Annals of Hepatology 28 (2023) 101123

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Editorials

# Gut dysbiosis in alcoholic liver disease: Wonderful dilemma?

ARTICLE INFO

*Keywords:*
Gut microbiota
Liver disease
Cirrhosis
Ecosystem

The gut microbiota can be briefly described as an ecosystem crowded by several forms of life and in particular bacteria, viruses, archaea, protozoa, fungi and yeasts. According to its differentiated composition, we can recognize digestive, metabolic and immune-modulatory functions [1].

More than 3 million of deaths every year result from harmful use of alcohol, and this represents the 5.3% of all deaths worldwide. In particular, the highest percentage is secondary to digestive diseases (21%) and more than 90% of these are secondary to liver cirrhosis [2]. The spectrum of alcoholic liver disease (ALD) ranges from simple steatosis to cirrhosis. Usually, the histological stages of ALD can be stratified in three parts: simple steatosis, alcoholic hepatitis (AH), and chronic hepatitis with fibrosis or cirrhosis. In this setting, alcohol consumption modulates the composition of gut microbiota with intestinal bacterial dysbiosis [3]. In addition, in drinker subjects the gut dysbiosis can also be explained by low dietary intake and poor quality diet [4].

ALD dysbiosis, is represented by a significant reduction of Bacteroids and an increase in Proteobacteria [5]. Also, has been described in literature that patients with alcohol-related cirrhosis have a reduction in some species as *Bifidobacterium spp*, *Clostridiales XIV*, *Lachnospiraceae*, *Lactobacillus spp*, *Ruminococcaceae*, and an increase in Enterobacteriaceae, including *Bacteroidaceae* and *Escherichia coli* [6].

Alcohol ingestion has been shown to disrupt the gut barrier, to increase intestinal permeability, and to induce bacterial translocation. Consequently, the deranged intestinal permeability can pathologically allow the passage of entire or fragments microbial antigens in the blood stream. Then, there is the beginning of a systemic micro-inflammatory cascade ending into the liver. This cascade is typical of ALD patients. Heavy drinkers, binge drinkers and ex-drinkers with liver cirrhosis can share the common destiny of mutagenic process involving in the hepatocarcinogenesis [7].

Thus, the interaction between gut dysbiosis and ALD is finer than expected. Running the factors responsible for gut dysbiosis in ALD, there are: diet, alcohol and its metabolite as acetaldehyde, reduced gastrointestinal motility and immune system down-regulation within the liver and gut, last but not least, altered bile acids flow and metabolism [8]. The latter have got more and more importance in ALD pathophysiology. They are mainly involved in lipid metabolism but directly affect the synthesis of antimicrobials molecules through the induction of the nuclear farnesoid receptor X (FXR) expression within the enterocytes [9]. This results in even more impaired intestinal permeability.

However, the tale about dysbiosis and ALD is not new. Specifically, there is updated evidences on the precise interaction between liver disease stage, alcohol and other factors. Patients with alcoholic cirrhosis not currently drinking had a worse gut dysbiosis vs. drinkers but without liver cirrhosis [8]. In detail, this dysbiosis had increased abundance of *Enterobacteriaceae* and decreased *Lachnospiraceae* and *Ruminococcaceae*. These findings are interesting as they support the hypothesis that ALD-associated dysbiosis runs despite abstinence. Reinforcing this data, it has been described that patients with liver cirrhosis and active drinkers have a worse dysbiosis accompanied by increased secondary bile acids pool and enterohepatic circulation vs. healthy subjects or liver cirrhosis patients on crawing [10]. Dubinkina et al. showed that, irrespective of liver cirrhosis, commensal microbial taxa were decreased because of alcohol intake. Intriguingly, it was reported a greater increase in levels of oral-origin microbiota. Also, Lactobacillaceae were more abundant in the feces of liver cirrhosis patients only. Starting from this last evidence, investigators hypothesized the potential use of Lactobacillaceae probiotics to treat ALD [11].

In alcoholic hepatitis, dysbiosis is different. The translational analysis by Llopis et al. in patients with different degree of ALD, reported increased abundance of pathogenic families of Enterobacteriaceae and Streptococcaceae [11]. Secondary bile acids were also increased according to alcoholic hepatitis severity. This feature was the same described in actively drinking patients with cirrhosis without alcoholic hepatitis. Furthermore, Grander et al. showed that the relative abundance of *Akkermansia muciniphila* was lowest in patients with alcoholic hepatitis, within their intestinal mucous layer [12]. Finally, Fusobacteria abundance within the blood circle was higher in ALD patients with active alcohol intake vs. healthy subjects. However, this abundance was lower in ALD patients with severe alcoholic hepatitis vs. with moderate or absent hepatitis.

As gut microbiota is composed by several species of microorganisms other than bacteria, we must recognize that patients with advanced liver cirrhosis have a high risk of fungal infections. The latter can, in turn, affect gut dysbiosis. From an animal model point of view, alcohol intake is able to induce fungal overgrowth from *Candida* spp.) which is significantly correlated with worse liver damage [13]. Interestingly, fungal cell wall $\beta$-glucan was able to generate liver

https://doi.org/10.1016/j.aohep.2023.101123

inflammation through binding the C-type lectin-like receptor CLEC7A localized on Kupffer cells.

From a human data point of view, ALD patients have higher susceptibility and related huge immune response to intestinal fungi compared vs. healthy subjects and, interestingly, patients with non-alcoholic liver cirrhosis. In a further study on patients with ALD-related liver cirrhosis, fecal fungal microelements diversity was significantly correlated with bacterial diversity [14]. From a practical point of view, the ratio of Bacteroidetes to Ascomycota was a biomarker for hospital readmission risk.

The study and analysis of the gut microbiota in ALD patients and its relationship is fascinating and still to be updated by researchers worldwide.

## Declaration of interests

None.

## References

[1] Mori H, Svegliati Baroni G, Marzioni M, Di Nicola F, Santori P, Maroni L, Abenavoli L, Scarpellini E. Farnesoid X receptor, bile acid metabolism, and gut microbiota. Metabolites 2022;12(7):647. https://doi.org/10.3390/metabo12070647.
[2] Huang DQ, Mathurin P, Cortez-Pinto H, Loomba R. Global epidemiology of alcohol-associated cirrhosis and HCC: trends, projections and risk factors. Nat Rev Gastroenterol Hepatol 2023;20(1):37–49. https://doi.org/10.1038/s41575-022-00688-6.
[3] Bajaj JS. Alcohol, liver disease and the gut microbiota. Nat Rev Gastroenterol Hepatol 2019;16(4):235–46. https://doi.org/10.1038/s41575-018-0099-1.
[4] Philips CA, Schnabl B, Bajaj JS. Gut microbiome and alcohol-associated liver disease. J Clin Exp Hepatol 2022;12(5):1349–59. https://doi.org/10.1016/j.jceh.2021.12.016.
[5] Lang S, Schnabl B. Microbiota and fatty liver disease-the known, the unknown, and the future. Cell Host Microbe 2020;28(2):233–44. https://doi.org/10.1016/j.chom.2020.07.007.
[6] Jung JH, Kim SE, Suk KT, Kim DJ. Gut microbiota-modulating agents in alcoholic liver disease: links between host metabolism and gut microbiota. Front Med (Lausanne) 2022;9:913842. https://doi.org/10.3389/fmed.2022.913842.
[7] Méndez-Sánchez N, Valencia-Rodriguez A, Vera-Barajas A, Abenavoli L, Scarpellini E, Ponciano-Rodriguez G, Wang DQ. The mechanism of dysbiosis in alcoholic liver disease leading to liver cancer. Hepatoma Res 2020;6:5. https://doi.org/10.20517/2394-5079.2019.29.
[8] Kong B, Zhang M, Huang M, Rizzolo D, Armstrong LE, Schumacher JD, Chow MD, Lee YH, Guo GL. FXR deficiency alters bile acid pool composition and exacerbates chronic alcohol induced liver injury. Dig Liver Dis 2019;51(4):570–6. https://doi.org/10.1016/j.dld.2018.12.026.
[9] Mori H, Svegliati Baroni G, Marzioni M, Di Nicola F, Santori P, Maroni L, Abenavoli L, Scarpellini E. Farnesoid X Receptor, Bile Acid Metabolism, and Gut Microbiota. Metabolites. 2022;12(7):647. https://doi.org/10.3390/metabo12070647.
[10] Fairfield B, Schnabl B. Gut dysbiosis as a driver in alcohol-induced liver injury. JHEP Rep 2020;3(2):100220. https://doi.org/10.1016/j.jhepr.2020.10022.
[11] Dubinkina VB, Tyakht AV, Odintsova VY, Yarygin KS, Kovarsky BA, Pavlenko AV, Ischenko DS, Popenko AS, Alexeev DG, Taraskina AY, Nasyrova RF, Krupitsky EM, Shalikiani NV, Bakulin IG, Shcherbakov PL, Skorodumova LO, Larin AK, Kostryukova ES, Abdulkhakov RA, Abdulkhakov SR, Malanin SY, Ismagilova RK, Grigoryeva TV, Ilina EN, Govorun VM. Links of gut microbiota composition with alcohol dependence syndrome and alcoholic liver disease. Microbiome 2017;5(1):141. https://doi.org/10.1186/s40168-017-0359-2.
[12] Grander C, Adolph TE, Wieser V, Lowe P, Wrzosek L, Gyongyosi B, Ward DV, Grabherr F, Gerner RR, Pfister A, Enrich B, Ciocan D, Macheiner S, Mayr L, Drach M, Moser P, Moschen AR, Perlemuter G, Szabo G, Cassard AM, Tilg H. Recovery of ethanol-induced Akkermansia muciniphila depletion ameliorates alcoholic liver disease. Gut 2018;67(5):891–901. https://doi.org/10.1136/gutjnl-2016-313432.
[13] Bajaj JS, Reddy RK, Tandon P, Wong F, Kamath PS, Biggins SW, Garcia-Tsao G, Fallon M, Maliakkal B, Lai J, Vargas HE, Subramanian RM, Thuluvath P, Thacker LR, O'Leary JG. Prediction of fungal infection development and their impact on survival using the NACSELD cohort. Am J Gastroenterol 2018;113(4):556–63. https://doi.org/10.1038/ajg.2017.471.
[14] Sokol H, Leducq V, Aschard H, Pham HP, Jegou S, Landman C, Cohen D, Liguori G, Bourrier A, Nion-Larmurier I, Cosnes J, Seksik P, Langella P, Skurnik D, Richard ML, Beaugerie L. Fungal microbiota dysbiosis in IBD. Gut 2017;66(6):1039–48. https://doi.org/10.1136/gutjnl-2015-310746.

Ludovico Abenavoli*
Emidio Scarpellini
*Department of Health Sciences, University Magna Graecia, Catanzaro 88100, Italy*
*Translationeel Onderzoek van Gastro-enterologische Aandoeningen (T.A. R.G.I.D.), Gasthuisberg University Hospital, KU Leuven, Herestraat 49, Leuven 3000, Belgium*

*Corresponding author.
*E-mail address:* l.abenavoli@unicz.it (L. Abenavoli).