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Leaky Gut in Patients with Diarrhea-Predominant Irritable Bowel Syndrome and Inactive Ulcerative Colitis

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Key Words
Intestinal barrier · Irritable bowel syndrome · Permeability · Ulcerative colitis

Abstract
Background/Aims: Defective epithelial barrier has been implicated in the pathogenesis of irritable bowel syndrome (IBS) and inflammatory bowel diseases. The aim of this study was to investigate gut permeability in patients with inactive ulcerative colitis (UC) and in patients with IBS. ***Methods:*** IBS patients of the diarrhea-predominant (IBS-D) and of the constipation-predominant subgroup (IBS-C), patients with inactive UC and healthy subjects were enrolled. Gut permeability was evaluated by measuring 24-hour urine excretion of orally administered ^{51}Cr-EDTA. Clinical symptoms were evaluated in IBS-D patients and correlated to colonic permeability. ***Results:*** There was a significant decrease in the proximal small intestinal permeability in IBS-C patients compared to controls (0.26 ± 0.05 vs. 0.63 ± 0.1%; $p < 0.05$). Distal small intestinal permeability showed no significant difference in the studied group of patients compared to controls. Colonic permeability of IBS-D and inactive UC patients was significantly increased compared to controls (2.68 ± 0.35 and 3.74 ± 0.49 vs. 1.04 ± 0.18%; $p < 0.05$, $p < 0.001$). Colonic permeability of IBS-D patients correlated with stool frequency. ***Conclusions:*** Elevated gut permeability is localized to the colon both in IBS-D and in inactive UC patients.

Introduction

The intestinal epithelium is faced with the dual task of providing a barrier while also allowing nutrient and water absorption; therefore, its integrity is crucial to maintain physiological function and prevent diseases. A defective epithelial barrier function, which can be measured as increased gut permeability, has been implicated in the pathogenesis of both irritable bowel syndrome (IBS) and inflammatory bowel diseases (IBD).

IBS is a gastrointestinal disorder characterized by abdominal pain and altered bowel habit, for which there is no apparent structural basis. Recently, there is growing evidence for microinflammation of the intestinal and colonic mucosa to play a role in IBS pathogenesis [1–4]. It is also well established that impaired intestinal barrier function could facilitate the passage of luminal antigens

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and lead to a mucosal immune response [5]. Nevertheless, gut permeability in IBS was reported enhanced in 50% of postinfectious IBS patients, which is in agreement with a study showing increased small intestinal permeability in both the postinfectious and sporadic forms of IBS, characteristically in the diarrhea-predominant subtype [6–8]. In accordance, the report on the 'Walkerton epidemic' – a waterborne outbreak of acute gastroenteritis in Walkerton, Ont., Canada – proved subtle increase in small intestinal permeability in a large number of patients with IBS; however, in vitro studies suggest enhanced permeability in colonic biopsies of IBS patients compared to healthy subjects [9, 10]. Therefore, it seems that gut permeability in IBS is altered, though the data on the subgroup of IBS patients affected and the exact localization of the defective barrier are still contradictory. Thus, identifying the role of defective mucosal barrier in IBS pathomechanism and symptom generation may be an important landmark in better understanding the disease.

Ulcerative colitis (UC) and Crohn's disease, collectively known as IBD, share the principals of their pathogenesis, namely immunodysregulation and intestinal hyperpermeability. Epithelial barrier impairment is considered important in IBD for two reasons: on the one hand, it leads to increased luminal antigen exposition of the lamina propria, i.e. immune cells which further aggravate the inflammatory process, and on the other hand, it enables ions and water to move passively into the intestinal lumen, resulting in diarrhea. Although there is strong evidence for barrier dysfunction in IBD [11], it still remains unclear whether this is the primary cause of the disease or a consequence of mucosal inflammation. The presence of hyperpermeability in noninvolved segments of the intestine of Crohn's disease patients as well as in first-degree relatives has been reported [12–14] and increased permeability has also been associated with an increased risk of relapse [15, 16]. Data are, however, less abundant on paracellular permeability regarding UC. An increase in gut permeability has previously been reported in clinically active UC, which was also shown to correlate with disease severity [11, 17, 18]. Still, gut permeability has not yet been evaluated in remission of the disease.

Therefore we aimed: (1) to measure intestinal and colonic permeability of patients with IBS of the diarrhea- (IBS-D) and of the constipation-predominant subtype (IBS-C), (2) to investigate a possible correlation between increased gut permeability and clinical symptoms in IBS-D patients, and (3) to measure intestinal and colonic permeability in patients with UC in remission.

Methods

Study Participants

Thirty patients fulfilling the Rome III criteria for IBS participated in the study, of which 18 were IBS-D patients (25–68 years, mean age 49 years, 12 females, 6 males), 12 were IBS-C (37–65 years, mean age 56 years, 10 females, 2 males). None of the IBS patients related the onset of their symptoms to infectious gastroenteritis. Organic gastrointestinal disorders were excluded by detailed blood and stool analyses, serological assays for celiac disease, lactose-hydrogen breath test and colonoscopy. Thirteen patients with inactive UC (partial Mayo score ± SEM: 1.3 ± 0.2; CRP (mg/dl) ± SEM: 3.8 ± 1.3) that were previously shown to have either left-sided colitis or pancolitis were also enrolled (29–72 years, mean age 47 years, 10 females and 3 males). Ten voluntary subjects, free of any gastrointestinal symptoms, served as controls (38–65 years, mean age 49 years, 8 females, 2 males). Patients and voluntary subjects with impaired renal function, alcohol consumption, using NSAIDs, prokinetics, antihistamines or immunosuppressive agents were excluded from the study. UC patients were required to be exclusively on 5-ASA maintenance therapy. The study protocol was approved by the Human Investigation Review Board, University of Szeged. All subjects provided written and informed consent to participate.

Permeability Measurement with ^{51}Cr-EDTA

To measure intestinal and colonic permeability after an overnight of fasting, participants emptied their bladders and consumed ^{51}Cr-EDTA (Perkin Elmer Life Sciences, Boston, Mass., USA) of 1.8 MBq activity dissolved in 100 ml of water, followed by 200 ml of standard meal (Nutridrink, Nutricia, Budapest, Hungary) containing 300 kcal. Study participants were requested to restrain from drinking for 3 h and from eating for 5 h. Gut permeability was evaluated by measuring 24-hour urine excretion of orally administered ^{51}Cr-EDTA, where time periods were chosen to relate to permeability within the proximal (0–3 h) and distal (3–5 h) small intestine and the large bowel (5–24 h) [18–20]. Urinary output was recorded for each period and the radioactivity of 1-ml aliquots was counted by a gamma-counter (Packard Cobra, Canberra Packard, UK) in duplicates. Gut permeability was expressed as percentage of urinary excretion of the orally administered dose of ^{51}Cr-EDTA (%).

Evaluation of Symptoms in IBS-D Patients

IBS-D patients were asked to fill out a questionnaire, regarding their clinical symptoms at the time of the permeability measurement. Stool frequency (/week) and consistency (according to the Bristol stool scale), frequency of abdominal pain, distension and bloating (/week), intensity of abdominal pain, distension and bloating and quality of life (visual analogue scale, VAS; %) were evaluated and correlated to colonic permeability.

Statistics

Data are presented as means ± SEM. For all statistical analysis GraphPad Prism 4.0 (GraphPad, San Diego, Calif., USA) was used. Multiple comparisons for permeability of different patient groups were analyzed by repeated measures of one-way ANOVA, followed by Tukey's post-test. The unpaired t test was used to evaluate colonic permeability data in subgroups of UC patients. Linear regression was applied to establish correlation between clinical symptoms and permeability. Statistical significance was accepted at $p < 0.05$.

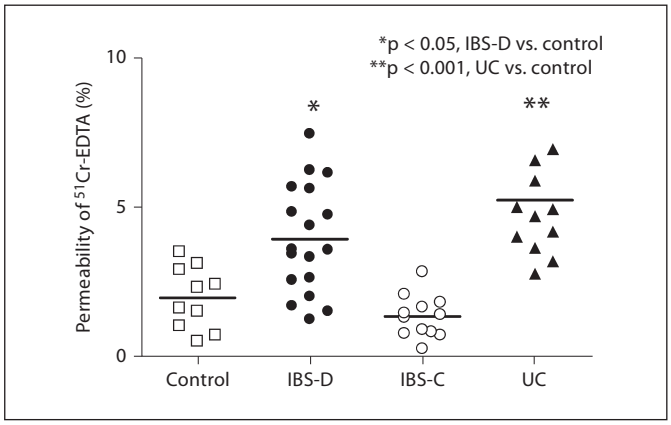

Fig. 1. 24-hour excretion of ^{51}Cr-EDTA in subgroups of IBS and inactive UC patients compared to control subjects.

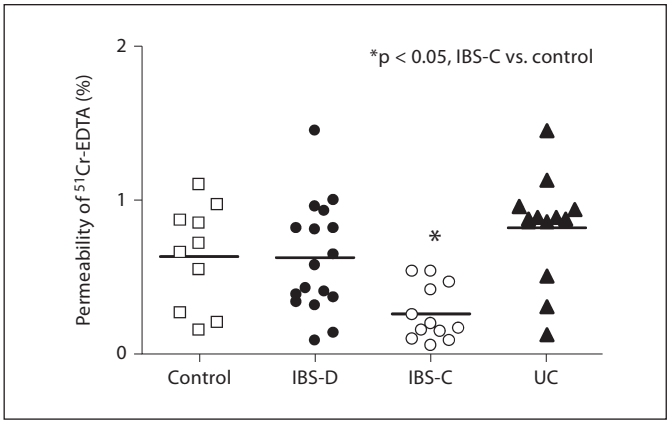

Fig. 2. Excretion of ^{51}Cr-EDTA measured between 0 and 3 h after ingestion in subgroups of IBS and inactive UC patients compared to control subjects, which represents proximal small intestinal permeability.

Results

The 24-hour urinary excretion of orally administered ^{51}Cr-EDTA showed a significant increase in the IBS-D and UC groups of patients compared to control subjects (3.93 ± 0.43 and 5.39 ± 0.61 vs. 1.97 ± 0.33%, $p < 0.05$ and $p < 0.001$, respectively). Gut permeability in IBS-C patients remained as low as that of controls, showing no significant difference (1.34 ± 0.2%; fig. 1).

Results were consistent with the above when time periods were chosen to relate to permeability within the proximal (0–3 h) and distal (3–5 h) small intestine and the large bowel (5–24 h) during 24-hour urine excretion of orally administered ^{51}Cr-EDTA. There was no significant difference in the proximal small intestinal permeability in IBS-D and inactive UC patients compared to controls (0.63 ± 0.08 and 0.82 ± 0.09 vs. 0.63 ± 0.1%, respectively). However, proximal small intestinal permeability of IBS-C patients was significantly decreased compared to controls (0.26 ± 0.05%; $p < 0.05$; fig. 2). Gut permeability did not show any significant difference regarding the distal small intestine in the diarrhea- and constipation-predominant subgroups of IBS patients, and patients with inactive UC compared to control subjects (0.61 ± 0.12, 0.39 ± 0.08, 0.83 ± 0.09 vs. 0.43 ± 0.07%, respectively; fig. 3).

Colonic permeability of IBS-C patients remained as low (0.69 ± 0.12%) as that of control subjects, showing no significant difference. On the contrary, colonic permeability of IBS-D patients proved to be significantly higher compared to healthy controls (2.68 ± 0.35 vs. 1.04 ± 0.18%; $p < 0.05$). Furthermore, colonic permeability of patients with inactive UC was also found to be significantly elevated compared to control subjects (3.74 ± 0.49 vs. 1.04 ± 0.18%; $p < 0.001$; fig. 4a). There was no significant difference in colonic permeability between patients with previous endoscopic diagnosis of left-sided colitis or pancolitis (3.26 ± 0.43 vs. 4.31 ± 0.94%, n.s.; fig. 4b).

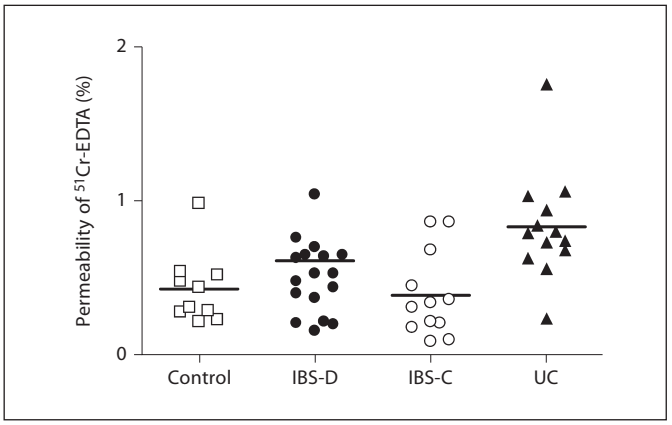

Fig. 3. Excretion of ^{51}Cr-EDTA measured between 3 and 5 h after ingestion in subgroups of IBS and inactive UC patients compared to control subjects, which represents distal small intestinal permeability.

Stool consistency, frequency of abdominal pain, distension and bloating, intensity of abdominal pain, distension and bloating or quality of life did not show correla-

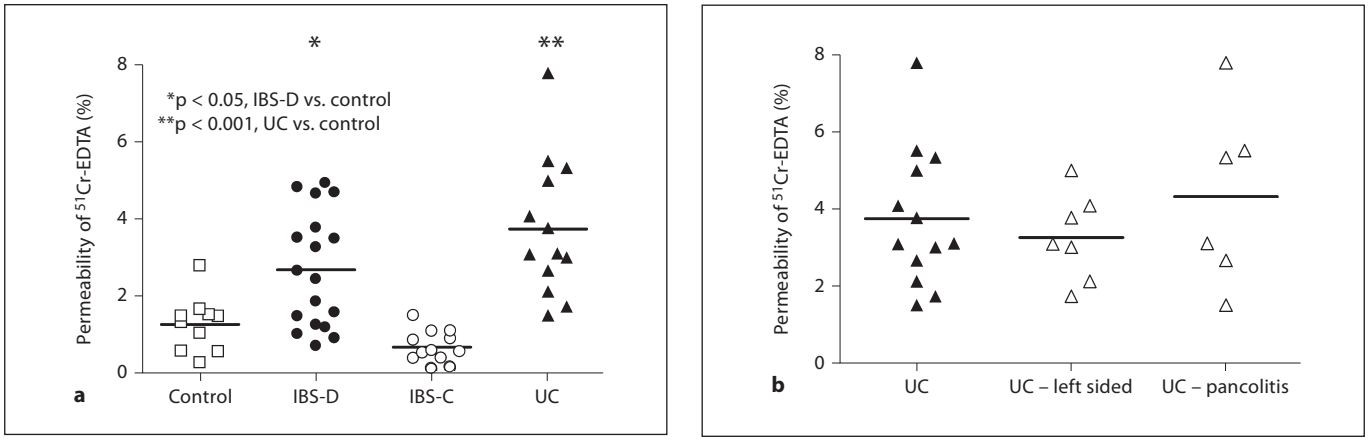

Fig. 4. a Excretion of ^{51}Cr-EDTA measured between 5 and 24 h after ingestion in subgroups of IBS and inactive UC patients compared to control subjects, which represents colonic permeability. **b** Comparison of colonic permeability in patients with inactive left-sided colitis and pancolitis.

Table 1. Correlation between clinical symptoms and colonic permeability in IBS-D patients

	IBS-D patients mean ± SEM	Correlation (Pearson r)	UC patients mean ± SEM	Correlation (Pearson r)	Correlation (p value)
Number of stools (/week)	19.5 ± 3.34	0.62			0.0057
Stool consistency (Bristol stool scale)	4.94 ± 0.26	–0.23			n.s.
Frequency of abdominal pain (/week)	8.44 ± 2.04	0.27			n.s.
Intensity of abdominal pain (VAS, %)	53.33 ± 6.3	–0.22			n.s.
Frequency of abdominal distension (/week)	7.83 ± 2.03	0.24			n.s.
Intensity of abdominal distension (VAS, %)	56.94 ± 5.33	–0.05			n.s.
Frequency of bloating (/week)	5.0 ± 0.97	–0.3			n.s.
Intensity of bloating (VAS, %)	50 ± 5.17	–0.11			n.s.
Quality of life (VAS, %)	45.28 ± 5.24	0.02			n.s.
Number of stools (/week)			1.92 ± 0.33	–0.13	n.s.

tion with increased colonic permeability in IBS-D patients (table 1). Nevertheless, stool frequency showed good correlation with colonic permeability in IBS-D patients (r = 0.62; p = 0.005; fig. 5). Colonic permeability of inactive UC patients did not show correlation with stool frequency.

Discussion

The present study shows that proximal intestinal permeability measured from 0 to 3 h after oral consumption of ^{51}Cr-EDTA showed no significant difference in IBS-D or inactive UC patients compared to controls; however, in IBS-C patients a significant decrease was found. Distal small intestinal permeability was similar in all studied groups of IBS, inactive UC patients and healthy controls. Colonic permeability of IBS-C patients remained as low as that of control subjects; however, colonic permeability of IBS-D patients and UC patients in remission was significantly higher than that of healthy controls. We also established that among clinical symptoms evaluated, increased stool frequency correlated with the increase in colonic permeability in IBS-D patients.

The limitation of our study is that clinical remission in UC patients was assumed based on the partial Mayo score and serum CRP level, which does not always guarantee mucosa healing in IBD patients.

The intestinal barrier is composed of the secreted mucus layer, the structural barrier of epithelial cells and the

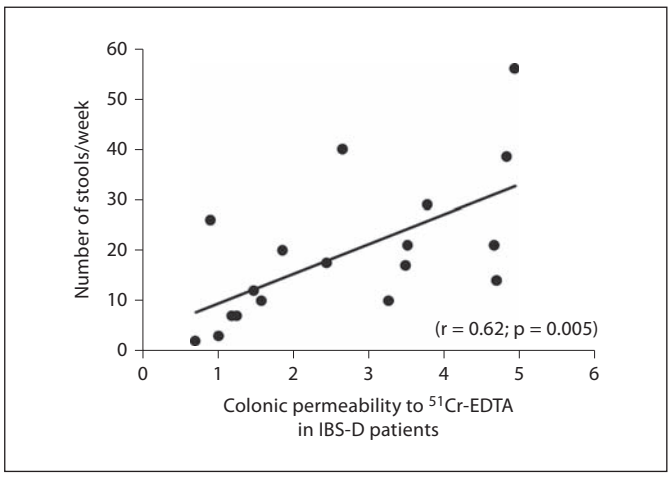

Fig. 5. Correlation of stool frequency and colonic permeability in IBS-D patients.

underlying nonepithelial mucosal cells, mainly leukocytes with regulatory function [21]. The main constituent of the intestinal barrier is the single layer of epithelial cells, where the paracellular space between adjacent cells is sealed by intercellular tight junctions, which represent the rate-limiting step for paracellular transit. Naturally, the barrier is severely compromised when epithelial cells are lost, as occurs in erosions and ulcerations of active IBD, however recent data spotlight on less striking alterations, namely on altered tight junction function both in IBS [10, 22] and in IBD [23, 24], which may serve as a structural basis for altered gut permeability.

According to recently published data, subgroups of IBS patients affected by impaired permeability and the localization of the defective barrier are still matters of contradiction. Our results show that epithelial barrier dysfunction is localized to the colon and is restricted to the diarrhea-predominant subtype of IBS patients. This is in accordance with our previous observations that fecal supernatants of IBS-D patients with high serine-protease activity were able to evoke immediate increase in paracellular permeability on colonic strips of mice in contrast to supernatants of IBS-C patients or healthy subjects [20]. Our previous data also provided in vitro evidence that the increase in colonic paracellular permeability is dependent on serine-protease activity and protease-activated receptor 2; therefore, we may speculate that the high concentration of serine proteases in the colonic luminal content of IBS-D patients [25] are also able to induce permeability changes in vivo. Present results are also in agreement with a report on increased permeability of colonic biopsies from IBS patients [10]. Our data are in contrast with a recent study, showing no difference in gut permeability between IBS patients and healthy controls measured by the lactulose/mannitol test and polyethylene glycols (PEGs) of different molecular weight [26]. Evidence shows that saccharides are degraded by colonic bacteria and PEG recovery in ileostomy patients is similar to that of healthy controls [27, 28]. Thus, in contrast to ^{51}Cr-EDTA [29], neither of these compounds can be considered ideal to measure colonic permeability, where we localized the barrier dysfunction. Dysregulation of epithelial barrier function leads to increased exposure to luminal antigens, bacterial translocation and to activation of the mucosal immune system. Low grade inflammation of the intestinal mucosa, increased number of mast cells, T cells and proinflammatory cytokines has lately been verified by several studies on IBS, mostly being present in the ileocoecum and in the colon [1–4, 30]. This is in accordance with our results regarding the localization of increased permeability of IBS-D patients.

Our results show that the ^{51}Cr-EDTA excretion of IBS-C patients is significantly decreased in the first three hours of the experiment compared to controls, which we rather attribute to the fact that in healthy subjects ^{51}Cr-EDTA reaches its peak concentration in the serum within 1–2 h after administration [20]; however, in IBS-C patients who are known to bear with delayed gastric emptying [31] marker absorption may be delayed. In support, there was no significant decrease in the 24-hour ^{51}Cr-EDTA excretion between IBS-C patients and controls.

Until recently, reports on the correlation between gut permeability and IBS symptoms are contradictory [7, 8, 32]. In our present study, we add new information in that we show that among several clinical symptoms evaluated, stool frequency correlates well with colonic permeability in IBS-D patients. A similar correlation between colonic permeability and stool frequency cannot be observed in UC patients with low partial Mayo score, which also supports the theory of a different underlying pathomechanism.

Epithelial barrier defect in UC is characterized by three mechanisms: in moderate-to-severe inflammation leaks correlate with epithelial erosions/ulcers and in mild forms leaks are considered to be either foci of epithelial apoptosis or altered epithelial tight junction structure [33, 34]. So far, little information has been available on the mechanism of epithelial barrier defect in UC in remission. We have shown that colonic permeability is impaired in inactive UC irrespective of the extension of the

disease, when comparing left-sided colitis or pancolitis patients. These novel findings regarding increased colonic permeability in inactive UC are in agreement with the fact that myosin light chain kinase (MLCK) expression, which is a key enzyme in regulating cytoskeletal contractility and thus tight junction permeability, is also increased in patients with histologically inactive UC [35]. It has also been recently reported that in UC patients cathepsin-G and its selective receptor, proteinase-activated receptor 4 (PAR4) are overexpressed compared to controls, factors that are known to be involved in inducing increased colonic paracellular permeability in animal models [36]. In inflamed mucosa of patients with UC upregulation of pore-forming claudin-2 tight junction protein has been reported; however, no such changes were seen in inactive disease [23, 24]. Though little is yet known about structural alterations in the epithelial tight junction in inactive UC and one might speculate that it offers a plausible explanation for the persistent 'leaky gut', it needs further evaluation.

In conclusion, our results show that impaired epithelial barrier function is localized to the colon and is restricted to the diarrhea-predominant subtype of IBS patients. Our finding that increased colonic permeability in IBS-D patients correlates with stool frequency indicates that defective epithelial barrier function may contribute to the development of gut dysfunction and symptom generation. Furthermore, the increased colonic permeability of UC patients with remission implicates that there is no complete restoration of epithelial barrier function even in remission of the disease. However, the question whether altered barrier function makes a primary or secondary contribution to IBS and IBD pathogenesis still persists, and restoring barrier function remains a future therapeutic objective.

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Disclosure Statement

The authors have no competing interests.

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