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SHORT COMMUNICATION

Effects of oligofructose on glucose and lipid metabolism in patients with nonalcoholic steatohepatitis: results of a pilot study

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Objective: In experimental animals, recent results suggest that the addition of inulin-type fructans such as oligofructose (OFS) in the diet decreases triacylglycerol accumulation in the liver tissue. Therefore, we have investigated the effect of daily ingestion of OFS in seven patients with nonalcoholic steatohepatitis (NASH), confirmed by liver biopsies.
Design: They received 16 g/day OFS or maltodextrine (placebo) for 8 weeks in a randomized double-blind crossover design. Energy intake, body composition, liver steatosis and blood parameters were analysed after 4 and 8 weeks of dietary supplementation.
Results: Compared to placebo, OFS decreased significantly serum aminotransferases, aspartate aminotransferase after 8 weeks, and insulin level after 4 weeks, but this could not be related to significant effect on plasma lipids.
Conclusion: This pilot study supports the putative interest of OFS in the management of liver diseases associated with abnormal lipid accumulation in humans.
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Introduction

Inulin-type fructans are natural components of the diet (asparagus, garlic, onion, etc). Once ingested, they are largely fermented by colonic bacterial strains such as bifidobacteria, leading to interesting intestinal and systemic effects (Roberfroid & Delzenne, 1998).

Oligofructose (OFS)—a short-chain fructan obtained from chicory root inulin—has been shown to protect Wistar rats against liver triglycerides (TAG) accumulation induced by fructose and to lessen hepatic steatosis occurring in obese Zucker fa/fa rats (Kok *et al*, 1996; Daubioul *et al*, 2000, 2002).

Steatosis, in some cases, degenerates towards fibrosis, cirrhosis, and premature death resulting from liver failure (Agrawal & Bonkovsky, 2002; Yu & Keeffe, 2002; Zafrani, 2004). In humans, nonalcoholic steatohepatitis (NASH) is an asymptomatic disease often discovered incidently through elevation of serum aminotransferases on routine laboratory studies, or hepatomegaly examination and/or on discovery of liver hyperechogenicity on ultrasound (Agrawal & Bonkovsky, 2002). NASH is particularly frequent in patients with obesity, diabetes or hyperlipidaemia (Reid, 2001; Chitturi *et al*, 2002; Yu & Keeffe, 2002). No effective medical or nutritional treatment (except food restriction) has been proposed for patients with NASH until now (Luyck *et al*, 2000). Therefore, we performed a pilot study in patients with NASH to evaluate the influence of a prolonged (8 weeks) ingestion of OFS on serum parameter attesting of liver integrity, and/or lipid or glucose homeostasis.

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Subjects and methods

Patients were recruited from medical practitioners in the gastroenterology department of the Cliniques Universitaires St Luc (Brussels, Belgium). The study protocol was approved by the Ethical committee of the Université catholique de Louvain. Informed consent was obtained from each subject. They were selected through exhibition of abnormal elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl transferase levels (Table 1). No recent use of antibiotics or lipid-lowering medications, negative testing to hepatitis B and C, no alcohol abuse, and no evidence of genetic hemochromatosis were required. NASH was confirmed by liver biopsies performed in all subjects. Biopsies were scored for necro-inflammatory grade and fibrosis stage according to Brunt *et al* (1999).

Seven participants completed the study. The clinical and biological characteristics of the subjects are given in Table 1 (reference values of normal fasting glucose and lipid concentration are presented in Table 2). They were randomly assigned in a double-blind, crossover, placebo-controlled design over two 8-week periods of dietary supplementation and separated by a washout period of minimum 5 weeks.

In all, 8 g OFS (Raftilose P95®) or maltodextrine (placebo) were supplied as powder packed in paper bags supplied by ORAFTI (Tienen, Belgium). Patients were asked to take two packs per day, at breakfast and dinner, and to bring back unconsumed doses to allow assessment of compliance.

Fasting blood samples were collected on weeks 0, 4, and 8 of each treatment period and also 2 weeks after the end of the dietary supplementation for biochemical analysis. An abdominal ultrasound was also performed to assess the liver fatty infiltration at the end of each period.

Data were checked for normality and log transformed before statistical analysis was performed with the Minitab program. The effects of OFS and placebo were compared by an ANCOVA model with fixed factors: treatment, time, treatment × time, random (=period), response 0 (=response at time 0, ie before treatment administration) and a random factor: patient.

Results and discussion

The present study is the first one devoted to the analysis of the effect of OFS supplementation on liver function, in patients presenting NASH. As shown in Table 2, OFS led to a decrease in AST level, which was not observed during the placebo treatment. ALT activity was more moderately decreased by OFS (non significant). Even if these effects prelude an improvement of liver function, the analysis of the pictures obtained by the liver ultrasonography at the beginning and at the end of each period did not reveal any difference of liver size following both treatments.

Triglyceridaemia is often used as indirect criteria of steatosis. Some data obtained in normo- or moderate hyperlipidaemic patients suggest that the daily consumption of about 10 g inulin for several weeks decreases triglyceridaemia and/or cholesterolaemia (Brighenti *et al*, 1999; Jackson *et al*, 1999). In our study, a decrease in triglyceridaemia due to OFS was observed in three patients out of seven (non significant).

Our previous experimental studies in obese Zucker rats showed that the improvement of steatosis by OFS was not linked to any effect on triglyceridaemia, but would rather be the consequence of a lower dietary intake during the

Table 1 Clinical characteristics of the subjects at the time of screening

Parameters / *Patient no.*	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Age (y)	48	57	58	56	37	66	60
Sex, M/F	M	M	M	M	M	M	M
Weight (kg)	68.9	98	97	85	52.2	121.3	93.8
Height (m)	1.78	1.76	1.78	1.75	1.58	1.89	1.58
BMI (kg/m^2)	21.7	31.6	30.6	27.8	20.9	34.0	37.6
NASH grade							
Fat infiltration	Moderate	Severe	Severe	Moderate	Severe	Moderate	Severe
Necroinflammation	Absent	Moderate	Mild	Moderate	Absent	Moderate	Mild
Fibrosis	Absent	Moderate	Mild	Mild	Absent	Absent	Severe
Baseline fasting blood values							
AST (UI/l)[a]	31	39	66	98	27	65	113
ALT (UI/l)[b]	61	54	86	191	51	81	194
Glucose(mg/dl)	100	106	103	98	86	110	148[c]
Triacylglycerol (mg/dl)	84	93	138	73	93	123	145
Total cholesterol (mgl/dl)	189	200[c]	178	228[c]	239[c]	215	148

[a]AST, aspartate aminotransferase.
[b]ALT, alanine aminotransferase.
[c]Prior fasting levels above the reference values: normal ranges for glucose < 70–110 mg/dl; triacylglycerol < 250 mg/dl, and cholesterol < 200 mg/dl.

Table 2 Fasting plasma parameters of subjects before, after 4 and 8 weeks of daily consumption of placebo or OFS

Tests	*Normal range*	*Placebo*			*OFS*		
		Week 0	*Week 4*	*Week 8*	*Week 0*	*Week 4*	*Week 8*
AST (UI/l)[a]	6–33	66±10	56±9	63±10	60±15	48±9	53±11*
ALT (UI/l)[b]	14–63	106±20	91±18	97±19	102±23	79±16	83±17
γGT (UI/l)[c]	7–50	82±31	78±28	72±24	114±27	99±33	109±35
Total bilirubin (mg/dl)	0.3–1.2	1.1±0.10	1.0±0.1	1.1±0.1	1.0±0.1	0.9±0.1	1.0±0.1
Alkaline phosphatase (UI/l)	28–94	59±9	61±10	59±10	60±6	66±6	66±8
Uric acid (mg/dl)	2.7–7.7	6.5±0.4	6.3±0.5	6.3±0.5	6.2±0.5	6.3±0.5	6.4±0.4
Glucose (mg/dl)	70–110	118±10	120±11	128±17	122±20	102±4	110±7
Insulin (mU/l)	2–25	14.0±2.3	14.9±3.0	15.4±3.1	17.2±6.3	9.9±2.7	14.9±4.0
C-peptide (pmol/l)	343–1803	985±178	1139±313	1204±372	1360±678	665±148	1227±435
Triacylglycerol (mg/dl)	<180–250	127±26	148±19	111±18	130±20	124±13	99±12
Total cholesterol (mg/dl)	<190–250	196±9	195±13	184±13	190±12	202±7	186±12
LDL cholesterol (mg/dl)	<115–160	127±9	125±13	117±12	122±11	131±10	121±10
HDL cholesterol (mg/dl)	>55–35	43.3±5.0	40.6±4.6	44.9±5.4	41.5±5.2	46.2±4.9	45.9±5.3

Values are mean±s.e.m., $n=7$.
[a]AST, aspartate aminotransferase.
[b]ALT, alanine aminotransferase.
[c]γGT, gamma-glutamyl transferase.
*$P<0.05$ *vs* placebo.

treatment, leading to a decrease in visceral fat mass (Daubioul *et al*, 2000). Patients were asked to record food intakes during 3 days of each treatment period including one weekend day. According to self-report, subject's lifestyles, daily energy carbohydrate (sugar + starch) and fibre intake remained constant throughout the study, as did body weight, BMI and body composition (% fat mass and fat-free mass) (data not shown). Since abdominal fat mass seems to be involved in the development of steatosis, a measurement of waist/hip ratio would have been informative (Bergman *et al*, 2001).

Disturbed insulin response, often associated with metabolic syndrome, has been implicated as a factor contributing to the pathogenesis of NASH (Chitturi *et al*, 2002; Pagano *et al*, 2002). In this study, there were no significant changes in glucose, insulin or C-peptide fasting concentrations between the two dietary treatments. However, a nonpersistent decrease in insulin (17.2±6.3; 9.9±2.7 mU/l) and C-peptide (1360±678; 665±148 pmol/l) concentrations was observed after 4 weeks of OFS treatment.

In conclusion, in this pilot study, our results support the improvement of hepatic enzymes in NASH patients receiving a dietary supplementation with dietary fructans. Hepatic lipogenesis and TAG synthesis is involved in nonalcoholic fatty liver disease (Diraison *et al*, 2003). On the other hand, hepatic TAG synthesis is decreased by OFS in rats, and also in healthy human volunteers (Delzenne & Williams, 2002; Letexier *et al*, 2003). It would therefore be important to assess a 'dynamic' analysis of fatty acid metabolism through tracer methodology in NASH patients receiving OFS, to approach the biochemical mechanism underlying this effect. The influence of OFS feeding—a nutrient which is well tolerated by patients at the dose proposed here (2×8g/day)—would require further study, with a longer treatment, namely in patients exhibiting obesity and hypertriglyceridaemia associated with steatosis.

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References

Agrawal S & Bonkovsky HL (2002): Management of nonalcoholic steatohepatitis: an analytic review. *J. Clin. Gastroenterol.* 35, 253–261.

Bergman RN, Van Citters GW, Mittelman SD, Dea MK, Hamilton-Wessler M, Kim SP & Ellmerer M (2001): Central role of the adipocyte in the metabolic syndrome. *J. Investig. Med.* 49, 119–126.

Brighenti F, Casiraghi MC, Canzi E & Ferrari A (1999): Effect of consumption of a ready-to-eat breakfast cereal containing inulin on the intestinal motility and blood lipids in healthy male volunteers. *Eur. J. Clin. Nutr.* 53, 726–733.

Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA & Bacon BR (1999): Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am. J. Gastroenterol.* 94, 2467–2474.

Chitturi S, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, Karim R, Lin R, Samarasinghe D, Liddle C, Weltman M & George J (2002): NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology* 35, 373–379.

Daubioul CA, Rousseau N, Demeure R, Gallez B, Taper HS, Declerck B & Delzenne NM (2002): Dietary fructans, but not cellulose,

decrease triglyceride accumulation in the liver of obese Zucker fa/fa rats. *J. Nutr.* 132, 967–973.

Daubioul CA, Taper HS, De Wispelaere LD & Delzenne NM (2000): Dietary oligofructose lessens hepatic steatosis, but does not prevent hypertriglyceridemia in obese Zucker rats. *J. Nutr.* 130, 1314–1319.

Delzenne NM & Williams CM (2002): Prebiotics and lipid metabolism. *Curr. Opin. Lipidol.* 13, 61–67.

Diraison F, Moulin P & Beylot M (2003): Contribution of hepatic *de novo* lipogenesis and reesterification of plasma non esterified fatty acids to plasma triglyceride synthesis during non alcoholic fatty liver disease. *Diabetes Metab.* 29, 478–485.

Jackson KG, Taylor GR, Clohessy AM & Williams C (1999): The effect of daily intake of inulin on fasting lipid, insulin and glucose concentrations in middle-aged men and women. *Br. J. Nutr.* 82, 23–30.

Kok N, Roberfroid M & Delzenne N (1996): Dietary OFS modifies the impact of fructose on hepatic triacylglycerol metabolism. *Metabolism* 45, 1547–1550.

Letexier D, Diraison F & Beylot M (2003): Addition of inulin to a moderately high-carbohydrate diet reduces hepatic lipogenesis and plasma triacylglycerol concentrations in humans. *Am J. Clin. Nutr.* 77, 559–564.

Luyck FH, Lefebvre PJ & Scheen AJ (2000): Non-alcoholic steatohepatitis: association with obesity and insulin resistance, and influence of weight loss. *Diabetes Metab.* 26, 98–106.

Pagano G, Pacini G, Musso G, Gambino R, Mecca F, Depetris N, Cassader M, David E, Cavallo-Perin P & Rizzetto M (2002): Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome : further evidence for an etiologic association. *Hepatology* 35, 367–372.

Reid AE (2001): Nonalcoholic steatohepatitis. *Gastroenterology* 121, 710–723.

Roberfroid MB & Delzenne NM (1998): Dietary fructans. *Annu. Rev. Nutr.* 18, 117–143.

Yu AS & Keeffe EB (2002): Nonalcoholic fatty liver disease. *Rev. Gastroenterol. Disord.* 2, 11–19.

Zafrani ES (2004): Non-alcoholic fatty liver disease: an emerging pathological spectrum. *Virchows Arch.* 444, 3–12.