The sugar absorption test
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The intestinal mucosal barrier protects the human body against penetration by various noxes, such as bacteria, viruses, toxins, and antigens, but simultaneously serves as a selective inlet for more beneficial substances such as nutrients. In the neonatal period, the barrier is 'physiologically' more permeable for macromolecules and food proteins than in adulthood. This phenomenon can, in part, be explained by the immaturity of the digestive tract and the immune system. Evidence exists that the increased uptake of intact food proteins in early infancy could play a role in the development of various clinical disorders, including food allergy, coeliac disease and pancreatic insufficiency, but this uptake might also be important for the normal development of oral tolerance.

In chapter 1, first the non-immunologic and immunologic defense mechanisms of the intestinal mucosal barrier and their development in the neonatal period are reviewed, especially their relation to the 'physiologically' decreased barrier function. Then, the principle of measurement of the intestinal mucosal barrier by intestinal permeability for macromolecules is explained. The characteristics of the most common probes, $^{51}$Cr-EDTA, polyethylene glycols, proteins, horseradish peroxidase and sugars, are reviewed, and an overview of the results of studies performed with these probes in the last 6 years is given. Based on the characteristics and test results of these probes, we chose the sugars, lactulose and mannitol, as probe molecules for our intestinal permeability test, the sugar absorption test (SAT).

The aims of this thesis were to validate the SAT by determination of reference values, repeatability of the test and the laboratory assay in healthy controls. Furthermore, to determine the value of the sugar absorption test for clinical practice by studying intestinal permeability in several diseases which are thought to be related to an impaired intestinal barrier in early infancy, both immunologic gastrointestinal disorders, cow's milk allergy (chapter 3) and coeliac disease (chapter 4), and nonimmunologic gastrointestinal disorders, pancreatic insufficiency (chapter 5).

We validated the SAT by determination of the reference values of the SAT, permeability for lactulose, mannitol and sucrose and the lactulose/mannitol ratio, in 30 children and 40 adults. The repeatability of the test, in 29 controls with an interval of 1 day, was good. The repeatability of the laboratory assay for the SAT, in 26 patients, in the laboratories of clinical chemistry of both the University Hospital of Groningen and Rijnstate Hospital of Arnhem was excellent.

After validation of the sugar absorption test (SAT) in healthy controls, we determined the value of the SAT for clinical practice by 2 studies with the SAT in cow's milk allergy. Cow's milk allergy can be defined as proven or likely immunologically mediated reactions to cow's milk associated with reproducible clinical symptoms of the gastrointestinal tract, the skin or the respiratory tract. The symptoms must strongly decrease or disappear on elimination of cow's milk from the diet and aggravate or reappear on challenge with cow's milk. Intestinal permeability is thought to play a role in the pathophysiology of cow's milk allergy. Furthermore, it is a common disease in early infancy, often the first presentation of the atopic syndrome.

In the first study, we showed that intestinal permeability as measured by the SAT, increases during cow's milk challenge in infants with clinically positive cow's milk challenges compared to children with
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clinically negative cow’s milk challenges. This difference was reduced to non-significant levels after pretreatment with disodium cromoglycate (2x100mg), a drug thought to prevent cow’s milk allergic reactions. However, pretreatment with disodium cromoglycate did not reduce the number of clinically positive cow’s milk challenges. We conclude that disodium cromoglycate, in this dosage, reduces the local intestinal reaction but does not prevent the extra-intestinal response. As children with cow’s milk allergy had normal values of intestinal permeability on a cow’s milk free diet, it seems unlikely that an increased intestinal permeability is a primary factor for the development of cow’s milk allergic reactions.

In the second study, (chapter 3.3) we compared changes in clinical symptoms and intestinal permeability, as measured by the SAT, during treatment with two different cow’s milk hydrolysates (casein vs whey) in infants suspected of cow’s milk allergy. Furthermore, we determined the predictive value of several laboratory parameters (eosinophils, total IgE, IgE RAST against cow’s milk, soy, egg white) on the clinical outcome of the cow’s milk challenge in these infants. Although we found no difference in the clinical symptom score or intestinal permeability between both groups at any time during the study, we can not exclude that a difference between both hydrolysates might exist due to the small number of patients. No laboratory parameter could predict the clinical outcome of cow’s milk challenge. This study shows the problems related to evaluation of dietary treatment in infants suspected of cow’s milk allergy. A larger, less complicated study is necessary to give a more definite answer to the aims of this study.

Beside cow’s milk allergy, coeliac disease is another immunologic disorder related to food ingestion. In coeliac disease, gluten cause a different immunologic reaction which leads to damage of the small bowel mucosa. The diagnosis of coeliac disease is based on histologic changes, including villous atrophy, in small intestinal biopsies on a gluten containing diet, with recovery on a glutenfree diet. We performed 3 studies related to coeliac disease.

In the first study, (chapter 4.2) we showed that the SAT had a much higher sensitivity for coeliac disease than the D-xylose test, either in blood or urine, whereas the specificity was equal for all three tests.

In the second study, (chapter 4.3) we determined both the predictive value of the SAT, using lactulose and mannitol, for villous atrophy in the diagnostic process of children suspected of CD, as well as the relation of the SAT, permeability for mannitol, lactulose and the lactulose/mannitol ratio, with several morphologic characteristics of the small bowel mucosa in a subgroup of these children. The positive and negative predictive values of the SAT for villous atrophy were 92% and 84% respectively. Permeability for mannitol was best related to the villous surface, permeability for lactulose to the crypt volume, and the Lactulose/Mannitol ratio to the histological classification (according to routine pathology and to a modification of the Marsh criteria). We conclude that an increased intestinal permeability in active coeliac disease is due to both an increased permeability for lactulose and decreased permeability for mannitol. In coeliac disease, the increased permeability for lactulose seems to be related to changes in the crypts, whereas the decreased permeability for mannitol seems related to changes in the villi. The SAT can be helpful in the timing of pre- and postchallenge biopsies, and follow up of coeliac disease patients.

First degree risk for (the development of) coeliac disease occurs mainly in first degree relatives of patients with coeliac disease in first degree relatives of patients with coeliac disease and in patients with type 1 diabetes. A lower intestinal permeability might point towards the development of coeliac disease but the SAT might be helpful in this process.

After studying intestinal permeability in cystic fibrosis, pancreatic insufficiency occurs mainly in a decreased intestinal permeability in cystic fibrosis. We studied intestinal permeability in cystic fibrosis and four healthy groups. In cystic fibrosis, intestinal permeability increased by increased permeability for lactulose and decreased permeability for mannitol after 2 weeks, but not by increased permeability for mannitol. We conclude that increased intestinal permeability in cystic fibrosis is due to a decreased permeability for lactulose and increased permeability for mannitol.

In the third study, (chapter 4.4) we studied the effect of increased intestinal permeability on the absorption of nutrients in cystic fibrosis patients. After study, we determined intestinal permeability in cystic fibrosis patients and healthy controls. We found no change by increased permeability for lactulose in cystic fibrosis patients compared to healthy controls. We conclude that increased intestinal permeability in cystic fibrosis is not due to an increased permeability for lactulose in cystic fibrosis patients.
First degree relatives of patients with coeliac disease have an increased risk for (the development of) coeliac disease. In the third study, (chapter 4.4) we determined intestinal permeability and small bowel histology in first degree relatives of patients with coeliac disease and compared the results with patients with coeliac disease and controls. We found that intestinal permeability in first degree relatives, without villous atrophy, was higher than in controls but lower than in coeliac disease patients. An increased intestinal permeability might be related to constitutional factors in people susceptible to develop coeliac disease and might detect latent coeliac disease. Therefore the SAT might be helpful in family studies in coeliac disease.

After studying intestinal permeability in immunologic disorders, we studied intestinal permeability in a nonimmunologic disorder, exocrine pancreatic insufficiency. (chapter 5) In childhood, exocrine pancreatic insufficiency occurs mainly in patients with cystic fibrosis. We measured intestinal permeability in cystic fibrosis- and noncystic fibrosis patients with pancreatic insufficiency and found that intestinal permeability was increased in both groups. In cystic fibrosis patients, we found that intestinal permeability did not change by increasing pancreatic enzyme supplementation by 30-50% for 2 weeks, nor by decreasing the osmolarity of the test solution of the SAT by 75%. We conclude that an increased intestinal permeability in cystic fibrosis probably a consequence of pancreatic insufficiency, and is not related to the dose of pancreatic enzyme supplementation nor the osmolarity of the test solution. The increase is due to an increased permeability for lactulose which might point towards a defect in the tight junctions of the villi and/or the crypts.