

World Journal of *Gastroenterology*

World J Gastroenterol 2024 November 21; 30(43): 4597-4688



EDITORIAL

- 4597 Potential of traditional Chinese medicine in the treatment of nonalcoholic fatty liver disease: A promising future
Zhang WY, Wang MH, Xie C
- 4602 Comprehensive approach to esophageal variceal bleeding: From prevention to treatment
Singh S, Chandan S, Vinayek R, Aswath G, Facciorusso A, Maida M

ORIGINAL ARTICLE**Retrospective Study**

- 4609 Plasma DNA methylation detection for early screening, diagnosis, and monitoring of esophageal adenocarcinoma and squamous cell carcinoma
Liu XJ, Pi GL, Wang S, Kai JD, Yu HF, Shi HW, Yu J, Zeng H
- 4620 Lenvatinib, sintilimab combined interventional treatment *vs* bevacizumab, sintilimab combined interventional treatment for intermediate-advanced unresectable hepatocellular carcinoma
Han RY, Gan LJ, Lang MR, Ren SH, Liu DM, Li GT, Liu YY, Tian XD, Zhu KW, Sun LY, Chen L, Song TQ

META-ANALYSIS

- 4636 Prevalence of *Helicobacter pylori* infection in China from 2014-2023: A systematic review and meta-analysis
Xie L, Liu GW, Liu YN, Li PY, Hu XN, He XY, Huan RB, Zhao TL, Guo HJ

LETTER TO THE EDITOR

- 4657 Managing crawling-type gastric adenocarcinoma with endoscopic techniques and postoperative monitoring
Yang JC, Chen LX, Hu B
- 4660 Elafibranor alleviates alcohol-related liver fibrosis by restoring intestinal barrier function
Sun YQ, Wu Y, Li MR, Wei YY, Guo M, Zhang ZL
- 4669 Advances in artificial intelligence for predicting complication risks post-laparoscopic radical gastrectomy for gastric cancer: A significant leap forward
Wang HN, An JH, Zong L
- 4672 Portocaval shunts' role in gut microbiota and hepatic encephalopathy: The gut-to-brain pathway
Yakut A
- 4677 Improving early diagnosis of multiple endocrine neoplasia type 1 by assessing the gastrointestinal symptoms, hypercalcemia, and elevated serum gastrin
Velikova T, Lazarov V

- 4682** Interplay of gut microbiota, glucagon-like peptide receptor agonists, and nutrition: New frontiers in metabolic dysfunction-associated steatotic liver disease therapy

Guney-Coskun M, Basaranoglu M

ABOUT COVER

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INDEXING/ABSTRACTING

The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJG* as 4.3; Quartile: Q1. The *WJG*'s CiteScore for 2023 is 7.8.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Xiao-Mei Zheng; Production Department Director: Xu Guo; Cover Editor: Jia-Ru Fan.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF

Jian-Gao Fan (Chronic Liver Disease)

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

November 21, 2024

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PUBLISHING PARTNER

Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

POLICY OF CO-AUTHORS

<https://www.wjgnet.com/bpg/GerInfo/310>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

PUBLISHING PARTNER'S OFFICIAL WEBSITE

<https://www.shca.org.cn>
<https://www.zs-hospital.sh.cn>

Portocaval shunts' role in gut microbiota and hepatic encephalopathy: The gut-to-brain pathway

Aysun Yakut

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade C

Creativity or Innovation: Grade C

Scientific Significance: Grade B

P-Reviewer: Yuan T

Received: August 13, 2024

Revised: September 11, 2024

Accepted: October 9, 2024

Published online: November 21, 2024

Processing time: 78 Days and 11.1 Hours



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Abstract

I read the study by Zhao *et al* with great interest. Although the study design was quite complicated, it was successful in raising awareness of science and relevant researchers. Thirty patients with liver cirrhosis and portal hypertension secondary to chronic hepatitis B were included in the study. They were treated for variceal bleeding and underwent trans-jugular intrahepatic portosystemic shunt to prevent the recurrence of variceal bleeding and to reduce portal pressure. The authors evaluated the effects of changes in gut microbiota (GM) on hepatic encephalopathy secondary to portocaval bypass. The GM is greatly affected by local and general factors, including herbal and medical drugs, a person's dietary characteristics (carnivorous, vegan, vegetarian), supplementary foods, drinking water sources, and living in a city center or town. Therefore, I congratulate Zhao *et al* for their concise and comprehensive study on a multifactorial subject.

Key Words: Chronic hepatitis B; Liver cirrhosis; Transjugular intrahepatic portosystemic shunt; Intestinal microbiota; Hepatic encephalopathy

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Core Tip: The gut microbiota (GM) has evolved with the host and has become an integral part of the human body. The GM is highly dynamic and changes depending on the person's diseases, diet, habits, living area, water sources and many other factors. Changes in GM abundance can affect some basic immunological, metabolic, structural and neurological functions of the human body. Therefore, the GM has important effects on both the physical and mental health of an individual. In this beautiful study by Zhao *et al* examining GM changes after trans-jugular intrahepatic portosystemic shunt, the effect of the dynamic process in GM and its relationship with hepatic encephalopathy are beautifully described.

Citation: Yakut A. Portocaval shunts' role in gut microbiota and hepatic encephalopathy: The gut-to-brain pathway. *World J Gastroenterol* 2024; 30(43): 4672-4676

URL: <https://www.wjgnet.com/1007-9327/full/v30/i43/4672.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v30.i43.4672>

TO THE EDITOR

Introduction

Chronic hepatitis B (CHB) is a chronic disease that progresses to liver fibrosis and cirrhosis[1]. It is the leading cause of liver cirrhosis in Asian populations. Portal hypertension is the leading cause of mortality and morbidity in patients with liver cirrhosis. Portal hypertension is a condition in which the portal pressure gradient between the portal vein and the inferior vena cava exceeds 5 mmHg. The main factors that cause this pressure increase are fibrosis and regenerating nodules in the sinusoids, which cause an increase in intrahepatic vascular resistance, while the portal pressure gradient is increased by the addition of vasoconstriction resulting from sinusoidal endothelial dysfunction. The body develops collaterals to reduce the increase in portal pressure and balance it with systemic pressure. When the hepatic venous pressure gradient increases to 10 mmHg or more, varices develop in the portal and caval venous systems at the esophago-gastric junction[2]. The increase in hepatic venous pressure gradient causes variceal bleeding, vasodilation in splanchnic arterioles, and a decrease in arterial blood flow in the systemic circulation, leading to systemic hypotension[2]. In contrast, renal vasoconstriction develops with the neurohumoral contribution of the renin-angiotensin-aldosterone system, causing water and sodium retention in the body[2]. As a result of this complex pathogenesis, portal hypertension can be the main trigger for the development of serious complications such as variceal bleeding, ascites, hepatic encephalopathy (HE), hepatorenal syndrome, hepato-pulmonary syndrome, porto-pulmonary syndrome, and hepatic hydrothorax, which may develop during decompensation of cirrhosis. Spontaneous or therapeutic portosystemic shunts cause toxins such as intestinal ammonia and bacterial metabolites to pass directly into the caval system without passing through the portal system, leading to HE. In the management of portal hypertension, nonselective beta-blockers are the first-line medical treatment to reduce portal pressure and its complications. A recent meta-analysis reported that in addition to propranolol, carvedilol was effective in preventing decompensation and improving survival in patients with compensated cirrhosis[3]. In select patients with liver cirrhosis who had recurrent variceal bleeding and were unresponsive to endoscopic band ligation therapy and prophylaxis, trans-jugular intrahepatic portosystemic shunt (TIPS) placement can improve control of cirrhosis complications such as variceal bleeding and ascites and also improve survival in selected patients with liver cirrhosis who failed medical therapy to reduce portal pressure[4]. The preventive TIPS (pTIPS) strategy was demonstrated in a meta-analysis conducted at the Baveno VII workshop on 1327 participants with Child-Pugh score B decompensated cirrhosis and variceal bleeding. In this meta-analysis, pTIPS was compared with medications and endoscopy, resulting in improved bleeding and ascites control and increased 1-year survival in both subgroups[5]. A recent meta-analysis of 12 trials comparing TIPS with standard care for the prevention of refractory ascites and recurrent variceal bleeding showed that TIPS reduced the incidence of further decompensation (hazard ratio: 0.44; 95%CI: 0.37–0.54) and improved survival (2-year cumulative survival probability for TIPS = 0.71 *vs* standard care 0.63; $P = 0.0001$)[6]. In this editorial, Zhao *et al*[7] demonstrated that changes in gut microbiota (GM) in patients with portal hypertension may influence the development of HE. This study analyzed the changes in GM composition before and after TIPS in Chinese patients with liver cirrhosis and portal hypertension secondary to the hepatitis B virus (HBV), showing that patients without HE exhibited higher GM-related synergism than those with HE. The present study highlighted the need for further discussion of our awareness that GM synergy may predict HE risk after TIPS placement.

CHB

Chronic liver disease causes approximately 2 million deaths worldwide each year[8]. The World Health Organization estimates that 3.5% of the world's population carries the CHB virus (HBV), with 68% of these infected individuals in the Western Pacific (115 million) and Sub-Saharan Africa (60 million)[8]. CHB is a chronic disease that can progress to liver fibrosis and compensated and decompensated liver cirrhosis. Although its prevalence has decreased with universal childhood hepatitis B vaccination programs, HBV carriers are still at risk for chronic liver disease[8].

Trans-jugular intrahepatic portocaval shunt

TIPS is recommended to reduce portal pressure and reduce the risk of rebleeding in decompensated cirrhotic patients with acute variceal bleeding that cannot be controlled by medical and endoscopic band ligation or in decompensated cirrhotic patients with successful endoscopic band ligation but with recurrent variceal bleeding at any time during hospitalization[9]. To manage complications like HE, the decision to perform TIPS should be made with a multidisciplinary approach led by a hepatologist in collaboration with interventional radiology, transplant surgery, nephrology, cardiology, chest diseases, and hematology. The importance of this multidisciplinary approach is emphasized by the protocol specified in Advancing Liver Therapeutic Approaches (ALTA). The ALTA protocol has simplified the management of patients with TIPS by simplifying the complex classification of TIPS indications, new procedural techniques, TIPS stent technology, and TIPS indications[10]. The probability of developing HE is very high in patients with spontaneous or therapeutic shunts. HE is a brain dysfunction that occurs in patients with liver cirrhosis due to severe hepatocellular insufficiency or the presence of portal-to-systemic shunts. The presence of spontaneous portal-to-systemic shunts (SPSS)

may also be responsible for the chronic course of HE. Overt HE is seen in 30%-40% of patients with liver cirrhosis during the natural history of their disease[11]. However, it is difficult to estimate the true epidemiology. A total of 46%-70% of cirrhotic patients with refractory HE have SPSSs on radiological imaging. HE prevalence rates are estimated to be much higher in cirrhotic patients with TIPS and spontaneous or surgical shunts[12-14]. Although medical treatments such as lactulose, rifaximin, and L-ornithine L-aspartate are used in to treat HE, they have their own contradictory aspects. The aim is to reverse the evolving change in consciousness and to provide symptom relief rather than to provide curative treatment to the patient. Options for recurrent/persistent HE include fecal transplantation, TIPS revision, and closure of possible splenorenal shunts[10].

GM

GM has a close relationship with the brain and other systemic organs. GM and a series of metabolites affect the brain through various pathways, such as blood circulation, neuronal transmission, or neurohumoral transmission. It is critical to better understand the synergistic pathway within the gut-brain axis (GBA)[15]. In this editorial by Zhao *et al*[7], they analyzed the changes in GM in patients with liver cirrhosis secondary to CHB and recurrent variceal bleeding after TIPS and presented how certain bacterial species may shape the host GBA. They also aimed to estimate the contribution of the GM changes to the development of HE and evaluated the bacterial composition that may affect host immunity and nerve functions between the HE group and the non-HE group after TIPS. No significant difference was observed in GM abundance between the two groups. However, although it is not clear how bacteria, their products, or metabolites trigger HE between the two groups, the exact mechanism of action and signaling pathways could not be determined. However, the changes in GM in patients with TIPS and the pathogenic microorganisms in the HE group were reported. *Haemophilus* and *Eggerthella* abundance increased in the HE group after TIPS placement, while *Anaerostipes*, *Dialister*, *Butyrivibrio*, and *Oscillospira* decreased. *Eggerthella*, *Streptococcus*, and *Bilophila* abundance increased in the non-HE group, while *Roseburia* and *Ruminococcus* decreased. On the other hand, pathogenic *Morganella* bacteria were seen in the HE group but not in the non-HE group. In another animal experiment study, *Staphylococcaceae*, *Enterobacteriaceae*, and *Lactobacillaceae* abundance was present in the large intestine of HE mice, while *Staphylococcaceae*, *Streptococcaceae*, and *Enterobacteriaceae* species had higher abundance in the small intestine. In addition, TNF- α and IL-1 β concentrations were higher in the circulation in these mice and were associated with systemic inflammation[16]. In another study, *Enterobacteriaceae*, *Fusobacteriaceae*, and *Veillonellaceae* were detected in cirrhotic patients with HE, while serum IL-2, IL-13, and IL-23 concentrations were higher and positively correlated[17]. These increased proinflammatory cytokines correlated with the severity of HE and were independent of the stage of liver cirrhosis and the amount of ammonia[18]. The blood-brain barrier does not allow the passage of microorganisms, metabolites, and cytokines in the circulation due to its tight junctions, but proinflammatory cytokines such as TNF- α , ILs, and interferon disrupt the expression of endothelial tight junction proteins, destroy cerebrovascular endothelial cells, activate astrocytes for the inflammatory process, and change their expression and transport pathways in the blood-brain barrier. This situation disrupts the integrity of the blood-brain barrier and further increases surface permeability. This proinflammatory signal initiated by systemic inflammation crosses the damaged blood-brain barrier and forms the basis of the neuroinflammatory response that develops in the brain[18]. Considering that innate immunity affects GBA in this way, it is necessary to consider a very complex spectrum.

Li *et al*[19] showed that GM abundance was changed in patients with CHB compared to patients without CHB. This showed that there is an interaction between the liver and intestine, which can affect the brain and other systems. Supported by animal and human studies, GM changes as HBV-associated liver fibrosis begins and progresses. Therefore, evaluating GM changes after TIPS may not be meaningful alone. However, since the cohort was of the same standard in the study design, it was very important to evaluate GM changes in HE after TIPS. This study showed that GM is quite important and can be affected by manipulative procedures. Zhao *et al*[7] reported that bypassing the portal flow in patients with therapeutic shunts is not the only factor that predisposes patients to HE and that GM may also affect HE through its metabolites and proinflammatory cytokines.

Determining whether microbiota is a suitable disease biomarker and comprehending the temporal and causal links between GM and HE development are critical. Translational methods and larger-scale clinical trials are unquestionably required to assess the effectiveness of microbial therapies in patients, such as probiotics and rifaximin therapy. It is established that the portal system raises the risk of developing HE by entering the systemic circulation right after the shunt. However, this is not seen in every shunted patient, while HE is seen in some shunted patients. The importance of GM can be better understood by early analysis and early treatment of GM. Studying the mechanisms underlying a certain immunological or neurological effect that occurs in the presence or absence of a particular bacterial species or in particular pathogenic conditions will need the use of this methodology. In this instance, the study highlights the need for further research to determine whether and how certain bacterial products or metabolites play a role in the development or maintenance of a disease. The aim of future research should be to identify the precise mechanisms behind the GM-induced pro- and anti-inflammatory responses[15]. For that reason, it will become even more crucial to understand the precise functions of specific bacterial compounds and metabolites within the central nervous system and how they enter the system.

CONCLUSION

In the process of human evolution, it has been increasingly understood in various studies that GM is closely related to human health. The exciting study by Zhao *et al*[7] suggests that the presence of pathogenic *Morganella* in HE development after TIPS may provide prophylaxis against possible HE development after shunt treatment by eliminating this strain and

replacing commensal pathogens. In addition, HE can be treated by provoking the presence of commensal bacterial strains in GM instead of standard treatment in decompensated cirrhotic patients with *Morgenalla* strains, eliminating or replacing the abundance of pathogenic GM. This approach is an important result of how to develop better effective interventions and personalized treatment strategies.

FOOTNOTES

Author contributions: Yakut A designed the overall concept and outline of the manuscript, wrote and edited the manuscript, and performed the literature review.

Conflict-of-interest statement: The author declares that she has no conflict of interest.

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Corresponding Author's Membership in Professional Societies: Turkish Society of Gastroenterology.

S-Editor: Lin C

L-Editor: Filipodia

P-Editor: Zheng XM

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