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Probiotics: a possible role in treatment of adult and pediatric non alcoholic fatty liver disease

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Dear Editor:

Sir, we read with much interest the Concise Review by Doctors Machado and Cortez-Pinto on gut microbiota and nonalcoholic fatty liver disease (NAFLD) appearing in the July-August issue of Annals of Hepatology.[1] The Authors correctly pointed out that, based on preliminary experiments on different NAFLD animal models and different bacterial strains of probiotics, it would be expected that interventions which modulate intestinal microbiota may be beneficial also in human obesity related liver dysfunction. In this regard they mentioned the two non-randomized pilot studies[2,3] quoted by the Cochrane meta-analysis of Lirussi, *et al.*[4] as the only meager evidence available at present.

We would suggest to consider that results of the first one,[2] however, are strongly puzzled by co-treatment with prebiotics and antioxidants, i.e. two other alleged components of NAFLD therapeutic arsenal.[5] The second study,[3] instead, investigated the outcome of liver dysfunction parameters and oxidative stress markers using probiotics as the single treatment in different categories of adult chronic liver disease including only a subgroup of NAFLD patients for whom liver function tests data were not shown.

Here we recommend, therefore, to contemplate also two other recent pilot, double blind, randomized clinical trials[6,7] which appeared subsequent to 2007 meta-analysis by Lirussi. These studies compare in table 1.

The first RCT[6] evaluated the effects of a 12 week course treatment with 500 million of *Lactobacillus bulgaricus* and *Streptococcus thermophiles*/day in adult patients with biopsy proven NAFLD. Even though anthropometric parameters and cardiovascular risk factors remained unchanged in both treated and control groups, probiotic treatment resulted in a significant improvement of aminotransferases levels.

The second RCT[7] was carried out by our group in obese children with NAFLD unable to comply with lifestyle interventions. We showed that a short (8 weeks) course of probiotic treatment with *Lactobacillus GG* (12 billion CFU/day), irrespective of changes in BMI z score and visceral fat, determined a significant decrease (with normalization in 80% of cases) in alanine aminotransferase values. This was associated also to a significant reduction of anti peptidoglycan-polysaccharide antibodies (i.e. an alleged small intestinal bacterial overgrowth marker), while tumor necrosis factor-α, and ultrasonographic bright liver parameters remained fairly stable.

Although several aspects of probiotics beneficial action in NAFLD (e.g. type of strain and doses) still need further elucidation, altogether, these other data confirm and strengthen Doctors Machado and Cortez-Pinto preliminary conclusions.[1] That is, intestinal flora manipulation warrants consideration as a therapeutic tool to treat obesity related liver dysfunction of adult and pediatric individuals who are noncompliant to its difficult mainstay treatment, i.e. weight loss through slimming diets and lifestyle interventions.[5,7]

As even minimal weight and lifestyle changes may affect the biochemical and imaging parameters of NAFLD,[8] we suggest that future probiotics studies –regardless of an existing controlled harm– should still be designed as short-term trials, strictly registering patients' anthropometric changes. This precaution will help to circumvent the unpredictable effects of lifestyle changes that have hitherto usually confounded the results of a number of long-term studies with this and other treatments in the challenging obese patients population.[5]

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Table 1. Probiotics treatment studies in adults and in children with NAFLD

Authors (reference)	Loguercio, *et al.*[2]	Loguercio, *et al.*[3]	Aller, *et al.*[6]	Vajro, *et al.*[7]
Year of publication	2002	2005	2011	2011
Type of study	Open label.	Open label	Double blind RCT	Double blind RCT
Number patients/disease	10/NASH.	22/NAFLD	30/NAFLD	20/NAFLD
Mean age (years)	37 (range 29-56)	37 (range 29-56) 44.3 ± 15.1 placebo group.	49.4 ± 10.9 treated group.	10.7 ± 2.1
Treatment	Different bacteria strain, prebiotic, antioxidants.*	VSL#3	*Lactobacillus bulgaricus* and *Streptococcus thermophilus* 500 millions CFU	*Lactobacillus GG*
Primary end-point	Aminotransferase and GGT variation, cytokines, lipid peroxidation markers.	Aminotransferase and GGT variation, cytokines, lipid peroxidation markers (MDA, 4-HNE), nitrosothiols (S-NO).	Aminotransferase and GGT variation, cytokines (TNF α, IL6).	ALT and GGT variation, liver echogenicity, TNF α values, H2BT, PG- PS IgA, hepatorenal-US ratio.
Results	Δ ALT-64.5 ± 26.5%; Δ GGT-55.2 ± 31.3% ($p < 0.01$ *vs.* basal values). Decreased lipid peroxidation (significant value, not shown)	AST; ALT; GGT: data not shown for NAFLD patients. Significant reduction ($p < 0.01$) of MDA, 4-HNE, and S-NO.	Decrease in probiotic treated group of ALT: 67.7 ± 25.1 to 60.4 ± 30.4 ($p < 0.05$); AST 41.3 ± 15.5 to 35.6 ± 10.4 ($p < 0.05$); GGT: 118.2 ± 63.1 to 107.7 ± 60.8 ($p<0.05$). Unchanged in placebo group. Cytokines unchanged.	Δ ALT and PG-PS IgA treated *vs.* control $p < 0.03$ for both. ALT normalization 8/10 cases in treated *vs.* 3/7 in placebo.
Length of treatment	2 months.	3 months.	3 months.	2 months
Diet regimen	Not supervised.	Not supervised.	Dietary record before and after treatment.	Changes not encouraged.
Anthropometric parameters	Not supervised.	Not supervised.	Weight, BMI, waist to hip circumference, fat mass: all unchanged.	BMI Z score, US visceral fat, weight, height, waist: all unchanged.

**Lactobacillus acidophilus, Bifidus, Rhamnosus, Plantarum, Salivarius, Bulgaricus, Lactis, Casei, Breve,* + FOS Fructo-oligosaccharides as prebiotic + vitamins B6, B2, B12, D3, and C + folic acid, Zn oxide, Fe gluconate and K iodure. ALT: alanine aminotransferase U/l. AST: aspartate aminotransferase U/l. BMI: body mass index. GGT: gamma glutamyl-transpeptidase U/l. 4-HNE: 4-hydroxynomenal. H2BT: hydrogen breath test. MDA: malondialdheyde. NAFLD: non alcoholic fatty liver disease. NASH: non alcoholic steato-hepatitis. PG-PS: peptidoglycan-polysaccharide. RCT: randomized clinical trial. TNF: tumor necrosis factor. US: ultrasonography.

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