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Review Article

Intestinal Microbiota Transplantation and Chronic Alcoholism

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Abstract

Numerous articles appear in world literature on various conditions that can be modulated with intestinal microbiota transplantation, with no exception being a topic as transcendent as chronic alcoholism and its different complications. Highlighting alcoholic hepatitis and alcohol-nutritional liver cirrhosis. This has motivated us to carry out a review, although small, in order to evaluate the different trends of the effect of microorganisms on frequent or rare conditions, becoming a new strategy, not insignificant.

The increase in alcohol consumption has impacted the most serious process of liver disease: "Alcoholic hepatitis". As the number of cases increases, on the one hand good medical action is made difficult, and on the other hand morbidity and mortality are increased, which puts us in an uncomfortable position in the face of this growing number of cases. Fortunately, evidence is growing that many chronic alcoholic liver diseases have a close connection with the intestinal microbiota.

Keywords: *Chronic Alcoholic Liver Disease (CALD); Alcoholic Hepatitis (AH); Microbiome (M); Intestinal Microbiota (IM); Fecal Microbiota Transplantation (FMT)*

Introduction

Effects of alcohol

Chronic alcoholic liver disease (CALD) has a reciprocal influence with the patient's genetics (microRNA), as well as with environmental and epigenetic factors. Facts to take into account, since more than two billion people in the world consume alcohol. Of these, around 75 million are classified as alcoholic disorders. Its severity is driven by the amount ingested, duration, sex, age and obesity [1].

Alcohol disturbs the function of the intestinal barrier, stimulating the translocation of microbial lipo-polysaccharides towards the liver and portal circulation, developing dysbiosis, and it is possible that biotics and fecal microbiota transplantation (FMT) reduce this effect. Without specifying whether the incidence on the intestinal microbiome (M) is an effect or a cause [2].

It has been noted that specific dysbiosis contributes to the presence of alcoholic hepatitis (AH). This fact was confirmed in mice, when an increase in hepatic T lymphocytes and natural killer T lymphocytes was observed, and as a consequence an increase in capillary permeability, liver necrosis and bacterial translocation, as well as CD45+ and CD4+ T lymphocytes.

A second FMT regenerated the liver conditions caused by alcohol [3].

On the other hand, in chronic alcoholic liver disease (CALD), immunological involvement of the mucosa is observed, associated with dysfunction of the intestinal microbiota (IM). The benefits of FMT are increasingly recognized more categorically [4].

CALD generate numerous disorders, among which AH, breast cancer, colorectal cancer, upper digestive tract cancer, alcohol-nutritional liver cirrhosis and dementia stand out. And it also produces beneficial effects such as the prevention of cardiovascular disease; as long as 14 drinks per week in women or 21 drinks per week in men are not exceeded (United Kingdom-Denmark) [5]. The cardio-protective effect being better in older people. The clinical guidelines point out that abstinence from alcohol, pentoxifylline and corticosteroids, as well as from surgical procedures, is the gold standard in the treatment of CALD.

Intestinal dysbiosis

These alterations in the structure of commensal communities are extremely frequent and are detected in various conditions, which is why they are considered to contribute to different pathologies. It is made up of *Firmicutes* and *Bacteroidetes* as the most frequent, as well as *Actinobacteria* and *Proteobacteria*, small in number, more persistent in all individuals [6]. A transcendent example is what happens in inflammatory bowel disease (IBD); Even when not fully knowing how he acts. Dysbiosis is very frequently present in M sequencing studies. It occurs when bacterial homeostasis is disrupted and there are 3 types: 1) Depletion of beneficial bacteria, 2) Excessive production of potentially pathogenic bacteria and 3) loss of diversity [7]. In summary, CALD generates quantitative and qualitative alterations, such as: mucosal inflammation, intestinal barrier disorders and the most significant alteration in the taxonomic composition of IM.

Human microbiome and severe alcoholism

IM can intervene in the growth of CALD complications. A decrease in *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* was observed, as well as an increase in *Enterobacteriaceae*. And in the phylum, more *Proteobacteria* and less *Bacteroidetes*. Concluding, that the effects of IM, linked to dysbiosis, are very similar in all studies [8]. IM distinguishes alcohol consumption from AH, although it does not differentiate the severity of the condition. The differential abundance of the families *Ruminococcaceae, Veillonellaceae, Lachnospiraceae, Porphyromonadaceae* and *Rikenellaceae* are responsible for the existence of a different signature in AH than that found in heavy alcohol consumers [9].

Intestinal bacterial endotoxins contribute to the generation of tissue lesions, as well as organ failure. Likewise, chronic intake affects M, causing the inflammatory status and endotoxemia, with a decrease observed with the administration of non-absorbable antibiotics or *Lactobacillus* [10].

The deregulation of metabolism, due to the presence of alcohol in the intestine, leads to colon carcinogenesis. IM is known to reconcile immune responses at the intestinal mucosal surface and instigate the presence of pro-inflammatory T helper 17 and regulatory T cells in the intestine. Possessing a positive effect in reversing obesity and hepatic steatosis [11].

Gut-microbiota-brain axis

This axis has been considered, as it is used by microorganisms, and can affect behavior with alcohol addiction [12].

IM and its metabolites have been identified as significant in the pathophysiology of chronic alcohol intake [13]. The gut-microbiota-liver-brain axis is a bidirectional information interaction system between the central nervous system (CNS) and the gastrointestinal tract, in which IM plays a key role.

Gorky K [14] through an interesting article, he reports how the neuroprotective vagal afferent signal is modulated, and the neuroinflammatory effects that occur in the amygdala, involving microglia and astrocytes, with an effect on neural cells. Likewise, it confirms the communication of the brain through vagal afferents, with the involvement of the nodose ganglion.

To date, the affectation of the physiology of the neurochemical phenotype and neuronal function, as an effect of bacterial modifications, has been established.

Now, it is not yet fully understood how the devices underlying the gut-microbiota-liver-brain axis occur, and it has been pointed out that dysbiosis itself and increased permeability in the intestine are involved. This last phenomenon is known as "leaky gut" [15].

It is good to know that alcohol consumption usually generates changes in the composition of the M, even before liver disease develops, which gives us enough time to act to correct it, perhaps, using the function of microorganisms, above all, the related to bile acids [16]. Nor should we omit that the intestine-microbiota-liver-brain axis can be used as a system to reduce the frequent relapse into alcoholism, considering that these patients are not candidates for liver transplantation. On the other hand, in this axis, the systemic chronic low-grade inflammation generated by alcohol consumption is the cause of cognitive disorders [17]. Therefore, it is worth keeping IM in eubiosis, since otherwise, there will be liver and intestinal conditions and neuroinflammation. The axis is part of the development of numerous diseases and can be used for their treatment [18].

Function of the intestinal barrier in severe liver disease

Knowing that the integrity of the intestinal membrane is vital for the M, and the immunological interactions it carries out, we must take care of it to avoid the inflammatory process and the passage of pathogenic organisms and toxins, associated with polysaccharides. The interaction is carried out between the local immune system, the intestinal epithelium and inflammatory cells.

By strengthening the intestinal barrier we prevent bacterial translocation from appearing, as microorganisms pass to the lymph nodes of the mesentery, to the blood circulation and to sterile, extra-intestinal places. Translocation is common in CALD, due to involvement of the intestinal barrier and increased permeability, laying the foundation for the presence of bacterial peritonitis, infections, hepatorenal syndrome, bleeding from esophageal varices, hepatic encephalopathy and hepatocellular carcinoma [19].

Accepting that the processes that generate alterations in bacterial diversity and consequently host function are not yet completely known, and that we require more studies aimed at this knowledge, we can bring together current understandings to guide the process, since articles will surely appear that elucidate the pathophysiology. The intestinal barrier is the initial defense, preventing bacteria and their byproducts from passing through to the lamina propria, where dendritic cells act. Although the above is known, IM disorders that alter function in the host have not been fully determined [20].

Physical activity, as well as diet, intervenes in the condition of the intestinal barrier and when this occurs, changes in bacterial species such as: *Roseburia, Streptococcus* and *Rothia* have been found [21].

Alcoholic hepatitis

Modifications of IM alter the enterohepatic circulation of bile acids and influence the appearance of acute and chronic liver disorders. Likewise, dysbiosis and alteration of the intestinal barrier, with its consequent deterioration in intestinal permeability, play a significant role in these processes. Such is the case of AH, in which patients with massive alcohol intake generate cognitive deterioration, a tendency towards drug addiction and anxiety, prior to the appearance of the terrible disease, as well as high mortality in the first ninety days [22].

AH has several facets of treatment. In the initial process, FMT, as well as the administration of biotics (*Bifidobacteria* and *Lactobacilli*), increase beneficial bacteria, with a decrease in depression and anxiety. Clustered regularly interspaced short palindromic repeats (CRISPR) may be another possible research target [23].

In more severe cases of AH, several therapies have been considered, including corticosteroids, nutritional therapy, pentoxifylline and FMT, observing that after transplantation beneficial modulation of M, deregulating inflammation, infections and oxidative stress [24]. Improvement is evidenced by a decrease in bilirubin, sodium and, as an excessive alteration, the amount of flatus [25]. Comparing the treatment between prednisone and FMT, they are very similar in the first 28 days, but from that moment on, FMT far surpasses the use of corticosteroids, new taxa appearing, with a reduction of pathogens such as *Campylobacter* and anaerobes; For this reason, FMT is considered a good alternative in severe AH [26].

Short chain fatty acids and alcoholic hepatitis

In CALD, short chain fatty acids (SCFA) producing microorganisms, such as *Lachonospiraceae* and *Ruminococcaceae*, tend to decrease, reducing the positive effect of the intestinal barrier and permeability; Therefore, the use of SCFA has been considered as therapy in these conditions. Pohl K, and his group [27], reviewed the impact of SCFA in studies -most of them in animals, on the problem and concluded that better permeability is observed and all with improvement in the condition in the liver. While Zhang T [28] and his group observe in nonalcoholic fatty liver disease, butyrate improves hepatic inflammation and steatosis. Visekruna V and Luu M [29], include the effect of secondary bile acids, supporting the hypothesis that the metabolites of commensal microorganisms affect carcinogenesis and growth of inflammation, acting as powerful modulators of immunity and metabolism. While secondary bile acids exert specific action on immune and innate responses [30].

Alcohol-nutritional liver cirrhosis and alcoholic hepatitis

There is universal recognition of alcohol toxicity, developing hepatic steatosis, up to AH, with histological modifications, such as the presence in hepatocytes of hyaline cytoplasmic inclusions, mega-mitochondria and peri-sinusoidal and peri-venular fibrosis [31].

In CALD, malnutrition severely affects the development of various conditions related to excessive alcohol intake, affecting cognitive potential. The process has various aspects and includes: increased protein catabolism, abnormal linkage between lipid metabolism and ethanol, inadequate intake, and abnormal digestion and absorption. Many of these patients present metabolic syndrome, which requires subtlety in management. If the problem persists, it can be complicated by malnutrition and sarcopenia [32]. In addition, there is immunological deficiency of the intestinal mucosa, which is linked to IM alteration, making the use of FMT imperative [33]. Considering that many liver diseases have a basis in IM itself; For this, the dysbiosis index has been determined: *Lachnospiraceae* + *Ruminococcaceae* + *Veillonellaceae/Enterobacteriaceae* + *Bacteroidaceae*, support that predicts risks of decompensation. Remembering that proton pump inhibitors increase dysbiosis [34].

Steroids and serious liver conditions

There is controversy in the management of corticosteroids in severe liver conditions [35]. Xue R and Meng O [36] they state that the process that causes insufficiency is excessive systemic inflammation and that steroids usually improve inflammation and the immune

response, although their mechanism of action is discreetly explained, as is the case with recent studies of their molecular mechanisms. Corticosteroids reduce early deaths in patients with severe AH. Maddrey WC and her group [37] study 55 patients with AH and point out that the lengthening of prothrombin time and serum bilirubin leads to a decrease in mortality. Concluding that steroids reduce early mortality, without effect in late time, or the development of portal hypertension. Initially, the therapy of mild AH is aimed at stopping drinking alcohol, although, to date, there is no definitive management of the serious condition and the use of corticosteroids is contradictory, and with them, the risk of infection. Concluding that corticosteroid therapy has an adequate effect at the beginning, but once the process is established, there are usually no beneficial results. In addition, they are partially contraindicated in severe liver disease, gastrointestinal bleeding, pancreatitis and sepsis. For all these reasons, we are beginning to resort to the modulation of the innate immune system, or the inhibition of the intestine-microbiota-liver-brain axis [38].

Steroids and intestinal microbiota

If we point out that steroids carry out a significant action in the configuration of IM and in the host's immunity, we would perhaps be a little risky, although there are research works that determine this, for example that of Smirnova E and her group [39] who delve into the appreciation that the action of the IM in the AH has not yet been instituted.

Finding in the CALD depletion of *Bacteroidetes* and increase of: *Ruminococcaceae, Veillonellaceae, Lachnospiraceae, Porphyromonadaceae* and *Rikenellaceae*. While the AH had a greater number of *Proteobacteria*. SCFA producing microorganisms, such as *Lachnospiraceae* and *Ruminococcaceae*, showed a similar decrease to fecal SCFA. And they conclude that changes in IM are observed in the development of the condition, but not with its severity.

Glucocorticoids have a profound impact on immunity. And they do so through anti-inflammatory and immunosuppressive effects on adaptive and immune processes. They usually affect innate immunity, and improve adaptive immunity. Previous conditions shared by Ikuta K and her group [40]. They add that corticosteroids cancel the production of inflammatory cytokines by macrophages and the generation of IFN-and NK cells.

Steroids and fecal microbiota transplantation

Supporting the effect of corticosteroids on AH, another article, that of Pande A, and his group [41] report that prednisone shows small positive effects, showing mainly in the first 28 days, but not at 90, reducing the infectious processes due to the positivity of modulation by microorganisms; Therefore, the FMT must be considered, to which they reveal a positive impact. Same conclusions as observed by Kakihana K and her group [42], which add up to the same thing that occurs in the acute reaction in patients, with graft versus host, in stem cell transplantation.

Huang C and his team [43] report a comparative study between steroids and FMT in patients with inflammatory bowel disease and conclude that FMT is as effective as steroids for the remission of this condition and that the changes in TNF-α, IL-6 and IL-10, in blood would be achieved due to the effectiveness of the transplant.

There are other studies such as that of Cui B [44], in which the relationship between IM and excessive alcohol intake is reiterated, pointing out that the determination of metabolomes and microbiomes could be tests susceptible to diagnosis. Likewise, these studies can guide inflammatory processes, contributing to the death of hepatocytes and fibrosis.

They add that it is significant that microorganisms have 3 million genes, while there are only 23,000 at the cellular level. And it is worth delving deeper into the effect of FMT, biotics and antibiotics.

Antibiotics

Louvet A [45], and his group point out that in AH treated with prednisone and amoxicillin-clavulanate, survival at 2 months does not improve. They add: "The benefits of prophylactic antibiotics for hospitalized patients with severe alcohol-related hepatitis are unclear". Intestinal dysbiosis may limit the effect of paromomycin in CALD [46]. In a study related to fluoroquinolones, the diversity of IM decreased, with *Bacteroidetes* increasing, with an increase in pathogenic bacteria [47]. And it is concluded that antibiotics do not improve AH.

Biotics in alcoholism

Various studies indicate that modulation of IM through biotics or FMT are useful in patients with CALD. Reiterating that probiotics produce antimicrobials and also have an anti-inflammatory effect, improving the function of the intestinal barrier, through the development of its epithelium. They also modulate the immune system, blocking the release of cytokines, such as TNF-α, and stimulating the production of anti-inflammatory cytokines such as IL-10 and TGF-β.

To date, there is no approved therapeutic, and the use of probiotics has become attractive to researchers [48]. Gu Z, and his group [49], determine that both in animals and in patients with massive alcohol intake, biotics act positively and increase the β-oxidation of fatty acids, reducing lipogenesis and combating induced hepatic steatosis for alcohol. Highlighting *B. bifidum, L. plantarum 8PA3* and *Lactobacillus rhamnosus* GG.

Fecal microbiota transplantation

This procedure is becoming more accepted every day, due to the ease of performance, the minimum of complications, as well as its impact on modulation. Likewise, the establishment of non-pathogenic microorganisms is positive. And finally, bacteriocins are produced. There is competition against *C. difficile*, and intestinal membrane permeability is remedied [50]. It has been reported that invariant mucosal T cells are disrupted in severe AH. Being a probable cause of bacterial infections, due to its exhaustion. MAIT cells driven by IM generate positive actions within the FMT [51,52]. Because not all patients with AH are susceptible to management with corticosteroids, the possibility opens up for FMT or biotics to be used, since both reduce intestinal dysbiosis, a process that occurs in CALD [53]. In mice, FMT has been encouraging, with improvement in the condition in humans in initial studies, especially in AH, with better acceptance and minimal side effects [54].

Suk KT [55] reiterates that SIBO, increased intestinal permeability, dysbiosis, bacterial translocation and metabolite imbalance increase chronic liver disease, with good results from FMT, even when evidence is lacking.

Paratore M and his group [56] emphasize the relationship between IM and health effects and determine that by tuning M, homeostasis and health trends improve. And that FMT is one of the main vectors of the fact, by improving the recipient's intestinal microorganisms.

Conclusion

- More than two billion people in the world consume alcohol, which makes the process important in relation to health.
- A second FMT regenerates liver conditions caused by alcohol.
- Intestinal dysbiosis is linked to CALD.
- Intestinal bacterial endotoxins contribute to the generation of tissue lesions, as well as organ failure.
- The intestine-microbiota-liver-brain axis is a bidirectional system between the central nervous system and the gastrointestinal tract, in which IM is transcendent.
- If we strengthen the intestinal barrier we prevent bacterial translocation from appearing.

- Alterations of the intestinal M alter the enterohepatic circulation of bile acids and influence the appearance of acute and chronic liver disorders.
- If management is compared between corticosteroids vs. FMT, the latter is usually more favorable.
- AH treated with prednisone and amoxicillin-clavulanate does not improve survival at 2 months.
- The multiple physiology induced by biotics in chronic liver diseases makes this therapy relevant.
- SIBO, increased intestinal permeability, dysbiosis, bacterial translocation and metabolite imbalance increase chronic liver disease, with good results from FMT.

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