlated with TBIL, but not related to other indexes of liver function. It may be because IL-17A is a pro-inflammatory factor, and an initial factor of the incidence of chronic hepatitis B, rather than the pathogenic effector molecule, which recruits the neutrophils and other inflammatory cells, so it is not closely related to the degree of liver injury (23). It is necessary to further improve the experimental method and to perform large-sample and multi-level in-depth study, so that more meaningful research results can be obtained.

Liver cirrhosis and vitamin D. Liver cirrhosis is a chronic, progressive and diffuse disease with multiple causes, the main pathological change is the fibrous tissue-wrapped regenerative nodule and liver failure, portal hypertension and a variety of complications can occur in the late stage (24). Vitamin D is a fat-soluble vitamin, which is essential for the human body and exerts biological effects through the binding to vitamin D receptor (VDR). After the binding between them, 3% of genes in the body can be regulated (25), which is related to the bone metabolic disorder, cancer, autoimmune disease and other diseases (26). Studies have shown that the liver hypofunction in patients with liver cirrhosis causes vitamin D metabolic disorder, leading to low vitamin-D level (27,28). The mechanism of low vitamin D level in affecting occurrence of liver cirrhosis is still inconclusive. Petta et al (29) found that low vitamin D level is related to severe liver fibrosis and low response to interferon in chronic hepatitis C. Zuniga et al (30) showed that the low vitamin D level is associated with the non-alcoholic fatty cirrhosis. Drocourt et al (31) also found that vitamin D may affect the liver detoxification function through increasing the expression of P450 cytochrome, and its specific mechanism needs to be further studied. In this study, the serum

Table V. Analyses of correlation of serum IL-17A and vitamin D with liver function and HBV DNA level in patients with liver cirrhosis.

| Indexes | IL-17A | | | 25(OH)D | | | 1,25(OH)2D | | |
|---------|--------|--------|--------|--------|--------|--------|--------|--------|
|         | r      | P-value| r      | P-value| r      | P-value| r      | P-value|
| TBIL    | -0.45  | 0.00 a | 0.09   | 0.59   | 0.07   | 0.63   |        |        |
| ALT     | 0.08   | 0.62   | -0.40  | 0.01 a | 0.16   | 0.23   |        |        |
| AST     | 0.15   | 0.24   | -0.35  | 0.03 a | 0.10   | 0.48   |        |        |
| ALB     | 0.11   | 0.47   | -0.16  | 0.22   | -0.26  | 0.07   |        |        |
| GGT     | -0.25  | 0.08   | 0.24   | 0.06   | -0.05  | 0.75   |        |        |
| AKP     | -0.06  | 0.74   | 0.13   | 0.28   | -0.02  | 0.87   |        |        |
| PT      | -0.03  | 0.86   | 0.05   | 0.79   | 0.03   | 0.85   |        |        |
| HBV DNA | 0.04   | 0.83   | 0.28   | 0.04 a | 0.08   | 0.61   |        |        |

aP<0.05; TBIL, total bilirubin; ALT, alanine transaminase; AST, aspartate aminotransferase; ALB, albumin; GGT, glutamyltransferase; AKP, alkaline phosphatase; PT, prothrombin time; HBV, hepatitis B virus; DNA, deoxyribonucleic.

Table VI. Analyses of correlation of intestinal flora with serum IL-17A and vitamin D.

| Items              | IL-17A | | | 25(OH)D | | | 1,25(OH)2D | | |
|--------------------|--------|--------|--------|--------|--------|--------|--------|--------|
|                    | r      | P-value| r      | P-value| r      | P-value| r      | P-value|
| Enterobacteriaceae | 0.25   | 0.07   | -0.19  | 0.20   | -0.06  | 0.72   |        |        |
| Enterococcus       | 0.59   | 0.05 a | -0.24  | 0.10   | 0.21   | 0.16   |        |        |
| Staphylococcus     | 0.15   | 0.24   | -0.35  | 0.03   | 0.10   | 0.48   |        |        |
| Saccharomyces      | 0.01   | 0.90   | -0.14  | 0.35   | -0.26  | 0.07   |        |        |
| Lactobacillus      | -0.14  | 0.35   | 0.36   | 0.02 a | 0.15   | 0.26   |        |        |
| Bacteroides        | -0.07  | 0.66   | 0.09   | 0.58   | -0.04  | 0.83   |        |        |
| Bifidobacterium    | -0.08  | 0.60   | 0.04   | 0.80   | 0.05   | 0.74   |        |        |
| Clostridium        | -0.16  | 0.29   | 0.21   | 0.15   | 0.15   | 0.31   |        |        |
| Peptostreptococcus | 0.13   | 0.42   | 0.24   | 0.85   | 0.07   | 0.68   |        |        |

P<0.05.
vitamin D 25(OH)D and 1,25(OH)2D levels in patients in the hepatitis and liver cirrhosis groups were obviously lower than that in the normal control group. 25(OH)D was negatively correlated with AST, AKP and HBV DNA levels, but positively correlated with *Lactobacillus* (P<0.05). It was evident that the serum 25(OH)D in the normal control group and patients with chronic hepatitis B and liver cirrhosis showed an increasing trend, and was related to the liver function and viral load. Therefore, Vitamin D may become the protective factor in the pathogenesis of liver cirrhosis through coordination with intestinal dominant bacteria (*Lactobacilli*).

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

HM and JZ detected biochemical indexes. FY collected the specimens. JZ and CB contributed to the statistical analysis. HM and JZ detected biochemical indexes. FY collected the specimens. JZ and CB contributed to the statistical analysis. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee of Yantai Infectious Disease Hospital (Yantai, China), and the patients signed the informed consent.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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