Annals of Gastroenterology (2013) **26,** 23-28

Electrolyte and acid-base disorders in inflammatory bowel disease

Fotis Barkas, Evangelos Liberopoulos, Anastazia Kei, Moses Elisaf

University of Ioannina Medical School, Ioannina

Abstract

Inflammatory bowel disease (IBD) is a chronic inflammatory intestinal disorder encompassing two major entities: Crohn's disease and ulcerative colitis. Intestinal inflammatory processes reduce the absorption of sodium, chloride and calcium, while they increase potassium secretion. In addition, mild to severe metabolic alkalosis may occur in IBD patients, mainly depending on the severity of the disease and the part of the gastrointestinal tract being affected. The aim of this review is the presentation of the electrolyte and acid-base disturbances in IBD and how the activity state of the disease and/or treatment may affect them.

Keywords Acid-base disturbances, alkalosis, calcium, chloride, Crohn's disease, electrolytes, inflammatory bowel disease, pH, ulcerative colitis, potassium, sodium

Ann Gastroenterol 2013; 26 (1): 23-28

Introduction

Inflammatory bowel disease (IBD) represents a chronic inflammatory disorder of the intestine, generally classified by histopathological and clinical features into two major entities: Crohn's disease (CD) and ulcerative colitis (UC) [1]. UC is characterized by diffuse mucosal inflammation limited to the colon. It involves the rectum in about 95% of cases and may extend proximally in a symmetrical, circumferential, and uninterrupted pattern to involve parts or the whole of the large intestine [2]. On the other hand, CD is characterized by asymmetric, transmural and occasionally granulomatous inflammation affecting the gastrointestinal (GI) tract, most commonly the terminal ileum and colon, with the potential for systemic and extraintestinal complications [3]. CD-associated transmural inflammation often leads to fibrosis, obstructive complications, sinus tracts and fistulae, not typically seen in UC [1].

IBD-associated mucosal inflammation and the consequent impaired secretion and absorption of electrolytes often result in electrolytic and acid-base imbalance in IBD patients [4,5]. The main transport abnormality is the decrease in net sodium and chloride absorption, resulting in impaired water absorption or secretion [6]. The aim of this review is the presentation of the mechanisms through which electrolyte and acid-base disturbances take place in IBD and how the activity state of the disease and/or IBD treatment may affect them.

Department of Internal Medicine, University of Ioannina Medical School, Ioannina, Greece

Conflict of Interest: None

Correspondence to: Evangelos Liberopoulos, MD FASA FRSH, Ass. Professor of Internal Medicine, University of Ioannina Medical School, 45 110 Ioannina, Greece, Tel.: +30 26510 07502, Fax: +30 26510 07016, e-mail: vaglimp@yahoo.com

Received 13 February 2012; accepted 6 April 2012

Methods

We searched PubMed up to 20 January 2012 using combinations of the following keywords: inflammatory bowel disease, Crohn's disease, ulcerative colitis, electrolytes, ion disorders, acid-base, pH, metabolic. Original papers, review articles and case reports are included in the present review. Their references were scrutinized for relevant articles. For articles not written in English, only the abstracts were considered.

Electrolyte transport in the normal gut

The epithelial layer covering the inner surface of the mammalian colon is responsible for the transport of electrolytes. Consequently, apart from its motor function the colon has both an absorptive and a secretory function, moving large quantities of salt and water from the mucosal side towards the blood side or vice versa [7]. Therefore, the primary non-motor function of the mammalian colon is the absorption of 1.3-1.8 L of electrolyte-rich fluid per day, which accounts for 90% of the salt and water entering the proximal colon [8].

The key determinant of colonic water absorption is the rate of Na^+ absorption. This can be either electrogenic via the epithelial sodium channel (ENaC) or electroneutral via parallel $Na^+/H^+$and Cl^-/HCO_3^- exchange [9]. Specifically, in

electrogenic absorption of Na^+, apical Na^+ entry is passive, channel-mediated and inhibited by amiloride, while basolateral Na^+ extrusion is mediated by Na^+-K^+-ATPase (the electrogenic 'Na^+ pump') [9]. On the other hand, in electroneutral NaCl absorption, apical Na^+ uptake is mediated by Na^+-H^+ exchange, most likely linked with intracellular pH to apical Cl^-/HCO_3^- exchange [9]. As for the place in which these absorptive processes are located, the electrogenic absorption is confined to the surface epithelium and upper crypts of the distal colon [10], while the electroneutral one takes place in both crypts and surface epithelium of the proximal and distal colon [11].

Another major function of the colon is secretion of electrolytes, which is balanced by absorption. It has been suggested that secretion clears the crypts from mucus, secreted from goblet as well as columnar epithelial cells [12]. However, there is evidence that secretion is located in both surface epithelium and crypts [13]. A limited KCl secretion under resting conditions becomes a pronounced KCl/NaCl secretion upon stimulation by secretagogues or when exposed to bacterial toxins. In the absorbing colon and in the absence of secretagogues, release of K^+ to the luminal side is potential-driven and largely maintained by the ENaC. This leads to a luminal K^+ concentration which is above that of serum. As for the absorption of NaCl, polarized distribution of transport proteins is required for secretory salt transport. Secretory epithelial cells contain Cl^- and K^+ channels in their luminal membranes, allowing for secretion of KCl. In addition, after secretory stimulation and upon inhibition of absorption, paracellular transport of Na^+ facilitates secretion of NaCl [14-17].

As far as the Cl^- is concerned, the Na^+-K^+-ATPase and Na^+-2Cl^--K^+ co-transporter, and cystic fibrosis transmembrane conductance regulator (CFTR) are essential channels for Cl^- secretion. The apical Cl^- conductance is formed predominantly by CFTR, which has a central role in colonic ion transport. On their basolateral membranes, secretory cells contain Na^+-2Cl^--K^+ cotransporters that take up Cl^- from the serosal side of the epithelium together with Na^+ and K^+. Basolateral K^+ channels allow for the recycling of K^+ via the basolateral membrane, thus hyperpolarizing epithelial cells and maintaining the electrical driving force for Cl^- secretion [11,18].

In parallel to KCl, bicarbonate is secreted to the luminal side of the epithelium, producing an intestinal juice of slightly alkaline pH. There are several alternative pathways responsible for the bicarbonate transportation, such as 1) electrogenic HCO_3^- efflux, 2) HCO_3^- transport via a luminal Cl^-/HCO_3^- exchanger, or 3) via a short chain fatty acid (SCFA)/HCO_3^- exchanger [19-22].

Electrolytic disorders in IBD

Ulcerative colitis

A number of studies suggested that electrolyte deficiencies in UC patients may even be life-threatening, with the main transport abnormality being the decrease in net sodium and chloride absorption, resulting in impaired water absorption and secretion [24-28].

Active UC has been associated by Edmonds *et al* with a very low transmucosal electrical potential difference (PD) and loss of the characteristic ability of the mucosa to absorb sodium against considerable electrochemical gradients [29]. In addition, the increased plasma-to-lumen sodium flux rate suggesting increased leakiness of the mucosa and the loss of the active sodium absorption mechanism comprise active UC features. In contrast, in resolving UC, PD increases and the aforementioned disturbances in sodium transport are limited, while at full recovery epithelial function is normal. On the other hand, potassium secretion rate showed little difference at various stages of the disease. However, whereas normally the PD with the lumen negatively charged would tend to facilitate the flux of potassium into the lumen and lead to the establishment of an intraluminal steady-state concentration substantially greater than that of blood, the nearly normal secretion of potassium in UC with a PD almost zero suggested that potassium loss to the lumen was relatively excessive [29]. In fact, mucus collected from UC patients had a relatively high sodium and potassium content. Overall, the colonic absorption of sodium and water in ulcerative proctocolitis was impaired and the secretion of potassium increased compared with healthy subjects [30]. In addition, Sandle *et al* studied the net electrolyte and water transport in the rectum and the rectal PD in 3 groups before and 5 h after a simple i.v dose of steroids. The first group consisted of 9 patients with active UC, the second of 6 patients with inactive UC and the third of 17 control subjects. A strong reduction in PD and net sodium absorption was noticed in patients with active UC, while in those with inactive UC these transport parameters were normal [31]. Similarly, bilateral sodium isotope flux studies in distal colonic mucosa demonstrated decreased net sodium absorption in untreated UC patients due to a reduced mucosa to serosa unidirectional flux [32]. *In vitro* measurements of the net transport and simultaneous bidirectional flux rates of water and electrolytes across the human colonic epithelium demonstrated that in UC the colon becomes less absorptive and more secretory. Specifically, in the active phase of UC colon absorbs less water and sodium and secretes more potassium [33]. Specifically for potassium, an *in vitro* study showed that when the potassium content of normal mucosal cells was deliberately reduced and then returned to a suitable environment, they rapidly regained potassium in contrast with UC mucosal cells which continued to lose potassium, implying that mucosal cells in UC 'leak' potassium [34].

In another study, sodium absorption was studied in UC (n=11) proctocolectomized patients with radiologically normal small bowel. It was found that sodium absorption was not markedly diminished in the intestine of UC patients [35].

Rampton *et al* tested the hypothesis that the diarrhea of patients with active UC was due to inhibition of large intestinal salt and water absorption by enhanced local mucosal prostaglandin (PG) synthesis [36]. It was noticed that increased rectal mucosal PGE2 release varied inversely with sodium

absorption and directly with potassium secretion in UC patients. Also, higher PGE2 release was associated with less negative PD. However, flurbiprofen, a PGE2 synthesis inhibitor, was associated with deterioration of the transport of sodium and potassium instead of improving it. Thus, it was concluded that increased PGE2 production was unlikely to play a critical role in the abnormalities of electrolyte transportation found in UC [37].

For patients with UC the mean 24-h fecal weight was greater than normal. As far as fecal fluid was concerned, the mean concentrations of Na^+ and Cl^- were higher and concentrations of K^+ lower than levels in the normal subjects. On the other hand, fecal fluid from patients with ulcerative proctitis had a nearly normal ionic composition [38]. In another study, electrolytes were measured in 24-h fecal collections from UC (n=18), and 16 healthy subjects. Similarly, Na^+ and Cl^- concentrations were increased, while that of K^+ was very low [39].

Crohn's disease

A study assessing 63 patients with CD for electrolyte disorders demonstrated that 33% of them had low levels of serum sodium, potassium, calcium, and magnesium either alone or in combination [23].

In vitro measurements of the net transport and simultaneous bidirectional flux rates of water and electrolytes across the human colonic epithelium demonstrated that in CD there was a reversal of Na^+ and water flux, and K^+ secretion was increased. Additionally, it was noticed that where the disease was of such extent and severity as to demand panproctocolectomy and ileostomy, the losses of K^+, Na^+ and water were equal to or even exceeded those found in UC [33].

In another study, sodium absorption was studied in CD (n=10) proctocolectomized patients with radiologically normal small bowel. It was found that despite clinical and radiographic remission, sodium absorption was markedly diminished in the intestine of CD patients [35]. This was attributed to the fact that CD comprises a more generalized disease.

The ionic composition of fecal fluid from 13 patients with CD limited to the colon had lower mean sodium and chloride but higher potassium concentration and osmolality compared with fecal fluid from patients with diffuse UC. Thus, differences in the composition and perhaps the pathogenesis of the diarrhea of CD and UC could not be excluded. Of note, in comparison with normal subjects, increased potassium secretion and decreased sodium absorption were noticed in both inflammatory bowel syndromes [38].

Notable seasonal variations in vitamin D status and bone turnover markers have been reported in CD patients [40]. Specifically, the 25-hydroxyvitamin D was significantly lower (up to 65%) in CD patients compared with healthy subjects [41-45], potentially due to reduced intestinal absorption, disturbed enterohepatic circulation and reduced nutrient intake of vitamin D. Moreover, additional factors increasing hypocalcemia risk include winter season [42,46], smoking [45] and ethnicity [45,48].

Treatment

The acute effects of single pharmacological doses of glucocorticoid hormones on net electrolyte and water transport and electrical PD in the rectum was studied in control subjects and in patients with either active or inactive UC. It was noticed that glucocorticoids stimulated acute increases in rectal sodium and water absorption in control subjects and in patients with acute UC. The ability of systemically administered glucocorticoids to reduce diarrhea in UC was assumed to be related to direct effects on distal colonic sodium and water transport, as well as to their better known anti-inflammatory action [31]. It would therefore appear that the high doses of glucocorticoids used in the treatment of UC decrease diarrhea by exerting a direct stimulatory effect on electrogenic Na^+ absorption (and hence Cl^- and water absorption), in addition to their general anti-inflammatory action. The "mineralocorticoid-like" effects of high-dose hydrocortisone and methylprednisolone reflect considerable crossover binding to mineralocorticoid receptors, as well as the activation of glucocorticoid receptors [47,48]. Glucocorticoid receptor activation results in the stimulation of electroneutral NaCl absorption, and the glucocorticoids used to treat inflammatory bowel disease probably stimulate both electrogenic Na^+ absorption and electroneutral NaCl absorption in the distal colon and rectum [51].

In another study, electrolytes were measured in 24-h fecal collections from UC (n=18), CD (n=20) and 16 healthy subjects. Of the 38 IBD patients, 6 with UC and 8 with CD were on steroids during the trial. Two of the steroid-treated patients with UC and 2 with CD were on sulfasalazine. The comparison between UC patients on and off prednisone showed no significant difference regarding the fecal electrolyte concentration. On the other hand, CD patients on steroids had a lower fecal sodium concentration and a correspondingly increased potassium to sodium concentration level compared with those not on steroids [39].

In addition, inflammatory mediators have been noticed to stimulate electrolyte secretion and inhibit NaCl absorption [49]. Therefore, arachidonic acid metabolites may play a predominant role, which explains the beneficial effects of glucocorticoids, sulfasalazine and aminosalicylic acid in the treatment of IBD [32,50,51].

Furthermore, the contribution of tumor necrosis factor (TNF)-α to the inflammatory process and the excessive electrolyte secretion [52] is supported by the finding that in recent clinical trials, treatment with anti-TNF-α antibodies was very successful in downregulating the inflammatory process [53].

Overall, IBD is associated with disturbed electrolyte homeostasis. In fact, reduced sodium and chloride absorption and increased potassium secretion comprise the most common and critical abnormalities. In addition, calcium and magnesium are found to be reduced due to their reduced intestinal absorption and disturbed metabolism of vitamin D. Due to the fact that the electrolyte transport takes place mainly in colon, UC is typically associated with electrolyte disorders in

contrast to CD that might spare colon. Of note, IBD treatment limits the intestinal loss of the electrolytes.

IBD and acid-base homeostasis

In contrast to other secretory diarrheas, metabolic or mixed alkalosis comprises a common feature of both severe and complicated UC ('toxic megacolon'), while normal pH values were observed in UC of mild or moderate severity [46]. In fact, a linear correlation was found between pH, pulse rate, and plasma albumin [54]. Of note, the fecal fluid of 62 patients with UC in severe colitis was characterized by low fecal pH, bicarbonate, SCFA and very high lactate levels [55].

Similarly, CD patients with enteritis had a normal acid-base balance, while mild and moderate metabolic alkalosis was observed in enterocolitis and colitis [56]. These findings were related to the relationship between the site of lesions, fecal electrolyte losses, and systemic acid-base balance in CD [57].

In another study, proximal jejunal mucosa surface pH was examined in patients with CD confined to the large or distal small bowel. The proximal jejunal mucosa was obtained by biopsy from 15 patients with CD and 17 normal controls. The jejunal mucosa pH values were higher in the CD group compared with the control group [58]. Similarly, Lucas *et al* found that the pH of the small bowel in patients with CD was higher compared with patients with healthy mucosa after having measured the surface pH of human proximal jejunum in biopsy samples [59]. In other studies, intraluminal GI pH of the terminal ileum, the cecum and the right colon was also higher in both CD and UC patients compared with healthy volunteers [60,61].

In another study, patients with active CD and UC had similar GI pH values compared with patients in remission, suggesting that intestinal inflammation does not affect intestinal lumen pH [62].

On the other hand, studies demonstrated decreased colonic luminal pH in CD and UC patients compared with healthy subjects [63]. Extremely acidic proximal colonic pH (ranging between 2.3 and 3.4) was recorded in 6 patients with active UC [61,64]. In addition, elevated colonic luminal concentrations of SCFAs have been reported in active UC [65], with associated decreased colonic pH [66]. This may be explained by disturbed SCFAs absorption and utilization reported in some [67,68] but not all studies [69-71]. Of note, the effects of increased SCFAs or lactate concentrations on colonic luminal pH are likely to be buffered in active colitis by the presence of blood and mucus, although the quantitative importance of these mechanisms is uncertain [57]. Likewise, in other studies decreased fecal bicarbonate concentration due to reduced rectal mucosal bicarbonate secretion were found in patients with active UC and could account for the low pH of the colonic lumen [72,73].

Overall, IBD in the active phase causes mild to severe metabolic alkalosis especially when the colon is affected. This might be attributed to the decreased secretion of bicarbonates. On the other hand, when the disease is in remission or does not spare the colon, the acid-base homeostasis is not significantly disturbed.

Conclusions

IBD-associated mucosal inflammation and the consequent impaired secretion and absorption of electrolytes often result in electrolytic and acid-base imbalance in IBD patients. Reduced sodium and chloride absorption and increased potassium secretion comprise the most common and critical abnormalities. In addition, hypocalcemia may be observed, due to both limited calcium intestinal absorption and disturbed metabolism of vitamin D. Of note, due to the fact that the electrolyte transport takes place mainly in colon, UC is typically associated with electrolyte disorders in contrast to CD that might spare the colon. Moreover, IBD-treatment and remission limit electrolyte disturbances.

In contrast to other secretory diarrheas, IBD has been associated with mild or severe metabolic alkalosis depending on the severity of the inflammation and the part of the GI tract being affected. The alkalosis is attributed to the decreased bicarbonate secretion of the colon when it is affected. Hence, active UC may increase patient pH in comparison with CD that might not affect the colon. Large-scale epidemiological studies are required for a better insight into electrolyte and acid-base disorders in IBD patients.

References

1. Podolsky DK. Inflammatory bowel disease 1999: present and future promises. *Curr Opin Gastroenterol* 1999;**15**:283-284.
2. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults. American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 1997;**92**:204-211.
3. Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. *Am J Gastroenterol* 2009;**104**:465-483; quiz 464, 484.
4. Kunzelmann K, Mall M. Electrolyte transport in the mammalian colon: mechanisms and implications for disease. *Physiol Rev* 2002;**82**:245-289.
5. Debongnie JC, Phillips SF. Capacity of the human colon to absorb fluid. *Gastroenterology* 1978;**74**:698-703.
6. Kockerling A, Sorgenfrei D, Fromm M. Electrogenic Na^+ absorption of rat distal colon is confined to surface epithelium: a voltage-scanning study. *Am J Physiol* 1993;**264**(5 Pt 1):C1285-C1293.
7. Barbry P, Hofman P. Molecular biology of Na^+ absorption. *Am J Physiol* 1997;**273**(3 Pt 1): G571-G585.
8. Halm DR, Halm ST. Secretagogue response of goblet cells and columnar cells in human colonic crypts. *Am J Physiol Cell Physiol* 2000;**278**:C212-C233.
9. Sandle GI. Salt and water absorption in the human colon: a modern appraisal. *Gut* 1998;**43**:294-299.
10. Kockerling A, Fromm M. Origin of cAMP-dependent Cl^- secretion from both crypts and surface epithelia of rat intestine. *Am J Physiol* 1993;**264**(5 Pt 1):C1294-C1301.
11. Dawson DC. Ion channels and colonic salt transport. *Annu Rev Physiol* 1991;**53**:321-339.

12. Mall M, Bleich M, Schürlein M, et al. Cholinergic ion secretion in human colon requires coactivation by cAMP. *Am J Physiol* 1998;**275**(6 Pt 1): G1274-G1281.
13. Strabel D, Diener M. Evidence against direct activation of chloride secretion by carbachol in the rat distal colon. *Eur J Pharmacol* 1995;**274**:181-191.
14. Grotjohann I, Gitter AH, Köckerling A, et al. Localization of cAMP- and aldosterone-induced K+ secretion in rat distal colon by conductance scanning. *J Physiol* 1998;**507**(Pt 2):561-570.
15. Kerstan D, Gordjani N, Nitschke R, Greger R, Leipziger J. Luminal ATP induces K+ secretion via a P2Y2 receptor in rat distal colonic mucosa. *Pflugers Arch* 1998;**436**:712-716.
16. Mall M, Wissner A, Seydewitz HH, et al. Defective cholinergic Cl(-) secretion and detection of K(+) secretion in rectal biopsies from cystic fibrosis patients. *Am J Physiol Gastrointest Liver Physiol* 2000;**278**:G617-G624.
17. Schultheiss G, Diener M. Regulation of apical and basolateral K+ conductances in rat colon. *Br J Pharmacol* 1997;**122**:87-94.
18. Greger R. Role of CFTR in the colon. *Annu Rev Physiol* 2000;**62**:467-491.
19. Genz AK, v Engelhardt W, Busche R. Maintenance and regulation of the pH microclimate at the luminal surface of the distal colon of guinea-pig. *J Physiol* 1999;**517**(Pt 2):507-519.
20. Feldman GM, Stephenson RL. H^+ and $HCO3^-$ flux across apical surface of rat distal colon. *Am J Physiol* 1990;**259**(1 Pt 1):C35-C40.
21. Hasselblatt P, Warth R, Schulz-Baldes A, Greger R, Bleich M. pH regulation in isolated in vitro perfused rat colonic crypts. *Pflugers Arch* 2000;**441**:118-124.
22. Sullivan SK, Smith PL. Bicarbonate secretion by rabbit proximal colon. *Am J Physiol* 1986;**251**(4 Pt 1):G436-G445.
23. Beeken WL. Remediable defects in Crohn disease: a prospective study of 63 patients. *Arch Intern Med* 1975;**135**:686-690.
24. Lubran M, Mc AP. Potassium deficiency in ulcerative colitis. *Q J Med* 1951;**20**:221-232.
25. Posey EL, Bargen JA. Metabolic derangements in chronic ulcerative colitis. *Gastroenterology* 1950;**16**:39-50.
26. Smiddy FG, Gregory SD, Smith IB, Goligher JC. Faecal loss of fluid, electrolytes, and nitrogen in colitis before and after ileostomy. *Lancet* 1960;**1**:14-19.
27. Duthie HL, Watts JM, Dedombal FT, Goligher JC. Serum electrolytes and colonic transfer of water and electrolytes in chronic ulcerative colitis. *Gastroenterology* 1964;**47**:525-530.
28. Head LH, Heaton JE, Jr, Kivel RM. Absorption of water and electrolytes in Crohn's disease of the colon. *Gastroenterology* 1969;**56**:571-579.
29. Edmonds CJ, Pilcher D. Electrical potential difference and sodium and potassium fluxes across rectal mucosa in ulcerative colitis. *Gut* 1973;**14**:784-789.
30. Harris J, Shields R. Absorption and secretion of water and electrolytes by the intact human colon in diffuse untreated proctocolitis. *Gut* 1970;**11**:27-33.
31. Sandle GI, Hayslett JP, Binder HJ. Effect of glucocorticoids on rectal transport in normal subjects and patients with ulcerative colitis. *Gut* 1986;**27**:309-316.
32. Hawker PC, McKay JS, Turnberg LA. Electrolyte transport across colonic mucosa from patients with inflammatory bowel disease. *Gastroenterology* 1980;**79**:508-511.
33. Archampong EQ, Harris J, Clark CG. The absorption and secretion of water and electrolytes across the healthy and the diseased human colonic mucosa measured in vitro. *Gut* 1972;**13**:880-886.
34. Lockwood CM, Harris J, Clark CG. Intracellular potassium in diffuse proctocolitis. *Lancet* 1971;**1**:889-891.
35. Allan R, Steinberg DM, Dixon K, Cooke WT. Changes in the bidirectional sodium flux across the intestinal mucosa in Crohn's disease. *Gut* 1975;**16**:201-204.
36. Rampton DS, Sladen GE, Youlten LJ. Rectal mucosal prostaglandin E2 release and its relation to disease activity, electrical potential difference, and treatment in ulcerative colitis. *Gut* 1980;**21**:591-596.
37. Rampton DS, Sladen GE. Relationship between rectal mucosal prostaglandin production and water and electrolyte transport in ulcerative colitis. *Digestion* 1984;**30**:13-22.
38. Schilli R, Breuer RI, Klein F, et al. Comparison of the composition of faecal fluid in Crohn's disease and ulcerative colitis. *Gut* 1982;**23**:326-332.
39. Vernia P, Gnaedinger A, Hauck W, Breuer RI. Organic anions and the diarrhea of inflammatory bowel disease. *Dig Dis Sci* 1988;**33**:1353-1358.
40. McCarthy D, Duggan P, O'Brien M, et al. Seasonality of vitamin D status and bone turnover in patients with Crohn's disease. *Aliment Pharmacol Ther* 2005;**21**:1073-1083.
41. Andreassen H, Rix M, Brot C, Eskildsen P. Regulators of calcium homeostasis and bone mineral density in patients with Crohn's disease. *Scand J Gastroenterol* 1998;**33**:1087-1093.
42. Driscoll RH, Jr, Meredith SC, Sitrin M, Rosenberg IH. Vitamin D deficiency and bone disease in patients with Crohn's disease. *Gastroenterology* 1982;**83**:1252-1258.
43. Gilman J, Shanahan F, Cashman KD. Determinants of vitamin D status in adult Crohn's disease patients, with particular emphasis on supplemental vitamin D use. *Eur J Clin Nutr* 2006;**60**:889-896.
44. Haderslev KV, Jeppesen PB, Sorensen HA, Mortensen PB, Staun M. Vitamin D status and measurements of markers of bone metabolism in patients with small intestinal resection. *Gut* 2003;**52**:653-658.
45. Tajika M, Matsuura A, Nakamura T, et al. Risk factors for vitamin D deficiency in patients with Crohn's disease. *J Gastroenterol* 2004;**39**:527-533.
46. Sentongo TA, Semaeo EJ, Stettler N, et al. Vitamin D status in children, adolescents, and young adults with Crohn disease. *Am J Clin Nutr* 2002;**76**:1077-1081.
47. Marusic ET, Hayslett JP, Binder HJ. Corticosteroid-binding studies in cytosol of colonic mucosa of the rat. *Am J Physiol* 1981;**240**:G417-G423.
48. Turnamian SG, Binder HJ. Regulation of active sodium and potassium transport in the distal colon of the rat. Role of the aldosterone and glucocorticoid receptors. *J Clin Invest* 1989;**84**:1924-1929.
49. Traynor TR, Brown DR, O'Grady SM. Effects of inflammatory mediators on electrolyte transport across the porcine distal colon epithelium. *J Pharmacol Exp Ther* 1993;**264**:61-66.
50. Donowitz M. Arachidonic acid metabolites and their role in inflammatory bowel disease. An update requiring addition of a pathway. *Gastroenterology* 1985;**88**:580-587.
51. Hyun CS, Binder HJ. Mechanism of leukotriene D4 stimulation of Cl^- secretion in rat distal colon in vitro. *Am J Physiol* 1993;**265**(3 Pt 1):G467-G473.
52. Schmitz H, Fromm M, Bode H, et al. Tumor necrosis factor-alpha induces Cl^- and K^+ secretion in human distal colon driven by prostaglandin E2. *Am J Physiol* 1996;**271**(4 Pt 1):G669-G674.
53. Baert FJ, D'Haens GR, Peeters M, et al. Tumor necrosis factor alpha antibody (infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. *Gastroenterology* 1999;**116**:22-28.
54. Caprilli R, Vernia P, Colaneri O, Torsoli A. Blood pH: a test for assessment of severity in proctocolitis. *Gut* 1976;**17**:763-769.
55. Vernia P, Caprilli R, Latella G, Barbetti F, Magliocca FM, Cittadini M. Fecal lactate and ulcerative colitis. *Gastroenterology* 1988;**95**:1564-1568.
56. Perez GO, Oster JR, Rogers A. Acid-base disturbances in gastrointestinal disease. *Dig Dis Sci* 1987;**32**:1033-1043.
57. Caprilli R, Vernia P, Latella G, Frieri G. Consequence of colonic involvement on electrolyte and acid-base homeostasis in Crohn's

disease. *Am J Gastroenterol* 1985;**80**:509-512.
58. Cooper BT, Lucas M L, Lei FH, Blair JA, Cooke W. Abnormal jejunal surface pH in Crohn's disease-new evidence that Crohn's disease is a diffuse lesion of the gastrointestinal tract. *Gut* 1977;**18**:423.
59. Lucas ML, Cooper BT, Lei FH, et al. Acid microclimate in coeliac and Crohn's disease: a model for folate malabsorption. *Gut* 1978;**19**:735-742.
60. Press AG, Hauptmann IA, Hauptmann L, et al. Gastrointestinal pH profiles in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 1998;**12**:673-678.
61. Fallingborg, J, Pedersen P, Jacobsen BA. Small intestinal transit time and intraluminal pH in ileocecal resected patients with Crohn's disease. *Dig Dis Sci* 1998;**43**:702-705.
62. Ewe K. Schwartz S, Petersen S, Press AG. Inflammation does not decrease intraluminal pH in chronic inflammatory bowel disease. *Dig Dis Sci* 1999;**44**:1434-1439.
63. Sasaki Y, Hada R, Nakajima H, Fukuda S, Munakata A. Improved localizing method of radiopill in measurement of entire gastrointestinal pH profiles: colonic luminal pH in normal subjects and patients with Crohn's disease. *Am J Gastroenterol* 1997;**92**:114-118.
64. Raimundo AH, Evans DF, Rogers J, Silk DBA. Gastrointestinal pH profiles in ulcerative colitis. *Gastroenterology* 1992;**102**:A681.
65. Roediger WE. The colonic epithelium in ulcerative colitis: an energy-deficiency disease? *Lancet* 1980;**2**:712-715.
66. Rubinstein R, Howard AV, Wrong OM. In vivo dialysis of faeces as a method of stool analysis. IV. The organic anion component. *Clin Sci* 1969;**37**:549-564.
67. Chapman MA, Grahn MF, Boyle MA, Hutton M, Rogers J, Williams NS. Butyrate oxidation is impaired in the colonic mucosa of sufferers of quiescent ulcerative colitis. *Gut* 1994;**35**:73-76.
68. Roediger WE, Heyworth M, Willoughby P, Piris J, Moore A, Truelove SC. Luminal ions and short chain fatty acids as markers of functional activity of the mucosa in ulcerative colitis. *J Clin Pathol* 1982;**35**:323-326.
69. Allan ES, Winter S, Light AM, Allan A. Mucosal enzyme activity for butyrate oxidation; no defect in patients with ulcerative colitis. *Gut* 1996;**38**:886-893.
70. Finnie IA, Taylor BA, Rhodes JM. Ileal and colonic epithelial metabolism in quiescent ulcerative colitis: increased glutamine metabolism in distal colon but no defect in butyrate metabolism. *Gut* 1993;**34**:1552-1558.
71. Hove H, Holtug K, Jeppesen PB, Mortensen PB. Butyrate absorption and lactate secretion in ulcerative colitis. *Dis Colon Rectum* 1995;**38**:519-525.
72. Caprilli R, Frieri G, Latella G, Vernia P, Santoro ML. Faecal excretion of bicarbonate in ulcerative colitis. *Digestion* 1986;**35**:136-142.
73. Roediger WE, Lawson MJ, Kwok V, Grant AK, Pannall PR. Colonic bicarbonate output as a test of disease activity in ulcerative colitis. *J Clin Pathol* 1984;**37**:704-707.