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 16g/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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Keywords: Nonalcoholic steatohepatitis; humans; fructans; triacylglycerol; blood glucose; aminotransferases

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 (Robeertfoid & 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; Zafarani, 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 hyperlipidemia (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.
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 (Raffilose 995®) or maltodextrine (placebo) were supplied as powder packed in paper bags supplied by ORAPIT (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 x 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 insulin for several weeks decreases triglyceridaemia and/or cholesterolemia (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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patient no.</th>
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<th>5</th>
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<td>Age (y)</td>
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<td>56</td>
<td>37</td>
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<td>Sex, M/F</td>
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<td>Weight (kg)</td>
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<td>97</td>
<td>97</td>
<td>83</td>
<td>52.2</td>
<td>121.3</td>
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<td>Height (m)</td>
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<td>1.76</td>
<td>1.78</td>
<td>1.75</td>
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<td>1.89</td>
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<td>BMI (kg/m²)</td>
<td>21.7</td>
<td>31.6</td>
<td>30.6</td>
<td>27.8</td>
<td>20.9</td>
<td>34.0</td>
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<td>NASH grade</td>
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<td>Necroinflammation</td>
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<td>Baseline fasting blood values</td>
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<tr>
<td>AST (IU/L)</td>
<td>31</td>
<td>39</td>
<td>66</td>
<td>98</td>
<td>27</td>
<td>65</td>
<td>113</td>
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<tr>
<td>ALT (IU/L)</td>
<td>61</td>
<td>54</td>
<td>86</td>
<td>191</td>
<td>51</td>
<td>81</td>
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<td>Glucose (mg/dl)</td>
<td>100</td>
<td>106</td>
<td>103</td>
<td>98</td>
<td>86</td>
<td>110</td>
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<td>Triglycerol (mg/dl)</td>
<td>84</td>
<td>93</td>
<td>138</td>
<td>73</td>
<td>93</td>
<td>123</td>
<td>145</td>
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<td>Total cholesterol (mg/dl)</td>
<td>189</td>
<td>206</td>
<td>228</td>
<td>239</td>
<td>215</td>
<td>148</td>
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</table>

aAST, aspartate aminotransferase.  
bALT, alanine aminotransferase.  
cPrior fasting levels above the reference values: normal ranges for glucose <70-110 mg/dl; triglycerol <250 mg/dl, and cholesterol <200 mg/dl.

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treatment, leading to a decrease in visceral fat mass (Daubliou 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 lifestyle, 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 (Chitruiti 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 non-persistent 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 OSF 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 (D performer et al., 2003). On the other hand, hepatic TAG synthesis is decreased by OSF in rats, and also in healthy human volunteers (Delenezze & Williams, 2002; Leteix et al., 2003). It would therefore be important to assess a 'dynamic' analysis of fatty acid metabolism through tracer methodology in NASH patients receiving OSF, to approach the biochemical mechanism underlying this effect. The influence of OSF feeding—a nutrient which is well tolerated by patients at the dose proposed here (2 x 8g/day)—would require further study, with a longer treatment, namely in patients exhibiting obesity and hypertriglyceridaemia associated with steatosis.

Acknowledgements
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References
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Dietary fructans and nonalcoholic steatohepatitis


