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THE ROLE OF PROBIOTIC, PREBIOTIC, AND SYNBIOTIC SUPPLEMENTS IN OBESITY AND NON-ALCOHOLIC FATTY LIVER DISEASE

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Abstract – Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of conditions from simple steatosis to non-alcoholic steatohepatitis (NASH) and liver cirrhosis. NAFLD is the hepatic manifestation of metabolic syndrome, in which obesity is a key contributor. Rates of obesity and NAFLD have escalated across the globe and have become a priority health issue, yet limited therapies are available for the prevention and treatment of this disease. Due to growing evidence of the influence of the gut microbiota in obesity and NAFLD through the 'gut-liver axis', studies have recently provided evidence for the role of pro-, pre- and synbiotics in the prevention and treatment of these conditions. These '*biotics*' appear to positively influence various pathogenic processes, including gut microbiota composition, intestinal permeability and translocation of harmful by-products, which influence hepatic fat metabolism, proinflammatory and fibrotic processes. In this review, we present data pertaining to the role of '*biotics*' as a potential novel and targeted therapeutic strategy in the management of obesity and NAFLD.

Keywords: Probiotic, Prebiotic, Obesity, Liver disease, Non-alcoholic fatty liver disease.

PROBIOTICS

Probiotics are live bacteria that are thought to confer a benefit to human health. Several studies have demonstrated beneficial effects of probiotics on gut microbiota composition in obesity and non-alcoholic fatty liver disease (NAFLD). Michael et al[1] demonstrated that supplementation of *Bifidobacterium* and *Lactobacillus* to a weight loss regime in overweight patients led to significantly greater weight loss and improved anthropometric measurements. Similarly, patients who were administered probiotics after Roux-en-Y gastric bypass surgery were shown to have a reduction in triglyceride levels compared to those who received placebo, whilst reductions in anthropometric measurements and glycaemic profile were observed in both study arms[2]. Breastmilk derived *Lactobacillus,* and *Bifidobacterium* added *in vivo* to fecal microbiota from an obese child led to a beneficial increase in alpha diversity and reduced abundance of pathobionts *Proteobacteria, Escherichia, Shigella and Clostridium sensu stricto*[3]. Nasiri et al[4] reported that the supplementation of a combination of alpha-lipoic acid and probiotics comprising of several *Lactobacillus* species, *Bifidobacterium* species and *Streptococcus thermophiles* led to a more significant weight loss, improvement in waist circumference and lower C-reactive protein (CRP) in overweight patients, compared to placebo or either of the supplementation alone.

However, a randomized controlled trial by Banach et al[5] showed that the addition of probiotic yoghurt containing *Lactobacillus acidophilus* and *Bifidobacterium lactis* to a hypocaloric diet did not induce greater weight loss than a hypocaloric diet alone. Similarly, patients with NAFLD randomized to receive probiotics or prebiotics (in addition to a weight loss diet and a physical activity regime) did not have improvement in anthropometric measurements compared to placebo; however, those in the pro- and pre-biotic arms did have greater reduction in serum triglyceride and liver enzymes compared to placebo[6]. *In vitro* administration of *Bifidobacterium, Lactobacillus* and *Lacticaseibacillus* strains to normal weight and severely obese study participants did not lead to major alterations in gut microbiota composition, and significant differences in abundance in stool were only seen in the species that were added[7]. However, the four *Bifidobacterium* strains and *Lacticaseibacillus rhamnosus GG* successfully induced differences in markers of intestinal integrity in obese individuals, nearing the values seen in normal-weight counterparts[7]. However, Schellekens et al[8] reported that while *Bifidobacterium longum* supplementation in mice successfully reduced body weight, fat accumulation and increased glucose tolerance, this effect was not observed in overweight and obese humans.

Studies in high-fat diet-induced obese/NAFLD animal models showed that various strains of *Bifidobacterium* and *Lactobacillus* ameliorated NAFLD by reducing weight gain and improving energy expenditure, lipid metabolism, insulin resistance, gut barrier integrity and gut dysbiosis. Improvements in microbiota composition, including *Firmicutes/Bacteroidetes* ratio, increased abundance of *Lactobacillus*, *Bifidobacterium* and *Akkermansia*, and decreased abundance of *Desulfovibrionaceae* were observed[9-18]. Metformin in combination with *Lactobacillus leuteri* and metronidazole was found to be more effective than metformin alone in improving insulin resistance, lipid profile, and liver steatosis and were associated with normalisation of short chain fatty acids (SCFAs) and faecal *Firmicutes* and *Bacteroidetes* abundance[19]. Similarly, *in vitro* study of *Lactobacillus fermentum* administration led to a reduction in lipid accumulation and intracellular triglyceride production in preadipocytes, mediated by upregulation of AMPK and HSL phosphorylation[20].

In rats with D-fructose-induced hepatic steatosis, beneficial effects of 3 strains of *Lactobacillus* as well as *Bacillus coagulans* on reducing hepatic and serum triglyceride levels and markers of hepatic oxidative stress were observed[21]. A study of various strains of *Lactobacillus* and *Pediococcus* as single species or in combination showed improvement in cholesterol profile, hepatic steatosis, and inflammation, as well as systemic inflammatory markers in most species[22]. Dioletis et al[23] reported that the fermented soy beverage Q-CAN was associated with a significant increase in stool *Bifidobacterium* and *Blautia* abundance in lean participants, with a trend for this in obese participants and a significant increase in oral *Veillonellaceae* family abundance in lean participants.

Administration of Akkermansia municiphila isolated from human stool samples to high fat diet (HFD) fed mice inhibited weight gain, hepatic steatosis and low-grade gut inflammation and improved glucose homeostasis and gut barrier integrity[24]. Akkermansia muciniphila in combination with environmental enrichment was also effective in reversing NASH-induced cognitive damage in mice, including impaired spatial working memory and novel object recognition, but the same was not observed with Lacticaseibacillus rhamnosus GG25. Depommier et al[26] reported that the beneficial effects of Akkermansia muciniphila are not related to an overall change in the endcannabinoidome in obese individuals, but on univariate analysis found Akkermansia muciniphila counteracts the decrease of two endocannabinoidome lipids 1-Palmitoyl-glycerol (1-PG) and 2-Palmitoyl-glycerol (2-PG), which are endogenous activators of peroxisome proliferator-activated receptor alpha (PPARα).

PREBIOTICS

Prebiotics are substrates (such as dietary fibre) that are selectively utilised by gut microbiota to confer a health benefit. Inulin, is one such prebiotic which when administered to obese patients led to a decrease in *Desulfovibrio* and *Clostridium sensustricto* abundance and were associated with weight loss, reduced diastolic blood pressure and lower aspartate transaminase (AST) and insulin levels compared to placebo[27]. Inulin was also associated with a beneficial ef-

fect on mood in obese individuals, with a higher likelihood of benefit observed, particularly in individuals with a higher gut abundance of *Coprococcus*, higher levels of inflammatory cytokine IL-8, insulin resistance and adiposity[28]. In animal models, inulin supplementation showed mixed results. Ghosh et al[29] showed that restricted active phase prebiotic feeding consisting of resistant starch, fructooligosaccharide, inulin and xylooligosaccharide in high-fat diet-fed mice led to a change in the gut microbiome composition, including an increase in *Bifidobacterium*, *Akkermansia* and *Lachnospiraceae* abundance. This was associated with a greater weight-independent reduction in liver steatosis and serum cholesterol and increased production of propionate in the caecum compared to mice with unlimited access to the prebiotic[29]. Bao et al[30] showed that dietary addition of 5 g/kg body weight inulin ameliorates NAFLD in HFD fed mice by modulation of gut microbiota and suppression of lipopolysaccharide-Toll-like receptor 4-Mψ-Nuclear factor-κB-nod-like receptor protein 3 inflammatory pathway. Albouery et al[31] demonstrated that diets containing 200 g of inulin, in HFD fed mice, modulates gut microbiota and hepatic fatty acid composition. However, in a metabolic syndrome rat model, while a diet containing 20% inulin ameliorated hepatic injury, hypertension, and cardiac injury, it appeared to worsen hypertriglyceridemia[32]. An earlier study by Singh et al[33] reported that prolonged feeding of inulin, while attenuating metabolic syndrome in mice, led to cholestatic liver dysfunction and was associated with increased incidence of hepatocellular carcinoma. Furthermore, Pauly et al[34] suggested that even short-term feeding of a diet containing high concentration of inulin (30%) to pathogen-free wild type mice for 12 days led to liver damage and cholestasis with significant disturbance to bile acid metabolism.

Intake of prebiotic dietary fibre inulin-type fructans in obese patients was associated with an increased abundance of *Bifidobacterium* and reduction in faecal calprotectin[35]. Lensu et al36 demonstrated that prebiotic xylo-oligosaccharides target *Faecalibacterium prausnitzii*, resulting in amelioration of HFD-induced hepatic steatosis and metabolites linked to NAFLD in mice. The authors previously reported that Faecalibacterium prausnitzii abundance was reduced in NAFLD patients[37]. Polydextrose also prevented the accelerated weight gain in mice on obesogenic diet and led to an increased abundance of *Bacteroides* compared to controls[38]. This may be associated with reduced colonic transit time as previously demonstrated in studies such as one by Hengst et al[39]. Abernathy et al[40] demonstrated prebiotic activity of polylactose in HFD-mice, with its administration leading to a greater increased abundance of *Bifidobacterium* compared to established prebiotics polydextrose and fructooligosaccharides and reduced liver lipids and cholesterol compared to positive controls. Wang et al[41] showed the prebiotic potential of water-soluble dietary fibre from walnut meal which improved gut dysbiosis with increased diversity and increased relative abundance of SCFA-producing genera while demonstrating anti-obesity and anti-steatosis effects. High β-glucan barley flour demonstrated prebiotic effects in HFD fed mice, increasing the abundances of *Bifidobacterium* and *Lactobacillus* and concentrations of SCFAs, with positive correlations with increasing anti-inflammatory IL-10 expression[42].

Some studies[43-46] reported beneficial effects of resveratrol on hepatic steatosis, with alleviation of steatosis, inhibition of gut inflammation, improved gut barrier integrity and restoration of HFD-induced gut dysbiosis in mice, specifically increased abundance of *Bacteroidetes, Akkermansia municiphila, Ruminococcaceae, Blautia,* and *Allobaculum* and decreased abundance of *Desulfovibrio, Lachnospiraceae*, *Firmicutes* and *Proteobacteria.*

SYNBIOTICS

Studies of combination of pro- and prebiotic, known as synbiotics, have showed mixed results in obesity and NAFLD. Abhari et al[47] showed that a 12-week supplementation with inulin plus *Bacillus coagulans* in NAFLD patients led to favourable outcomes with reduced hepatic steatosis score in FibroScan and a significantly greater reduction in alanine aminotransferase (ALT) and γ glutamine transaminase (GGT), inflammatory markers tumour necrosis factor α and nuclear factor-κB activity compared to placebo. Similarly, in a randomized controlled trial among obese women who underwent low energy diet, while all groups (supplementation of probiotic, symbiotic and control) had beneficial metabolomic changes with reduced glycerol, increased arginine, glutamine and 2-oxoisovalerate, the synbiotic group (*Bifidobacterium lactis* and fruc-

tooligosaccharides) also had increased pyruvate and alanine and decreased citrate and BCAA[48]. Additionally, 24-week supplementation of *Lacticaseibacillius paracasei*, *Bifidobacterium breve* and galactooligosaccharides in obese adults with type 2 diabetes increased the gut abundance of *Bifidobacterium* and *Lactobacilli* and fecal concentration of SCFAs acetate and butyrate, but did not alter IL-6 levels, a surrogate marker for chronic inflammation[49].

In HFD fed mice, co-administration of *Lactobacillus casei* and prebiotics (soluble fibres, plant extracts) reduced serum cholesterol levels, markers of liver injury and weight gain, and improved insulin sensitivity[50,51]. Hu et al[52] showed that a combination of resveratrol and *Bifidobacterium* had greater efficacy in the alleviation of biochemical and inflammatory markers of obesity and NAFLD in HFD fed mice.

The combination of *Bacillus licheniformis* and xylooligosaccharides also showed positive effects in HFD-induced obese rats with inhibition of weight gain and normalization of lipid metabolism, with modulation of gut microbiota composition, specifically the abundance of *Prevotellaceae, Desulfovibrionaceae* and *Ruminococcaceae*[53]. Combination of *Bacteroides uniformis* and fibre reduced weight gain and adiposity in obese mice and mitigated altered IL22 signalling and hepatic inflammation[54].

In contrast, in a double-blind, randomized controlled trial of 104 NAFLD patients, administration of synbiotic agent (containing fructo-oligosaccharides plus *Bifidobacterium animalis* subspecies *lactis*) improved the faecal microbiome with an increase in *Bifidobacterium* and *Faecalibacterium* species and decrease in *Oscillibacter* and *Alistipes* species but did not reduce liver fat or markers of liver fibrosis[55]. In a randomized controlled trial of children with NAFLD, synbiotic administration consisting of inulin, *Lactobacillus,* and *Bifidobacterium* did not have a significant beneficial effect on BMI or markers of hepatic steatosis or fibrosis compared to placebo[56].

POSTBIOTICS

Postbiotics are by-products (metabolites) of metabolic processes carried out by gut microbiota. Studies demonstrating the beneficial effects in obesity and NAFLD are limited. Administration of urolithins, which are gut microbiota-derived metabolites of ellagitannins, to HFD mice was associated with reduced body weight and improved serum lipid profiles, while attenuating the HFD-induced reductions in *Bacteroidia* and expansion in *Clostridia* at the class level[57]. Osman et al[58] reported that lipolytic postbiotic from *Lactobacillus paracasei* had greater effects at reducing total serum cholesterol and triglycerides compared to atorvastatin but did not improve liver function or liver histopathology in rats. Whilst these results are promising, further studies are required to evaluate the efficacy of postbiotics in obesity and NAFLD.

CONCLUSIONS

Dysbiosis associated dysregulation of metabolic and proinflammatory responses appear to play a key role in the pathogenesis of obesity and NAFLD. Studies have shown that multiple mechanisms are implicated in this process but key pathways that may be subject to manipulation through gut-based therapies are yet to be defined. Whilst data is limited, there are promising signals that *'biotics'* supplementation may improve metabolic and proinflammatory processes that drive obesity and NAFLD progression making this an attractive therapeutic option. However, well designed mechanistic and clinical studies are required to confirm the efficacy of *'biotics'* prior to their implementation in clinical practice.

Conflict of Interest

The authors declare no conflict of interest.

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Authors' Contribution

Manuscript preparation: CK, JB, AZ. Critical Revision: CK, JB, AZ.

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