

## Increased serum amylase and lipase in fructose malabsorbers

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### Abstract

**Background:** Fructose malabsorption is frequently seen in the general population and is characterised by the inability to absorb fructose efficiently. Due to fructose malabsorption, fructose reaches the colon where it is broken down by bacteria to short fatty acids, CO<sub>2</sub> and H<sub>2</sub>. Bloating, cramps, osmotic diarrhea and other symptoms of irritable bowel syndrome are the consequence. We recently found that fructose malabsorption is associated with low plasma folic acid concentrations and low serum tryptophan and zinc. Because fructose malabsorption apparently is associated not only with malabsorption of other nutrients, but also with abdominal discomfort, it was of interest to examine whether mild pancreatitis may be involved. **Methods:** We retrospectively examined our data in 159 otherwise healthy adults (110 females, 49 males) aged 14–84 years (mean 45.6 ± 14.4 S.D.) with gastrointestinal complaints for serum amylase and serum lipase concentrations. The patients have been tested earlier for fructose malabsorption and lactose maldigestion by measuring breath H<sub>2</sub> concentrations after an oral dose of 25 g fructose and 50 g lactose, respectively, 1 week apart. **Results:** Fructose malabsorption (H<sub>2</sub> concentrations ≥ 20 ppm over baseline values) was detected in 107 of 159 individuals (67.3%). These subjects with fructose malabsorption presented with significantly higher serum amylase concentrations (73.1 U/l ± 25.7 S.D.) compared to individuals with normal fructose absorption (59.6 U/l ± 17.9 S.D.; *p* = 0.0009). Fructose malabsorbers also presented with higher serum lipase concentrations (122.0 U/l ± 100.3 S.D.) compared to normals (89.5 U/l ± 46.5 S.D.; *p* < 0.05). To determine whether this finding is a consequence of any sort of malabsorption syndrome or whether it is specific for fructose malabsorption, all subjects were screened for lactose maldigestion. Lactose maldigestion (H<sub>2</sub> concentrations > 20 ppm over baseline after lactose loading) was found in 50 of 159 individuals (31.4%). There were no significant differences in either amylase or lipase concentrations in lactose maldigestors. **Conclusion:** Serum amylase and lipase concentrations are higher in subjects with fructose malabsorption compared to normals. Therefore, fructose malabsorption should be considered as a differential diagnosis in moderately elevated serum amylase. © 2001 Elsevier Science B.V. All rights reserved.

**Keywords:** Fructose malabsorption; Fructose loading test; Amylase; Lipase; Breath test

### 1. Introduction

Fructose malabsorption syndrome is a disease which was first described by Hoekstra et al. [1] and Rumessen [2]. Patients with fructose malabsorption are unable to sufficiently absorb the ingested monosaccharide [3] probably due to a defect in the

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duodenal fructose transporter GLUT-5 [4], so that large quantities of fructose reach the colon. There, fructose is broken down by colon bacteria into short fatty acids, CO<sub>2</sub> and H<sub>2</sub>, which can be measured in the expired air. Bloating, abdominal discomfort and sometimes osmotic diarrhea are the consequences induced by the degradation products built by the colonic bacteria. It is believed that about 36% of the European population suffer from fructose malabsorption in a more or less severe form, and about half of them are symptomatic [5]. We recently found that fructose malabsorption is associated with early signs of mental depression [6], folic acid deficiency [7] and lower serum tryptophan concentrations [8], suggesting that fructose malabsorption is a symptom for a more complex gastrointestinal disorder. As fructose malabsorption is also a promoting factor for small intestinal overgrowth syndrome (SIBOS) [9] and pancreatic diseases are often associated with SIBOS [10], it was of interest to examine whether mild pancreatitis may play a role in the abdominal discomfort in subjects with fructose malabsorption. We therefore retrospectively examined our data from previous studies [7,11] for serum amylase and lipase concentrations in subjects with and without fructose malabsorption. In addition, we compared the same enzymes in subjects suffering from lactose maldigestion.

## 2. Material and methods

### 2.1. Patients

The subjects were recruited from an earlier study where we examined patients with fructose malabsorption for signs of psychiatric disorders [11] and for vitamin deficiencies [7]. A total of 159 otherwise healthy adults (110 females, 49 males), aged 14–84 years (mean  $45.6 \pm 14.4$  S.D.), who visited the physicians office for a medical health check-up and reported about gastrointestinal complaints in a health questionnaire, were studied. None of the patients showed signs of inflammatory bowel disease, any other chronic disease or infectious diseases, and none was under medication except for contraceptives in some females. All 159 patients underwent H<sub>2</sub>-breath testing after an oral load of fructose and after an oral

load of lactose 1 week apart. Blood samples were taken after an overnight fast for determination of amylase and lipase. In order to rule out non-H<sub>2</sub>-producers, a single hydrogen breath test in the non-fasting individual or a lactulose H<sub>2</sub>-breath test was performed some days before fructose H<sub>2</sub>-breath-testing. Non-H<sub>2</sub>-producers were excluded from the study.

### 2.2. Hydrogen (H<sub>2</sub>)breath tests

Breath hydrogen (H<sub>2</sub>) was measured using a Bedfont Gastrolyzer (Bedfont, Kent, UK). The H<sub>2</sub>-monitor used has been validated by several authors [12,13]. All tests were performed between 8:00 and 8:30 a.m., and body weight and height were measured. After a 12-h overnight fast, a baseline H<sub>2</sub>-breath test was performed. An oral dose of 25 g fructose or 50 g lactose was given in 250 ml of tap water, respectively, and H<sub>2</sub>-exhalation was monitored in 30 min intervals for at least 2 h. Maximum H<sub>2</sub>-exhalation (H<sub>2</sub>-max) after fructose or lactose load was monitored and the differences to baseline levels ( $\Delta$ H<sub>2</sub>) were calculated.

### 2.3. Blood analyses

Blood samples were drawn in a 7.5-ml syringe from fasting subjects for serum amylase and lipase measurements. Amylase (Aeroset™-System, Abbott Laboratories, IL, USA) and lipase (Aeroset™-System, Abbott Laboratories) were measured according to the manufacturer's instructions. Upper limits of normals were for amylase 110 U/l and for lipase 190 U/l, respectively.

### 2.4. Data analysis

Cut off point for the diagnosis of fructose malabsorption or lactose maldigestion was a rise of breath H<sub>2</sub> concentrations  $\geq 20$  ppm over baseline after loading with the respective sugar [1]. Subjects with a rise of breath H<sub>2</sub> concentrations  $< 20$  ppm over baseline were considered to be normal fructose absorbers or normal lactose digesters, respectively. The serum concentrations of amylase and lipase in the two corresponding groups were compared by Student's *t*-test and to test for association between elevated amylase or lipase with fructose malabsorption, Fisher's exact test was calculated, using a stan-

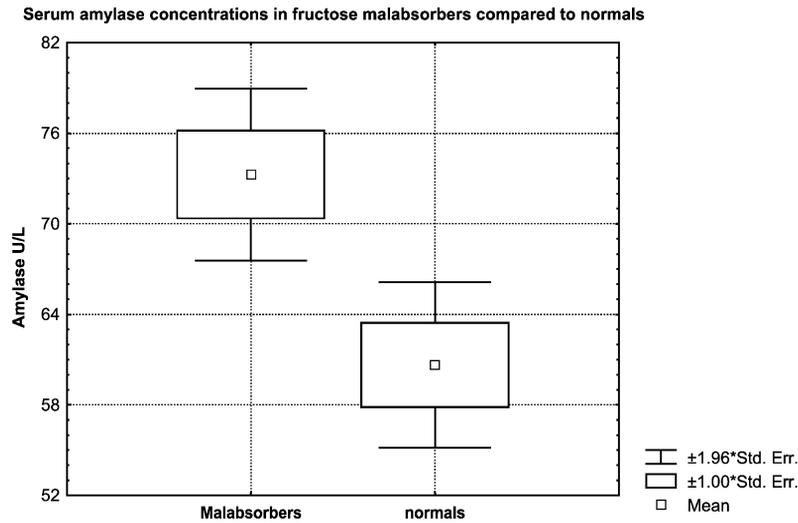


Fig. 1. Serum amylase concentrations in fructose malabsorbers compared to normals.

standard PC statistical program (Statistica for windows version 6.0) [14].

### 3. Results

After oral fructose administration, 107 of 159 (67.3%) patients (40 males and 67 females aged 45.4 years  $\pm$  14.1 S.D.) presented with  $\Delta H_2 \geq 20$  ppm. They were classified as fructose malabsorbers. The

remaining 52/159 (32.7%) subjects (9 males and 43 females aged 46.1 years  $\pm$  15.3 S.D) were normal fructose absorbers. Breath tests after lactose loading were positive ( $\Delta H_2 \geq 20$  ppm) in 50 of 159 (31.4%) subjects (13 males and 37 females, aged 49.2 years  $\pm$  14.8 S.D.) and negative in 109/159 (68.6%) subjects (36 males and 73 females, aged 44.0 years  $\pm$  14.0 S.D.).

Serum amylase levels were significantly higher in fructose malabsorbers (73.1 U/l  $\pm$  25.7 S.D.) com-

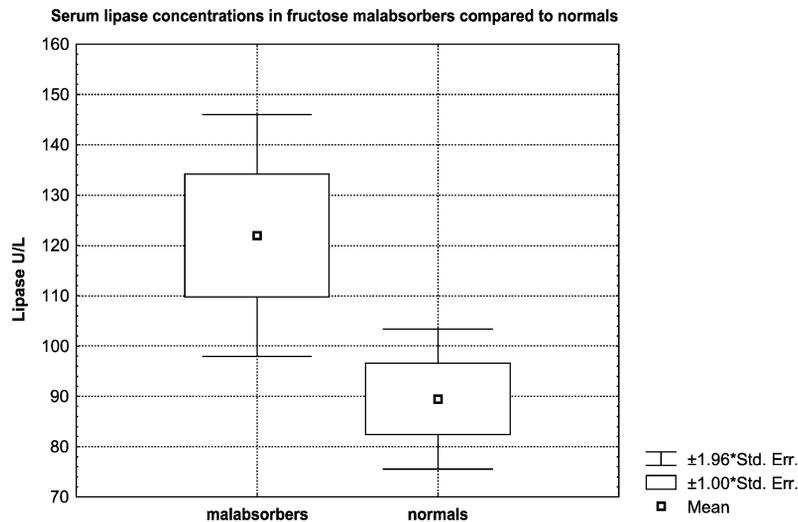


Fig. 2. Serum lipase concentrations in fructose malabsorbers compared to normals.

pared to normals ( $59.6 \text{ U/l} + 17.9 \text{ S.D.}$ ;  $p = 0.0009$ ) (Fig. 1). Serum lipase concentrations were also significantly higher in fructose malabsorbers ( $122.0 \text{ U/l} \pm 100.3 \text{ S.D.}$ ) compared to normals ( $89.5 \text{ U/l} \pm 46.5 \text{ S.D.}$ ;  $p = 0.049$ ) (Fig. 2).

No such differences were found in lactose maldigestors: Amylase ( $70.2 \text{ U/l} \pm 25.4 \text{ S.D.}$ ) compared to normal lactose digesters ( $67.9 \text{ U/l} \pm 23.7 \text{ S.D.}$ ;  $n = \text{n.s.}$ ); lipase ( $97.5 \text{ U/l} \pm 50.7 \text{ S.D.}$ ) compared to normals lactose digesters ( $111.3 \text{ U/l} \pm 92.7 \text{ S.D.}$ ;  $p = \text{n.s.}$ ). There was an influence of age, as far as the different serum amylase concentrations in males were only significant at an age over 40 years ( $75.6 \text{ U/l} \pm 29.4 \text{ S.D.}$ ; vs.  $53.1 \text{ U/l} \pm 16.5 \text{ S.D.}$   $p = 0.049$ ). In females, the differences were more pronounced ( $73.3 \text{ U/l} \pm 23.8 \text{ S.D.}$ ; vs.  $60.7 \text{ U/l} \pm 18.3 \text{ S.D.}$   $p = 0.004$ ) than in males.

A total of 13 of 159 studied subjects (8.2%) had elevated serum amylase concentration ( $> 110 \text{ U/l}$ ). Of these subjects, 12 (92.3%) were fructose malabsorbers and only one subject with elevated serum amylase was classified as normal fructose absorber. In the group with fructose malabsorption, 12/107 (11.2%) had elevated serum amylase concentrations and in the group with normal fructose absorption 1/52 (1.9%) had elevated serum amylase concentrations (Fisher's exact test:  $p = 0.037$ ).

#### 4. Discussion

In general practice, one often finds mildly elevated serum amylase without overt pancreatic disease. This finding is usually considered to be macroamylasemia, a benign acquired condition, characterised by a serum amylase unusually large in molecular size that has been found to occur in apparently healthy humans. Macroamylasemia is found as well in a variety of diseases including liver disease, diabetes, cancer, malabsorption and autoimmune disorders. Most commonly macroamylasemia results from the formation of immune complexes between amylase and immunoglobulins. On the contrary to macroamylasemia true hyperamylasemias are seen in pancreatic diseases and have also been shown to be associated with inflammatory bowel disease [15] and celiac disease [16] where it disappeared after a strict gluten-free diet [17].

Fructose malabsorption is one of the most common causes for chronic diarrhea due to a defect of the duodenal fructose transport system GLUT-5 [4]. We described earlier that fructose malabsorption is associated with low plasma folic acid [7], and low serum tryptophan [8] and zinc which may be promoting factors for the development of depression that apparently are associated with fructose malabsorption [6]. Besides these findings, fructose malabsorption seems to be a promoting factor for small intestinal bacterial overgrowth syndrome (SIBOS), which is known to be linked in the development of pancreatic diseases [10]. It was therefore of interest to examine whether fructose malabsorption may play a role in the development of pancreatic diseases.

In the present study, we found that fructose malabsorbers indeed had significantly higher serum amylase concentrations and lipase concentrations and elevated serum amylase was associated significantly with fructose malabsorption. We were not able to find this association in subjects with lactose maldigestion, which served as a control group. This result was more evident in females and in subjects that were older than 40 years. In the group we studied 13/107 subjects had (mildly) elevated serum amylase, 12 of these subjects had fructose malabsorption and only one subject with elevated serum amylase was a normal fructose absorber (Fisher's exact test:  $p = 0.037$ ). Unfortunately, we did not determine amylase clearance and/or amylase isoenzymes so we cannot say whether the increase in serum amylase concentrations in fructose malabsorbers is due to true hyperamylasemia or due to macroamylasemia. Further studies are needed to clarify this point.

Trespi and Ferrieri [10] reported about the coincidence of small intestinal bacterial overgrowth syndrome and chronic pancreatitis, however, the reason for this coincidence is not known. This finding was confirmed by other studies that showed an association of SIBOS with exocrine pancreatic insufficiency due to chronic pancreatitis [18]. Experimental studies showed an overgrowth of *Escherichia coli* 12 h after induction of pancreatitis in both the colon and distal small intestine [19]. Leveau et al. showed in the same study that a significant increase in the intestinal bacterial load increased the incidence of bacterial translocation to mesenteric lymph nodes. In a previous study, we found that fructose malabsorption may

present a promoting factor for the development of SIBOS [9]. In subjects with fructose malabsorption, chronically malabsorbed fructose leads to a raise of fermenting bacteria not only in the colon but also in the intestine with signs of chronic immune activation [9] and eventually leading to SIBOS. Thus, the probability may rise that some of these bacteria are translocated into the pancreatic duct leading to mild pancreatitis. This would explain why some patients with fructose malabsorption experience more pain than others and why some patients with fructose malabsorption present with mild elevated serum amylase and/or lipase. Our experience shows that the elevation of serum amylase/lipase in fructose malabsorbers tends to be chronically but diminish after dietary intervention. Further studies concerning this topic are on the way.

In summary, we believe that fructose malabsorption could be a promoting factor for the development of pancreatitis. We thus propose a possible relationship between hyperamylasemia and fructose malabsorption although potential pathophysiologic mechanisms are unknown. The diagnosis of pancreatic involvement in such cases may make an important contribution to therapy and fructose malabsorption should be considered as a differential diagnosis in moderately elevated serum amylase and/or serum lipase.

## 5. Conclusions

Serum amylase and lipase concentrations are higher in subjects with fructose malabsorption compared to normals. Therefore, fructose malabsorption should be considered as a differential diagnosis in moderately elevated serum amylase.

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