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Protocol G2B study

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ABSTRACT

Background:The gut microbiota is a key player in the regulation of metabolism, immunity and brain functions. Our previous studies have shown that chronic alcohol abuse induces a leaky gut and alterations of the gut microbiota composition, which are correlated with the severity of psychological symptoms, suggesting the involvement of the gut-brain axis in the development of alcohol use disorder (AUD).

Objectives:The Gut2Brain study aims at supplementing AUD patients with prebiotics (inulin) in order to 1) modulate the gut microbiota composition and 2) to evaluate its effect on gastrointestinal tolerance, patient behaviour, biological markers and nutritional intake.

Design:A randomized, double-blind, placebo-controlled study included 50 AUD patients hospitalized for a 3-week detoxification program (Brussels, Belgium). Patients were assigned to the inulin (n=25) or placebo group (maltodextrin, n=25). Recruitment was completed in December 2019.

Methods: Change in gut microbiota composition will be assessed using microbial 16S rRNA gene sequencing. Biological (metabolites, cytokines and liver function), psychological measurements and dietary anamnesis will be performed at the beginning and the end of the detoxification program (17 days of supplementation). Gastrointestinal tolerance will be assessed throughout the follow-up.
The Gut2Brain study was approved by the local ethics committee (2017/04JUL/354) and is registered at www.clinicaltrials.gov as NCT03803709.

Keywords: Prebiotic; Inulin; Alcohol use disorder; Gut microbiota; Nutrition; Psychological symptoms; Liver function; inflammation

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Dietary fiber intake in patients with alcohol use disorder: design and rationale of the Gut2Brain study

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1. Context and issues

Alcohol use disorder (AUD) is a major public health problem affecting 5 to 10% of the population in developed countries. It is associated with deleterious effects on physical and mental health but also with economical and psychosocial consequences [1]. Neurobiological studies have demonstrated alterations of some specific neurotransmitters especially those involved in the reward system and the emotional control (i.e dopamine, serotonin, glutamate, gamma-aminobutyric acid [GABA])[2, 3]. Pharmacological agents targeting these neurotransmitters have been developed in order to reduce the frequency of heavy drinking and alcohol craving but clinical studies reported a small efficacy of these drugs [4], and a high proportion of relapse (70%) among the recently detoxified AUD subjects [5].

The gut microbiota (10^{14} microorganisms living in the intestinal tract) is now considered a potential new therapeutic target in brain disorders [6–10]. Several studies demonstrated that alterations of gut functions related to microbiota can have an impact on cognition, mood and behavior [11–14].It has been shown that alterations of gut microbiota composition (decrease in beneficial bacteria such as *Lactobacillus*, *Bifidobacterium* and *Faecalibacterium*) and changes in the profile of bacterial

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metabolites are associated with mood disturbances in AUD [6, 7]. Our previous studies established a link between dysbiosis (overall changes in microbiota composition and activity) and intestinal permeability that promote the translocation of gut-derived bacterial components, such as lipopolysaccharides (LPS) and peptidoglycans (PGN), which are potent activators of the inflammatory response. The peripheral inflammation in AUD subjects has been shown to positively correlate with alcohol consumption and alcohol craving [7].

Nutrition plays a key role in microbiota shaping [15]. Adequate nutrition is crucial for mental health and psychiatric disorders management, but the scientific rationale behind the interest of dietary components that could act on brain function and immunity via the gut microbiota in this context is insufficiently studied [16–19]. Alcohol represents more than 40% of total caloric intake in AUD patients. In addition, our preliminary data have shown that alcoholic patients have an insufficient intake of dietary fiber (DF), that is to say lower than the Belgian nutritional recommendations. Indeed, the Superior Health Council of Belgium recommends a total amount of dietary fiber equal to or greater than 25 grams per day to ensure correct intestinal function. Fructan-type dietary fiber (inulin and fructo-oligosaccharides) is found naturally in many fruits and vegetables (Jerusalem artichokes, asparagus, artichokes, onions, garlic, chicory roots, bananas). They are interesting DF that respond to the definition of prebiotic: they are used as substrates by selective gut microorganisms and confer health benefit to the host [20]. The effects of dietary fructans on gut health and metabolism have been widely studied in the context of obesity and metabolic disorders. For instance, inulin-type fructan supplementation improves gut barrier function, decreases serum LPS and inflammatory cytokines in genetic and nutritional models of obesity [21]. Regarding the effect of prebiotics on the brain, supplementation of diet with fructo-oligosaccharides (FOS) in mice exerts antidepressant and anxiolytic effects, and reduces stress-induced corticosterone release and pro-inflammatory cytokines [22]. Boehme *et al* also shown that mixed prebiotics supplementation improves systemic and neuroinflammation but also brain function in middle aged mice [23]. Previous studies have shown the beneficial effect of inulin on cardio-metabolic risk in different mice models of obesity [24, 25]. A double-blind interventional study with inulin and FOS in obese women has shown an improvement of gut microbiota composition and specifically increased abundance of *Bifidobacterium* and *Faecalibacterium prausnitzii* [26]. These bacteria were negatively correlated with serum LPS levels in obese animals [26]. Interestingly, the bacteria that are promoted by inulin have been shown to be decreased in AUD patients that present depression [6]

A good digestive tolerance to DF supplementation has been observed in healthy subjects as well as in obese patients [27, 28]. However, it has never been tested in an AUD population.

The primary objectives of this academic research project, carried out in AUD patients, are as follows:

1. **To modulate the gut microbiota composition of AUD patients through inulin supplementation**
2. **To study the effects of inulin supplementation on gastrointestinal tolerance, patient behaviour, biological markers and nutritional intake**

2. Study protocol

a. Recruitment of participants:

The patients enrolled in this study will be recruited from the Alcohol Withdrawal Unit at St-Luc hospital, a standardized 3-week detoxification program. This program consists in 2 weeks at the hospital (week 1 and week 3) separated by one week at home (week 2). AUD patients are admitted in the unit on voluntary basis and they will be evaluated by a psychiatrist and a gastroenterologist in order to analyse the inclusion/exclusion criteria related to the study. After acceptance, eligible AUD patients will be randomly allocated to the “treated” (= inulin) or “placebo” (= maltodextrin) group. The goal being to enroll 50 patients.

Inclusion criteria for the study are listed below:

- male or female
- aged between 18 and 65
- caucasian
- French speaking
- alcohol drunk less than 48h before study enrolment

Exclusion criteria for the study are listed below:

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- Another addiction, except smoking
- Psychiatric comorbidity as described in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM5)
- Antibiotic, probiotic or fibers recent (<2 months) treatment (or other molecule modifying intestinal transit)
- Non-steroidal anti-inflammatory drugs or glucocorticoids recently taken (<1 month)
- Obesity: Body Mass Index<30kg/m2
- Bariatric surgery
- Type 1 or 2 diabetes
- Chronic inflammatory diseases (Crohn disease, coeliac disease, rheumatoid arthritis)
- Patients with known cirrhosis or significant hepatic fibrosis (≥F2) detected by Fibroscan (> 7.6 kPa)
- Pregnancy

Patients will be informed about the experimental procedures and the protocol of the clinical study. They will have to sign the informed consent form to participate.

b. Nutritional intervention

From October 2018 all patients corresponding to the criteria will be recruited to participate in a randomized, double-blind, placebo-controlled clinical study to test the effect of inulin supplementation (Fibruline, Cosucra). The placebo group is constituted by patients daily supplemented with maltodextrin.
In order to reduce the gastrointestinal side effects, the dose of inulin or maltodextrin will be gradually increased from 4 to 16 gram per day during the 17 days of treatment treatment (4g from Day 3 to Day 4; 8g from Day 5 to Day 14 and 16g from Day 15 to Day 19 of the detoxification program).

c. Sample size calculation

Sample size was estimated using G*Power based on the bifidogenic effect of inulin [26, 29]. A total sample size of 50 participants was estimated, with a 20% drop out during the study and 20 patients in each group completing the study provides 80% power to observe an effect size of 0.34 for the relative abundance of Bifidobacterium genus using a power calculation test with a 0.05 two-sided significance level.

d. Outcomes

Measurements will be performed twice, at the onset of alcohol withdrawal (T1 = before starting the prebiotic treatment) and at the end of the detoxification program (T2 = after 17 days of inulin supplementation).

Primary outcome

- Change in gut microbiota composition

Gut microbiota composition [Time Frame: on Day 2 and Day 19]
Relative abundance (percent) of bacterial taxa will be assessed by 16S rRNA gene sequencing (V3-V4 region). The primary outcome will be a significant increase in *Bifidobacterium* genus.

Secondary outcomes

- Evolution of gastro-intestinal tolerance [Time Frame: from Day 1 to Day 19]

Evolution of abdominal pain, bloating, satisfaction of intestinal transit, consequences of intestinal symptoms on daily life, total tolerance score, stool frequency, Bristol stool scale. These parameters will be determined using a French version of a self-reported questionnaire (Francis CY et al, 1997).

- Evolution of nutritional intakes [Time Frame: on week -1 before admission and Day 19]

1. Day 2: three 24-h recalls (retrospective method) will be administered by a trained dietician (two weekdays and one weekend day) during a face-to-face interview. Patients will be asked what they consumed the week before inclusion.
2. Week 2: During the second week of the program (at home) patients will be asked to complete a food diary in which they will

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register all the food and drinks consumed during 3 defined days (two weekdays and one weekend day). The participants will be instructed to specify all ingredients per eating moment: breakfast, morning snack, lunch, snack, dinner, and evening snack. Food quantities will be determined using validated photographs, exact quantity (grams/milliliters) or household measures.
Energy and nutrient intakes (macro-, micronutrients and fiber) will be evaluated using the Nubel Pro program (Nubel, Belgium) and the French food composition database (CIQUAL 2017). The baseline intake will be determined using three 24h-recall. The intake of the second week will be determined using the food diary.
Dietary fiber intake will be measured using a specific database (FiberTAG Project).

- Change in psychological parameters [Time Frame: on Day 2 and Day 19]

-Depression: Beck Depression Inventory (score 0-63). Higher score indicates higher depression level
-Anxiety: State-Trait Anxiety Inventory (score 20-80). Higher score indicates higher anxiety level.
-Craving: Obsessive Compulsive Drinking Scale: a total score (= obsession + compulsion) (0-40) and 2 sub-scores (Obsession (0-20) and Compulsion (0-20)) are calculated. Higher score indicates higher craving level.
-Sociability:Social situation test composed of 6 sub scores from 1 to 7: social high pleasant, social medium pleasant, social low pleasant and non-social high pleasant, non-social medium pleasant and non-social low pleasant
-Fatigue: Multidimensional Fatigue Inventory (MFI-20)
-Visual perspective task

- Impulsivity [Time Frame: on Day 19]

Urgency Premeditation Perseverance Sensation seeking impulsive behavior scale: score of different subscales are calculated: "urgency"(0-48), "lack of premeditation"(0-44), "lack of perseverance"(0-40), "sensation seeking"(0-48). Higher score in the different subscales indicates higher impulsivity level.

- Emotional intelligence [Time Frame: on Day 19]

The Trait Emotional Intelligence Questionnaire (TEIQue) 75 items

- Trauma [Time Frame: on Day 19]

Post-traumatic diagnostic scale: calculation of score is complex and described in the related publication Hearn, M, Ceschi, G., Brillon, P, Fürst, G., & Van der Linden, M. (2012). A French adaptation of the Post-traumatic Diagnostic scale. Canadian Journal of Behavioural Science, 44, 16-28.

- Change in albumin, pre-albumin [Time Frame: on Day 2 and Day 19]

It will be determined in blood sample

- Change in liver related parameters [Time Frame: on Day 2 and Day 19]

-CK18-M65 and liver enzymes will be determined in blood sample
-Hepatic fibrosis and/or steatosis : Elasticity by Fibroscan (kPa), controlled attenuation parameter (CAP)

- Change in inflammatory markers [Time Frame: on Day 2 and Day 19]

Cytokines and inflammatory markers levels will be determined in blood sample and/or in Human Peripheral Blood Mononuclear Cells (PBMC)

- Change in metabolic parameters and markers [Time Frame: on Day 2 and Day 19]

-Glucose: determined in a fasting blood sample
-lipid homeostasis: Cholesterol, triglycerides, free fatty acids will be determined in a fasting blood sample.
-Gut peptides (GLP-1, ghrelin, leptin, PYY) will be measured with a multiplex immunoassay (all in pg/ml).

- Change in metabolomic profile [Time Frame: on Day 2 and Day 19]

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Metabolomic analysis of biological samples (blood and/or stool) will be performed by Liquid chromatography-mass spectrometry (LC-MS), nuclear magnetic resonance (NMR) or Gas chromatography–mass spectrometry (GC-MS).

- Social network /sociogram [Time frame: on day 17]

We will collect data on patients' social support networks using an ego network mapping technique and analyse them with social network analysis (Hogan *et al.*, 2007; Wyngaerden F *et al*/2019)

- Relapse at 3, 6, and 12 months

The relapse (after the last day of the detoxification program) will be evaluated during phone calls.

- Change in Intestinal permeability and integrity

-a duodenal biopsy will be collected and the expression of the tight junctions regulating the intestinal permeability will be analyzed by sectional immunofluorescence and quantitative Polymerase Chain reaction [Time Frame: On day 3]
-A stool sample will be collected to analyse a marker of intestinal permeability: fecal albumin concentration [Time Frame: on Day 2 and Day 19]
-Markers of microbial translocation (ie. sCD14, LBP, PGRP etc) will be measured in serum. [Time Frame: on Day 2 and Day 19]

References

1. WHO | Global status report on alcohol and health 2018. WHO. http://www.who.int/substance_abuse/publications/global_alcohol_report/en/. Accessed 11 Jan 2019.
2. Gilpin NW, Koob GF. Neurobiology of alcohol dependence: focus on motivational mechanisms. Alcohol Res Health. 2008;31:185–95.
3. Clapp P, Bhave SV, Hoffman PL. How adaptation of the brain to alcohol leads to dependence: a pharmacological perspective. Alcohol Res Health. 2008;31:310–39.
4. JOHNSON BA. UPDATE ON NEUROPHARMACOLOGICAL TREATMENTS FOR ALCOHOLISM: SCIENTIFIC BASIS AND CLINICAL FINDINGS. Biochem Pharmacol. 2008;75:34–56.
5. Swift RM. Drug therapy for alcohol dependence. N Engl J Med. 1999;340:1482–90.
6. Leclercq S, Matamoros S, Cani PD, Neyrinck AM, Jamar F, Stärkel P, et al. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. Proc Natl Acad Sci USA. 2014;111:E4485-4493.
7. Leclercq S, De Saeger C, Delzenne N, de Timary P, Stärkel P. Role of inflammatory pathways, blood mononuclear cells, and gut-derived bacterial products in alcohol dependence. Biol Psychiatry. 2014;76:725–33.
8. Schachter J, Martel J, Lin C-S, Chang C-J, Wu T-R, Lu C-C, et al. Effects of obesity on depression: A role for inflammation and the gut microbiota. Brain Behav Immun. 2018;69:1–8.
9. Torres-Fuentes C, Schellekens H, Dinan TG, Cryan JF. The microbiota-gut-brain axis in obesity. Lancet Gastroenterol Hepatol. 2017;2:747–56.
10. Leclercq S, Cani PD, Neyrinck AM, Stärkel P, Jamar F, Mikolajczak M, et al. Role of intestinal permeability and inflammation in the biological and behavioral control of alcohol-dependent subjects. Brain Behav Immun. 2012;26:911–8.
11. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13:701–12.
12. Sharon G, Cruz NJ, Kang D-W, Gandal MJ, Wang B, Kim Y-M, et al. Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. Cell. 2019;177:1600-1618.e17.
13. Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. Nature Microbiology. 2019;:1.
14. Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: Regulation by the microbiome. Neurobiol Stress. 2017;7:124–36.
15. Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, et al. Environment dominates over host genetics in shaping human gut microbiota. Nature. 2018;555:210–5.
16. Jacka FN. Nutritional Psychiatry: Where to Next? EBioMedicine. 2017;17:24–9.
17. Mörkl S, Wagner-Skacel J, Lahousen T, Lackner S, Holasek SJ, Bengesser SA, et al. The Role of Nutrition and the Gut-Brain Axis in Psychiatry: A Review of the Literature. Neuropsychobiology. 2018;:1–9.
18. Firth J, Siddiqi N, Koyanagi A, Siskind D, Rosenbaum S, Galletly C, et al. The Lancet Psychiatry Commission: a blueprint for

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protecting physical health in people with mental illness. Lancet Psychiatry. 2019;6:675–712.
19. Molendijk M, Molero P, Ortuño Sánchez-Pedreño F, Van der Does W, Angel Martínez-González M. Diet quality and depression risk: A systematic review and dose-response meta-analysis of prospective studies. J Affect Disord. 2018;226:346–54.
20. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol. 2017;14:491–502.
21. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut. 2009;58:1091–103.
22. Burokas A, Arboleya S, Moloney RD, Peterson VL, Murphy K, Clarke G, et al. Targeting the Microbiota-Gut-Brain Axis: Prebiotics Have Anxiolytic and Antidepressant-like Effects and Reverse the Impact of Chronic Stress in Mice. Biol Psychiatry. 2017;82:472–87.
23. Boehme M, Wouw M van de, Bastiaanssen TFS, Olavarría-Ramírez L, Lyons K, Fouhy F, et al. Mid-life microbiota crises: middle age is associated with pervasive neuroimmune alterations that are reversed by targeting the gut microbiome. Molecular Psychiatry. 2019;:1.
24. Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, et al. Prebiotic effects: metabolic and health benefits. Br J Nutr. 2010;104 Suppl 2:S1-63.
25. Delzenne NM, Cani PD, Everard A, Neyrinck AM, Bindels LB. Gut microorganisms as promising targets for the management of type 2 diabetes. Diabetologia. 2015;58:2206–17.
26. Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PGB, Neyrinck AM, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut. 2013;62:1112–21.
27. Hiel S, Bindels LB, Pachikian BD, Kalala G, Broers V, Zamariola G, et al. Effects of a diet based on inulin-rich vegetables on gut health and nutritional behavior in healthy humans. The American Journal of Clinical Nutrition. 2019;109:1683–95.
28. Hiel S, Gianfrancesco MA, Rodriguez J, Portheault D, Leyrolle Q, Bindels LB, et al. Link between gut microbiota and health outcomes in inulin -treated obese patients: Lessons from the Food4Gut multicenter randomized placebo-controlled trial. Clinical Nutrition. 2020;:S0261561420301606.
29. Dehghan P, Gargari BP, Jafar-Abadi MA, Aliasgharzadeh A. Inulin controls inflammation and metabolic endotoxemia in women with type 2 diabetes mellitus: a randomized-controlled clinical trial. Int J Food Sci Nutr. 2014;65:117–23.

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