In the quest for treating alcohol liver disease

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eBioMedicine 2022;81: 104086
Published online xxx
https://doi.org/10.1016/j.ebiom.2022.104086

Alcohol-associated liver disease (ALD) is the leading cause of chronic liver disease.[1] While the majority of patient with alcohol use disorder only develop steatosis (90%), only a minority progress to more severe forms of liver disease (hepatitis and fibrosis) and its related complications (10-20%).[2] There is no specific drug approved for treatment of ALD and some highly selected patients with severe or evolved forms of ALD can be referred for liver transplantation. However, in patients with less severe ALD or non-eligible for liver transplantation there is no specific efficient therapy except alcohol withdrawal. Among the new therapeutic targets that have gained interest in the last years, modulation of intestinal microbiota and microbial derived metabolites have shown promising results in animal models of ALD. Inulin, a prebiotic, promotes the growth of beneficial bacteria such as *Bifidobacterium* and *F. prausnitzii,* two beneficial bacteria that are decreased in alcoholic use disorder (AUD) patients. [3,4]

In a recent issue of *eBioMedicine*, Amadieu et al.[5] published the results of a pilot, randomized, double-blind, placebo-controlled study in which the gut microbiota of AUD patients was modulated using a 3-weeks inulin supplementation during a period of abstinence.

Inulin supplementation did not improve liver damage, microbial translocation, and inflammatory markers over abstinence alone, neither in the whole population of AUD patients nor in a subgroup of patients suffering from early alcohol-associated liver disease, stratified according to clinical parameters. The authors observed even a less pronounced reduction of AST, ALT and IL-18 in patients supplemented with inulin as compared to placebo (maltodextrin). However, inulin supplementation induced different changes in gut microbiota composition including increased of the relative abundance of *Bifidobacterium* and *Dialister* and decreased *Bacteroides, Ruminococcus torques* group, Dorea and *Eubacterium ruminantium* group.

While the study did not find any improvement in ALD surrogate markers after inulin intake, the study was not designed to answer this question. This was a pilot study aimed to increase insight in the feasibility of such an intervention and provide preliminary data in order to decide if a confirmatory, thus longer and more expensive interventional trial would be interesting. Having this in mind, the calculation of the sample size was based on the bifidogenic effect of inulin, hypothesizing that an increase in *Bifidobacterium* will improve ALD. Therefore, the study is underpowered and is impossible to draw conclusions concerning the effect of inulin supplementation on ALD or its surrogate markers. However, inulin increased *Bifidobacterium* levels in all groups.

To reduce potential gastrointestinal side effects, the dose of inulin increased gradually to reach 16g of inulin. If the targeted dose is 16g, the patients were exposed to this dose for only 5 days (from day 15 to day 19 of the detoxification program) and therefore we could argue that this period is too short to observe an effect on the liver function irrespective of the increase level of *Bifidobacterium*. Moreover, a large number of patients relapsed to drinking (48% in the inulin group). The liver may need a longer period to recover and to reflect this in surrogate markers such as transaminases or inflammatory cytokines. In addition, as the intestinal microbiota may be involved in relapse, an increase in the treatment duration should be considered in further studies.

ALD is a complex disease and the changes observed in intestinal microbiota and its metabolites are not only limited to *Bifidobacterium*. ALD related microbial changes also include changes in *Bacteroides*, in both ALD patients and animal models of ALD.[6-8] Using other types of fibres such as pectin, capable of restoring *Bacteroides* levels, it is possible to alleviate experimental ALD. In the present study inulin supplementation decreased *Bacteroides* levels in the early ALD group. Therefore, the lack of effect could also be related to this imbalanced between *Bifidobacteria* and *Bacteroides*. Intervention combining different fibre types, with different effects on the intestinal microbiota should be conducted rather than focusing on a single fiber type. This strategy is also supported by preliminary, phase 1

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2022.104033

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studies that used interventions with a broader effect on intestinal microbiota, such as the faecal microbiota transplantation. These studies have shown biological and behavioral effects in the FMT groups but were conducted in patients with advanced ALD (cirrhosis or severe hepatitis).[9,10]

An unanticipated result of the study of Amadieu et al, is the increase in IL-18 levels in inulin supplemented subjects at the end of the intervention. This increase was not correlated with any changes in microbial composition. The authors hypothesized a potential link to *Bifidobacterium* that might produce alcohol. Nevertheless, the broad changes that inulin induces at both the microbial and metabolomic levels could mediate a paradox effect such an increase in pro-inflammatory cytokines and further investigations would be needed if this result is confirmed in longer studies.

Despite the lack of effect on liver damage in ALD, the study of Amadieu et al. is critical as it offers preliminary data that will help to better design, select and evaluate patients in further microbiome editing interventions in ALD patients.

Contributors

Both authors contributed equally to this commentary.

Declaration of interests

The authors have no potential conflicts of interest to disclose.

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