Probiotics as Potential Therapy in NAFLD

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Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease with an increasing prevalence, especially in Western countries. Supplementation with probiotics, live microorganisms, is a potential strategy for the management of NAFLD.

Keywords: steatosis ; dysbiosis ; fatty liver ; inflammation ; probiotic

1. Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is defined as the excessive fat accumulation in the hepatocytes, specifically triglycerides and free fatty acids, without abusive alcohol consumption as the principal cause [1][2][3]. NAFLD is directly related to obesity, hypertension, type 2 diabetes mellitus (T2DM), and dyslipidaemia, and thus it is considered the hepatic manifestation of metabolic syndrome (MetS) [4].

The estimated global prevalence of NAFLD is 25%. Specifically, the highest NAFLD prevalence is in the Middle East (32%) and South America (30%), and the lowest is in Africa (13%). The African prevalence could be biased because population surveys are rare on the continent. The prevalence in Europe is 24%, and in Spain, it is 20–29.9% [5][6]. Other references confirm that the global prevalence ranges between 20 and 30% [7]. In people with obesity, the NAFLD prevalence is 58–74% and 56% in people with T2DM [5]. Moreover, the prevalence of NAFLD increases with age and is more common in men, according to studies carried out in Spain, the United States, and southwest China [8][9][10].

Regarding liver histology, NAFLD has a slow evolution [5], but its pathological spectrum ranges from simple steatosis or fat accumulation in the liver (which tends to be asymptomatic), to more advanced diseases such as cancer or death. Steatosis can progress to steatohepatitis when the liver is inflamed, to cirrhosis when fibrotic lesions appear, and ultimately cancer. Steatosis and steatohepatitis are both reversible. They can be reversed by improving the lifestyle, but advanced stages of cirrhosis and cancer are irreversible. It should be noted that some people with steatohepatitis have developed cancer without the cirrhosis stage [11]. There is an increased risk of cardiovascular disease among patients with NAFLD, which also increases with the severity of the liver status [12][13]. In addition, subjects with NAFLD have an increased risk of death [14]. The mortality risk in subjects with NAFLD increases exponentially with the presence of liver fibrosis and its degree [15].

The first line of treatment for NAFLD is a lifestyle change, including diet and exercise, to reduce weight. Weight loss is very important to improve the NAFLD histopathological features. Nevertheless, pharmacological treatment is available for associated metabolic complications such as those related to T2DM, insulin resistance, obesity, and hyperlipidaemia. Pharmacological treatment is applied when a lifestyle change is not sufficient and/or when there is a clear diagnosis of fibrosis [16].

Thiazolidinedione (a ligand of the peroxisome proliferator-activated receptor gamma nuclear transcription factor (PPAR)-γ) reverses insulin resistance in the case of adipose tissue dysfunction, T2DM, and obesity in people with NAFLD [16]. Within the same drug family, Pioglitazone increases the plasma adiponectin levels, inhibits fatty acid synthesis in the liver, stimulates its oxidation, and promotes anti-inflammatory effects. Thus, Pioglitazone manages to improve the metabolic and histological profiles in people with fibrosis, T2DM, and NASH [17][18]. Vitamin E is also part of the treatment against NAFLD due to its antioxidant effects. It reduces inflammation, liver enzyme levels, and non-invasive fibrosis [19][20].

The best NAFLD treatment is actually the Mediterranean lifestyle, including a Mediterranean diet and regular physical activity, because it contributes to the improvement of MetS and a reduction in the NAFLD risk factors [21]. On the one hand, the Mediterranean diet is based on the intake of foods rich in antioxidants and anti-inflammatory compounds, fibre, and unsaturated fatty acids, and reduces the consumption of animal proteins and saturated fatty acids. Thus, the Mediterranean diet has benefits for cardiovascular disease, components of MetS, cancer, and overall mortality [22][23]. A

high adherence to the Mediterranean diet improves insulin resistance, fibrosis, and reduces liver fat evaluated through magnetic resonance imaging (MRI) [24]. On the other hand, an active lifestyle reduces high triglyceride levels and increases low-cholesterol–high-density lipoprotein (HDL) levels, helps with weight loss, and regulates blood pressure [25]. Thus, physical activity contributes to MetS, T2DM, and NAFLD positively [26][27]. Diet plus physical activity show better results in the improvement of NAFLD and its risk factors [28].

2. Microbiota and Probiotics in NAFLD

The WHO defines probiotics as “live microorganisms which when administered in adequate amounts confer a health benefit on the host”. Probiotics can have effects on several aspects of physiology, such as digestion, metabolism, and immunology. Moreover, probiotics can be presented as probiotic drugs, probiotic medical drugs, probiotic foods, non-oral probiotics, probiotic animal feed, probiotic dietary supplements, defined microbial consortia, and probiotic infant formula [29].

The probiotics in food and nutritional products can classically be classified into four large families: *Lactobacillus* species, *Bifidobacterium* species, other lactic acid bacteria, and non-lactic acid bacteria. The *Lactobacillus* genus has been one of the most studied, as it is a kind of probiotic commonly found in yogurt and yogurt-like products [30]. Nevertheless, the amount of CFU (colony-forming units) in common fermented yogurt and milk products may not reach the minimum for an adequate effect on the gut microbiome.

The microbiota refers to the microorganisms that colonize the human and animal body. Such microorganisms can be categorized according to their behaviour as commensals, mutualists, and pathogens. The microbiota frequently has specific functions for the organism and can be considered as an organ that impacts both health and disease. The initial colonization of the digestive system by microorganisms occurs due to the exposure of the offspring to the mother’s vaginal microbiome and changes through time according to the dietary intake in the adult microbiota [31]. The human gut microbiome is estimated to comprise between 10 and 100 trillion microorganisms, primarily bacteria [32]. Among the most common bacterial groups are Bacteroidetes and Firmicutes, while the majority of Archaea is Euryarchaeota [33].

Several diseases are related to dysbiosis in the intestinal microbes. As explained above, NAFLD is considered a systemic metabolic disorder, the result of the concomitant presence of NAFLD and metabolic syndrome. Components of the metabolic syndrome are related to dysregulation of the intestinal microbiota, as in NAFLD. NAFLD is related to some differences in the intestinal bacteria of humans, compared to healthy counterparts. In this sense, although the literature presents varied results of the changes observed in the microbiota in patients with NALFD compared to healthy patients, there is a certain uniformity in the bacterial signatures. The most consistent results describe an increase in the abundance of Proteobacteria and a decrease in Firmicutes at the phylum level [34]. At the family level, there is an increase in Enterobacteriaceae and a decrease in Ruminococcaceae and Rikenellaceae, and at the genus level there is an increase in *Bacteroides*, *Dorea*, *Escherichia*, and *Peptoniphilus* and a decrease in *Anaerosporobacter*, *Coprococcus*, *Eubacterium*, *Faecalibacterium*, and *Prevotella* [35][36]. Even in the early stages of NAFLD, dysbiosis in the gut microbial is present, which becomes more unstable with the NAFLD progression. At the most advanced stages of NAFLD or even cirrhosis, a very low number of beneficial bacteria can be found in the gut microbiome, but most importantly, potentially pathogenic bacteria are likely to be found [37]. This finding can be explained by people with NAFLD frequently following higher caloric dietary patterns [38]. High-fat diets are associated with gut dysbiosis by means of an increased intestinal epithelium permeability that occurs as a consequence of a disruption in both the mucus layer and the tight junctions. The result is an increased bacteria translocation and the presence in the portal venous system of bacterial products. As all blood from the gastrointestinal tract has to pass through the liver before entering the systemic circulation, the presence of bacterial products or bacteria in the portal blood increases the likelihood of bacterial liver colonization [39]. NAFLD itself, regardless of the diet, is also related to an increased intestinal permeability, which has been related to the induction of inflammatory pathways that contribute to NAFLD pathogenesis. The gut microbiome can induce the release of anti- or pro-inflammatory compounds [37]. Moreover, the gut microbes have an influence on triglyceride metabolism in the liver, nutrient absorption, and body metabolism by altering the content and type of several metabolites of proteins, fats, and bile acids. Some metabolites of the gut bacteria are related to the degree of steatosis and can induce fat accumulation in the liver [40]. It seems that the SCFAs (short-chain fatty acids) and polysaccharides synthesized by the gut bacteria are different in NAFLD than in healthy subjects. Both are crucial for the gut epithelium integrity and intrinsic immune defences. While SCFAs seem to promote NAFLD through some pathways, they are also beneficial as they regulate liver AMPK (adenosine 5′-monophosphate-activated protein kinase) activity [37]. Moreover, low-fat diets are related to healthier NAFLD and hepatic parameters, which can be related to the changes in gut epithelium permeability [41].

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