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Comparative study of SCFA and butyrate levels in chronic hepatitis versus cirrhosis patients

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ABSTRACT

BACKGROUND: Cirrhosis is a common complication of chronic liver disease and exerts a profound influence on gut microbiota and metabolic function. Short-chain fatty acids (SCFAs), particularly butyrate, are crucial to intestinal integrity and immunomodulation. The relationship between SCFA levels and the progression of liver disease is not well understood.

OBJECTIVES: The current study aimed to study the level of SCFAs and butyrate in fecal samples of patients with chronic hepatitis B, chronic hepatitis C, and compensated cirrhosis.

METHODS: The research was conducted at Dr. Saiful Anwar General Hospital, Malang, Indonesia, from January to June 2023. Fecal samples were collected and measured for SCFA and butyrate concentrations by gas chromatography. The comparison was made statistically by the Mann-Whitney U test between groups.

RESULTS: A total of 26 patients with chronic hepatitis B, chronic hepatitis C, or compensated cirrhosis were enrolled in the study. The overall mean SCFA level in the participants was 9.85 ± 4.78 mg/mL. The findings revealed no difference in the level of SCFA in chronic hepatitis patients and cirrhosis patients ($p = 0.72$). Likewise, there was no difference in butyrate levels between the two groups ($p = 0.37$).

CONCLUSION: During the present study, SCFA and butyrate levels were not significantly different in chronic hepatitis patients compared to cirrhosis patients. SCFA synthesis and use may be affected by various factors such as dietary patterns, microbiota diversity, and metabolic differences among individuals. Further studies with larger populations and dietary control are necessary to delineate the role of SCFAs in the pathogenesis of liver disease and therapeutic applications.

KEYWORDS: Cirrhosis; chronic hepatitis; short-chain fatty acids; butyrate; gut microbiota.

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INTRODUCTION

Cirrhosis is the most common consequence of chronic liver disease, characterized by progressive damage to hepatic parenchyma.[1] Clinically, cirrhosis is classified into two stages: compensated and decompensated. Decompensated cirrhosis manifests as hepatocellular failure and portal hypertension. Although traditionally regarded as an irreversible condition, recent studies suggest that cirrhosis may undergo partial regression under certain circumstances. However, the determinants of fibrosis regression are not yet fully understood.[2]

One of the most significant etiologies of cirrhosis is chronic infection with B and C hepatitis. B and C hepatitis infections are known to affect the gut-liver axis, a central mechanism involved in disease pathogenesis, intestinal barrier integrity, and gut microbiota.[3] Studies have confirmed that depletion of beneficial families of bacteria such as Lachnospiraceae and Ruminococcaceae leads to decreased production of SCFAs, notably butyrate. This lack has been considered to promote the development

of chronic hepatitis B and C into cirrhosis through promotion of endotoxin release and interference with conversion of bile acid.[4,5]

Chronic hepatitis B is estimated to have a prevalence of 7.1%, chronic hepatitis C of 1%, and cirrhosis of 3.5% in Indonesia.[6] Despite this significant disease burden, data on the status of the gut microbiota in the development of chronic hepatitis in Indonesia are scarce. SCFAs, in the form of butyrate, are known to be significant to gut health through the preservation of intestinal barrier function, modulation of inflammation, and serving as a source of energy for colonocytes.[7] Reduced levels of SCFAs in chronic liver disease patients have been suspected to play a role in disease progression.[8]

As modulation of gut microbiota could be involved in the pathogenesis of liver disease, the present study aimed to compare variations in fecal total SCFA and butyrate composition in chronic hepatitis B and C and cirrhotic patients. These metabolic alterations could provide new insight into the development of therapeutic strategies for decreasing the severity of liver disease.

METHODS

Study design

The cross-sectional study was conducted in Dr. Saiful Anwar General Hospital, Malang, Indonesia, during January-June 2023. For the sake of completion of the goals of the study, fecal samples were obtained from the patients with chronic hepatitis B, chronic hepatitis C, and compensated liver cirrhosis who presented at the hospital. These samples were tested to quantify the short-chain fatty acids (SCFAs) and butyrate concentrations, in a bid to test comparisons between patient groups. The study design was designed and conducted as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[9]

Ethical approval

This study was granted ethical approval by the Dr. Saiful Anwar General Hospital Health Research Ethics Committee with reference no. 400/050/K.3/102.7/2024. The study was conducted in adherence with the Declaration of Helsinki.[10] Full information regarding the objectives of the study, risk, and benefit was provided to all the participants. Informed written consent was taken from all the participants prior to their recruitment into the study. Voluntary participation and participants could withdraw at any moment without penalty. Financial or other reward to participants was not provided.

Participants and eligibility criteria

A total sampling method was employed, resulting in the inclusion of 26 patients who met the eligibility criteria. Inclusion criteria consisted of adults (aged >18 years) diagnosed with chronic hepatitis B or C, or compensated liver cirrhosis. Exclusion criteria included patients with decompensated cirrhosis, hepatocellular carcinoma, congenital liver disease, autoimmune disorders, chronic gastrointestinal conditions (e.g., Crohn's disease or ulcerative colitis), prolonged use of antibiotics or immunosuppressants, as well as those with severe infections or other malignancies.

Data collection

The study was conducted at the Gastroenterohepatology Clinic of Dr. Saiful Anwar General Hospital between January and June 2023. Fecal samples were collected from all participants using standardized collection kits. The samples were then transported

to Prodia Laboratory, Malang, for analysis of SCFA and butyrate concentrations using gas chromatography.

Covariates

The primary predictor variables in this study were the levels of SCFAs and butyrate obtained from fecal sample analysis. The outcome variable was the presence of liver cirrhosis in patients with chronic hepatitis B or C.

Statistical analysis

Data were presented as mean ± standard deviation (SD) for normally distributed variables or as median with interquartile range (IQR) for non-normally distributed variables. Normality was assessed using the Shapiro-Wilk test. Baseline characteristics were described using descriptive statistics according to data distribution. To assess differences in SCFA and butyrate levels between groups, an independent t-test was used for normally distributed data, and the Mann–Whitney U test was used for non-normally distributed data. A p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software.

RESULTS

Participant characteristics

Table 1 presents the baseline characteristics of the 26 patients enrolled in this study. The median age of participants was 53 years, with an interquartile range (IQR) of 22 to 73 years. The majority of participants were male (n = 15, 57.7%), while females accounted for 11 individuals (42.3%). The mean total fecal SCFA concentration was 9.85 ± 4.78 mg/mL. The median concentrations of specific SCFA components were as follows: acetate 61.5 mg/mL (IQR 40–75), propionate 17 mg/mL (IQR 11–34), valerate 2.85 mg/mL (IQR 1.4–8.2), and butyrate 1.25 mg/mL (IQR 0.3–4.8).

Comparison of SCFA and butyrate levels between patients with and without liver cirrhosis

Table 2 compares total SCFA and butyrate levels in the feces of patients with and without liver cirrhosis. Among the 9 patients with cirrhosis, only 1 patient (11.1%) exhibited decreased total SCFA levels. In comparison, 1 patient (5.9%) in the non-cirrhotic group also showed decreased SCFA levels; this difference was not statistically significant (p = 0.72). Regarding butyrate levels, 2 patients (22.2%) in the cirrhosis group had decreased concentrations, compared to 3 patients (17.6%) in the non-cirrhotic group; this difference was likewise not statistically significant (p = 0.37).

DISCUSSION

The findings of this study indicate that there were no significant differences in fecal SCFA and butyrate levels between patients with chronic hepatitis and those with liver cirrhosis. These results differ from previous studies, which have suggested that a decrease in SCFA levels is associated with disease progression in liver conditions.[11,12] Several factors may account for these findings, including individual variations in gut microbiota composition, dietary habits, and metabolic interactions that influence SCFA production. SCFAs, particularly butyrate, are key metabolites produced by the gut microbiota, playing critical roles in maintaining intestinal barrier integrity, modulating immune responses, and supporting liver metabolism.[7] A reduction in SCFA levels has been reported in patients with advanced liver disease, which may lead to increased intestinal permeability, bacterial translocation, and subsequent worsening of hepatic inflammation and fibrosis.[13] However, our study did not demonstrate statistically

significant differences in SCFA or butyrate levels between chronic hepatitis and cirrhosis groups, suggesting the possibility of compensatory mechanisms that help maintain SCFA levels despite disease progression.

Table 1. Characteristics of patients included in our study

Parameters	Participants (n=26)
Age, years, median (IQR)	53 (22 – 73)
Gender	
Male, n (%)	15 (57.7%)
Female, n (%)	11 (42.3%)
Total SCFA (mg/mL), mean ± SD	9.85 ± 4.78
Acetate, median (IQR)	61.5 (40 – 75)
Propionate, median (IQR)	17 (11 – 34)
Valerate, median (IQR)	2.85 (1.4 – 8.2)
Butyrate, median (IQR)	1.25 (0.3 – 4.8)

Note, data were presented in median (IQR) or mean ± SD.

One possible explanation for our findings is the heterogeneity in subjects' dietary fiber intake, as the production of SCFAs depends significantly on fiber intake. Malnutrition, which is frequent in cirrhotic patients, can affect SCFA synthesis and SCFA absorption. The composition of the gut microbiota has been shown to differ based on genetic, environmental, and lifestyle factors, leading to differences in SCFA production among subjects.[14] A second consideration is the impact of hepatic failure on metabolism of SCFAs. Although SCFAs are produced most profusely in the colon, they undergo extensive hepatic metabolism with use for gluconeogenesis and lipid synthesis.[14] Cirrhosis-related liver disease may therefore alter utilization of SCFAs instead of affecting fecal concentrations per se, and consequently produce equal SCFA levels in chronic hepatitis as in cirrhosis, independent of severity.[15] Moreover, portal hypertension—a hallmark of cirrhosis—may also influence gut microbiota structure and SCFA metabolism. Intestinal homeostasis is disturbed by elevated portal pressure, resulting in dysbiosis and aberrant SCFA absorption.[13] Nevertheless, the observation that no significant differences in SCFA levels among groups were found in this study suggests that these alterations may be more complex than initially anticipated.

Table 2. Comparison of total short-chain fatty acids and butyrate levels in the feces of patients with chronic hepatitis and liver cirrhosis

Short-chain fatty acids		Liver cirrhosis		p Value
		Yes (9)	No (17)	
Total SCFA levels, mg/mL	Decreased	1 (11.1%)	1 (5.9%)	0.72
	Normal	8 (88.9%)	16 (94.1%)	
Butyrate levels, mg/mL	Decreased	2 (22.2%)	3 (17.6%)	0.37
	Normal	7 (77.8%)	14 (82.4%)	

Note, data were presented in n (%).

Despite these results, this study has several limitations. The small sample size, bolstered by fecal sampling challenges and participant intolerance, could have restricted statistical power. Poor sampling methods and heterogeneous samples due to skewed data limitation also constrain the external generalizability of the outcomes. Potential solution variables such as uncontrolled food consumption and drug consumption could have intervened between SCFA levels. Future research must involve analysis of more comprehensive assessments of gut microbiota diversity and specific SCFA-producing bacterial species. More sophisticated techniques such as functional metagenomic sequencing and metabolomic analysis may provide further insights into the interactions between gut microbiota, SCFA production, and the

development of liver disease. Controlled diet and medication use must be included in future research to both significantly impact gut microbiota and SCFA concentrations. Lastly, research into therapeutic methods such as prebiotics, probiotics, and fecal microbiota transplantation can give future directions for modulation of SCFA production and augmentation of liver health. With the central role played by the gut-liver axis in liver disease, microbiota-targeted personalized medicine can be beneficial in delaying disease progression in chronic liver disease.

CONCLUSION

In this study, there was no significant difference in SCFA and butyrate concentrations in liver cirrhosis and chronic hepatitis patients. The finding suggests that SCFA concentrations are less likely to be directly associated with the advancement of liver disease, but eating habits, microbiota richness, and differences in metabolism between subjects may play a part. Future research must take these cues and investigate potential therapeutic approaches that try to manipulate SCFA levels as a part of liver disease treatment strategies.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocols of our study have been approved by local ethical committee.

CONFLICTS OF INTEREST

We have no conflict of interest

FUNDING SOURCES

We have no source of funding

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AUTHOR CONTRIBUTION

Conceptualization: SM; Data Curation: MF, IMR, AA, MR; Formal Analysis: MF, IMR, AA, MR; Investigation: MF, IMR, AA, MR; Project Administration: MF, IMR, AA, MR; Resources: MF, IMR, AA, MR; Methodology: MF, IMR, AA, MR; Software: MF, IMR, AA, MR; Visualization: MF, IMR, AA, MR; Supervision: SM; Validation: SM; Writing – Original Draft Preparation: MF, IMR, AA, MR; Writing – Review & Editing: SM. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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