FABAD J. Pharm. Sci., 26, 137-142, 2001

BİLİMSEL TARAMALAR / SCIENTIFIC REVIEWS

The Usefulness of Gut Permeability Test in Gastroenterology

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The Usefulness of Gut Permeability Test in Gastroenterology

Summary : *The intestinal barrier plays an important role in the pathogenesis of some gastroenterological diseases and its examination can be used in diagnosis and monitoring of some diseases and their course. Sugar absorption tests are non-invasive and non-expensive methods for examination of the intestinal barrier, namely for the measurement of intestinal permeability.*

Intestinal permeability is increased in patients with untreated celiac disease, with both the active inflammatory bowel diseases - Crohn`s disease and ulcerative colitis, with exocrine pancreatic insufficiency and drugs induced enteropathy, i.e.non-steroidal anti-inflammatory drug induced enteropathy.

Key Words: *Nucleosides, Anti-hepatitis Agents, HBV*

Received : 2.3.2001
Revised : 20.6.2001
Accepted : 20.8.2001

Gastroenteroloji'de Barsak Permeabilite Testlerinin Faydaları

Özet : *İntestinal bariyer bazı gastrointestinal hastalıkların, patojenezinde önemli bir rol oynar ve intestinal bariyer üzerinde gerçekleştirilen testler bazı hastalıkların teşhisi ve izlenmesinde kullanılabilir. Şeker absorpsiyon testleri intestinal geçirgenliğin ölçülmesi için kullanılan, invaziv ve pahalı olmayan testlerdir.*

İntestinal geçirgenlik çöliak hastalığında, aktif inflamatuar barsak hastalıkları olan Crohn hastalığı ve ülseratif kolitte, ekzokrin pankreas yetmezliğinde ve non-steroid anti-inflamatuar ilaçlar gibi bazı ilaçlarla indüklenmiş enteropatide artar.

Anahtar kelimeler : *Nükleositler, Anti-Hepatit bileşikler, HBV.*

Introduction

The intestinal mucosa forms a barrier between the internal and external environments, between the intestinal lumen containing potential antigen substances (such as e.g. bacteria, toxins, foodstuffs and other swallowed substances), and the submucosal space, where the cells of the immune system are located (GALT - gut-associated lymphatic tissue)[1,2].

The intestinal barrier is understood to be influenced by all mechanisms that are used by the organism in order to prevent penetration of macromolecular substances with antigenic potential into the internal environment. Under normal circumstances, only 1% of macromolecular substances penetrate this membrane, while under pathologic conditions (e.g.inflammation, ischemic-reperfusion damage of the intestine, damage of the intestinal mucosa caused by drugs and xenobiotics including alcohol), the amount of absorbed macromolecules increases and the risk of a systemic inflammatory or allergic reaction is also increased. The intestinal barrier is formed by unique connections of enterocytes (the intestinal barrier itself), and further by immunological and non-immunological components (see also table 1)[1,2]. Enterocytes are connected by tight junctions located on the luminal side of these cells. The immunological

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Table 1. The components of intestinal barrier

The intestinal barrier itself-connection of enterocytes by tight junctions
The immunological components - IgA secretion into bile and intestional lumen
The non-immunological components - presence of HCl and pepsin in stomach
– normal intestinal prestalsis
– presence of pancreatic and intestinal proteases in intestinal contents
– phlegm (mucus)
– unstirred water layer
– sufficient intestinal blood circulation
– intestinal peristalsis

components are formed by IgG and IgA antibodies, which are produced by lymphocytes from the gastrointestinal tract (GALT - gut-associated lymphatic tissue) and secreted into bile and mucus, and finally are formed in the intestinal lumen on the surface of enterocytes within the brush border area. The non-immunological components are formed by the presence of hydrochloric acid and pepsin in stomach lumen and the presence of pancreatic and intestinal proteases in the intestinal contents. Other factors such as mucus, and unstirred water layer on the surface of enterocytes, sufficient blood circulation in the intestinal mucosa and normal intestinal peristalsis must also be considered[1].

Gut (or intestinal) permeability is defined as an ability of the intestinal mucosa to permeate the macromolecules with antigenic potential from the intestinal lumen[1,3]. Large molecules (di- and trisaccharides, polypeptides and proteins) penetrate the small intestine mucosa via tight junctions and epithelial cells (M-cells); small molecules can penetrate the intestinal mucosa in various ways depending on how important they are for the human organism, e.g. glucose, amino-acids, di- and tripeptides can be absorbed by carrier-mediated transport systems using ATP. Other substances, e.g. fructose and xylose are absorbed by facilitated diffusion down a concentration gradient using a specific carrier or transporter, and other substances, such as mannitol and rhamnose simply diffuse passively along a concentration gradient[1-3].

According to the manner of penetration of substances through the intestinal mucosa and according to the intestine region, where these are absorbed, we can use various combinations of substances in order to examine various functions of the intestinal mucosa and various parts of the small intestine[2]. It is recommended that the substances used for examination of intestinal permeability should not be toxic, be water-soluble and not present in the organism under physiological or pathological conditions. The substances should also not be degraded either in the gastrointestinal tract, blood, or in any other organs, and after absorption should be completely eliminated in urine. We prefer those substances that fulfill the above-given requirements and are not expensive[1,2]. In order to examine intestinal permeability only chelates (e.g.EDTA, or DTPA), polyethyleneglycols of various molecular size, mono-, disaccharides and sugar-based alcoholes (lactulose, cellobiose, mannitol, rhamnose etc.) can be used[1-3].

The examination of intestinal permeability is performed usually using only one substance (e.g.^{51}Cr-EDTA) or a combination of several substances (e.g.lactulose/mannitol). When several substances are used, the risk of errors might originate from drinking insufficient amount of the test solution, deteriorated stomach emptying, fastening transit time, deterioration of the kidney functions, or incomplete collection of urine. The value of intestinal permeability is then determined as an index of absorbed substances by paracellular and transcellular routes (e.g.lactulose/mannitol)[1,2,3]. Saccharides in blood can be determined using enzymatic methods and liquid or gas chromatography. Intestinal permeability index is calculated as the ratio of the para- and transcellular absorbed saccharides. It is dependent on diuresis and on the amount of ingested substances[4].

Intestinal permeability tests with saccharides were introduced into common practice in 1974 by Menzies[3] and since that time have been tested in diagnostics and monitoring of various diseases.

The increasing value of intestinal permeability has been found in patients with untreated celiac disease[5-9] with inflammatory bowel diseases (IBD) - Crohn's disease and ulcerative colitis in the stage of

active inflammation[1,10-14]. Further increase of intestinal permeability can be found in patients with exocrine pancreatic insufficiency, mostly in patients suffering from cystic fibrosis[15,16], as well as in patients with non-steroidal anti-inflammatory drug induced enteropathy[17,18] and with enteropathy caused by cytotoxic agents[19,20].

The evaluation of intestinal permeability in diagnosis and monitoring of various diseases

CELIAC DISEASE

As regards patients with celiac disease, the gut permeability test can be used in diagnostics of the untreated illness, possibly also in monitoring of treatment by gluten-free diet[21].

Patients with untreated celiac disease show small intestinal mucosa villous atrophy. This leads to decreased absorption of monosaccharides and, on the contrary to increased penetration of disaccharides through tight junctions. Therefore gut permeability index rises in patients with untreated celiac disease, i.e. 10-30 times as opposed to the healthy population.

Another explanation lies in the different location of absorbed monosaccharides and disaccharides paracellularly in small intestinal mucosa. While mannitol is absorbed paracellularly in the area of the villus tips as well as in the area of crypts, lactulose is absorbed only in the area of crypts. Where the intestinal mucosa is atrophic, absorption of mannitol is decreased, while absorption of lactulose is higher in the area of crypts. It is a subject of dispute which of these theories is the correct. The truth is, however, that in patients with atrophic intestinal mucosa, absorption of disaccharides : lactulose, or cellobiose is higher, while absorption of monosaccharides, mannitol, and/or rhamnose is decreased, and permeability index is considerably increased. This fact has been ascertained in children[9,22,23], and adults[5-8,24]. The sensitivity of this test (cellobiose/mannitol) has been determined to be 96% and the specificity to be 70% in 1010 patients with celiac disease[8]. On comparison with a test performed using lactulose, and mannitol, which is considerably cheaper, values of sensitivity and specificity have been determined to be 89% and 54%[7] respectively, while negative predictive value was determined to be 99%, i.e. 95%[7,8]. Examination of intestinal permeability can thus be used in diagnosis and screening of untreated celiac disease of children and adults.

Examination of gut permeability can also be used in relatives of patients suffering from celiac disease who show, on average, increased values of the permeability index[6]. Another possible explanation is, nevertheless, also that increased gut permeability is found in patients with asymptomatic celiac disease who are more frequent among relatives of patients suffering from celiac disease[6].

After introduction of gluten-free diet, intestinal mucosa is renewed and at the same time gut permeability decreases to the normal values[25]. After adding gluten to patients suffering from celiac disease, intestinal mucosa is again damaged. This fact can be monitored by increasing the value of gut permeability through a saccharides test. After serving foodstuffs containing gluten to children with celiac disease, the index of permeability is increased, while examination of gut permeability can thus be used as a marker for performing small intestine biopsy[9].

Gut permeability test can thus be used together with clinical monitoring, for the purpose of examining anti-gliadine, anti-endomysium, and anti-reticuline antibodies, and monitoring of patient compliance with gluten-free diet[9,22-25].

Our experience is shown in table 2. 30 patients with untreated celiac disease were examined and results were compared with healthy controls. The patients with untreated celiac disease show significantly higher value of gut permeability using lactulose/mannitol

Table 2. Gut permeability in patients with celiac disease before and after treatment

	No	Age	LA/MA			
			mean	SD	minim	maxim
Celiac disease	30	38,700	0,303	0,451	0,020	2,330
Celiac disease after treatment	30	38,700	0,043*	0,047	0,014	0,085
Healthy controls	30	38,200	0,017*	0,008	0,001	0,032

* $p<0,001$

test in comparison with healthy controls. The value of gut permeability significantly decreases after treatment by gluten-free diet. The results are also shown in table 2.

INFLAMMATORY BOWEL DISEASES (CROHN'S DISEASE AND ULCERATIVE COLITIS)

Patients suffering from inflammatory bowel diseases, Crohn's disease, and ulcerative colitis have been found to have increased gut permeability both in saccharides-based tests, and chelates-based tests as well as polyethyleneglycol-based tests. It is a matter of discussion whether or not the damage to the intestinal barrier is the cause of Crohn's disease, or a symptom of inflammatory activity, and increased value of gut permeability is then the indicator of the extent of inflammation[10-14, 26-27]. In patients with ulcerative colitis at the silent stage, the gut permeability is within normal limits, while an increased value in active disease is related to damaging the intestinal barrier on the basis of active inflammatory conditions[11].

In patients with inflammatory bowel diseases the gut permeability is increased, i.e. namely in patients with Crohn's disease[10-14, 26-27], but also in patients with ulcerative colitis[11]. Increased gut permeability correlates with the activity of the disease[10,12,26,27], has also been found in some relatives of patients suffering from IBD[12]. Through the gut permeability test, Crohn's disease relapse can be predicted - with the sensitivity of 81%[13]. The value of gut permeability decreases after decreasing the disease activity - e.g. in patients treated by elemental diet[27], and also in patients treated by medicaments[28].

The value of gut permeability is not increased in patients with ulcerative colitis at the silent stage, but its value rises during the active stage of the disease [11].

As regards increased value of gut permeability in relatives of patients suffering from inflammatory bowel diseases, certain studies confirm increased gut permeability, other deny it. Based on our information, the value of gut permeability in relatives of these patients expressed by the lactulose/mannitol index is normal. We evaluated[9] relatives of patients with inflammatory bowel diseases and did not find any differences between these and healthy controls (see table 3)

Table 3. Gut permeability in relatives of patients with inflammatory bowel diseases

	LA/MA	
	mean	standard deviation
Relatives	0,023	0,012
Controls	0,019	0,012

It is considered that gut permeability examination is especially suitable in children with atypical symptomatology of Crohn's disease or celiac disease[29].

We evaluated small bowel permeability in patients with inflammatory bowel diseases, 69 patients with Crohn's disease (31 men, 38 women; in the average age 33,3 years) and 66 patients with ulcerative colitis (39 men, 27 women; in the average age 38,1 years) and compared with healthy controls. The small bowel permeability, measured as lactulose/mannitol index, increase in patients with active Crohn's disease or ulcerative colitis. (See also table 4.)

Table 4. Small bowel permeability in patients with inflammatory bowel diseases.

	LA/MA	
	mean	stand. deviation
CD-remission	0,028	0,018
CD-relapse	0,052	0,037
UC-remission	0,023	0,019
UC-relapse	0,106	0,197
Healthy controls	0,019	0,012

CD - Crohn's disease

UC - ulcerative colitis

LA/MA - index lactulose / mannitol

Discussion

The value of small bowel permeability is discussed in the following diseases :

a. Exocrine pancreatic insufficiency

The value of gut permeability is increased in patients with exocrine pancreatic insufficiency[30] for various reasons. Children with cystic fibrosis show increased

gut permeability for chelates and saccharides[15,16,31], while the highest values are reached by patients - homozygotes dF50[8]. In these patients, values of their gut permeability are as high as the values in patients with untreated celiac disease[31]. It is still a question to what extent insufficiency of pancreatic enzymes participates in damaging intestinal barrier and to what extent the actual damage of intestinal mucosa in cystic fibrosis participates in the same. The value of gut permeability does not change during the disease, or during infectious diseases of the respiratory tract, developing as complications of the lung form of cystic fibrosis[31].

b. Food allergy

The values of gut permeability in patients with food allergy are increased according to some studies[32-34], according to other studies the value of gut permeability is not different from healthy persons[2,36]. More exact differentiation of what types of food allergies cause higher gut permeability and what do not, has not been performed yet. Based on our experience[36], the value of gut permeability evaluated by the lactulose/mannitol index is equal to healthy controls.

c. Non-steroidal anti-inflammatory and cytostatic drug induced enteropathy

Gut permeability tests can be used in patients with enteropathy induced by non-steroidal anti-inflammatory drugs[18], when the value of gut permeability increases. The value of gut permeability also rises in patients with malignant tumours treated by cytostatics.

With 5-fluorouracil[19], according to recent studies, this increase correlates with the level of mucositis caused by chemotherapy and after decreasing the inflammation by treatment it reaches normal values again[20].

Conclusion

Sugar absorption tests are non-invasive tests that evaluate the integrity of the intestinal barrier, i.e. its ability to pass macromolecular substances from intestinal lumen. These tests have already been used in diagnostics of celiac disease, investigating non-symptomatic patients in risk groups, and evaluation of disease activity in patients with inflammatory bowel diseases etc., while other areas of gastroenterology are still awaiting application.

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