

ORIGINAL ARTICLE

Characterization of ulcerative colitis-associated constipation syndrome (proximal constipation)

Sally L James,* Daniel R van Langenberg,*  Kirstin M Taylor[†]  and Peter R Gibson[†] 

*Eastern Health Clinical School, Monash University, Box Hill Hospital, Box Hill and [†]Department of Gastroenterology, Alfred Hospital and Monash University, Melbourne, Victoria, Australia

Key words

anti-inflammatory therapy, constipation, fiber, functional gastrointestinal disorder, transit time, ulcerative colitis.

Accepted for publication 23 June 2018.

Correspondence

Professor Peter R Gibson, Department of Gastroenterology, Alfred Hospital, 99 Commercial Road, Melbourne, Vic. 3004, Australia.
Email: peter.gibson@monash.edu

Declaration of conflict of interest: There were no conflicts of interest with the development and research of this paper.

Author contribution: SJ and PG conceived of the study and completed its design. SJ carried out the study, performed most data analyses, and drafted the manuscript. PG participated in data interpretation and the finalization of the manuscript. DvL performed the majority of the statistical analyses and contributed to data interpretation and the manuscript drafting. KMT provided intellectual and writing input. All authors read and approved the final manuscript.

Introduction

The distribution of mucosal inflammation in ulcerative colitis (UC) encompasses distal proctitis to the involvement of the entire colon. Symptoms may reflect distribution of the inflammation—formed motions indicate more distal disease, while diarrhea suggests more widespread colonic involvement. Classic symptoms of colitis are fecal urgency, frequency and bloody diarrhea, but tenesmus, change in stool consistency and irregularity are also reported.¹ The term “proximal constipation” has been previously applied to the scenario where there is an accumulation of contents (denoted as “feces”) in the right colon, usually proximal to an area of inflammation.² It may be associated with symptoms such as reduced frequency of defecation, harder stool consistency, difficult passage of stool, bloating, cramping, and sensation of incomplete defecation. Symptoms such as cramping and tenesmus may be difficult to distinguish from active colitis and may be overlooked due, for instance, to the expectation of diarrhea in active UC.³

Abstract

Background: The syndrome of constipation with other abdominal symptoms (“proximal constipation”) in ulcerative colitis (UC) is commonly recognized by practitioners but is poorly described, with no recognized definition and little understanding with regard to prevalence and effect of therapies on disease outcomes. This study aimed to address these issues in a cross-sectional, consecutive series of patients with UC.

Methods: A working definition of proximal constipation was established. Consecutive patients were recruited, and their disease activity, recent medications, and investigations plus abdominal symptoms were assessed at a study visit. Relevant clinical data were also extracted from medical records.

Results: Of 125 patients with UC, (mean age 47, range 14–84 years, 61 male), 58 (46%) fulfilled the definition of proximal constipation. The main symptoms were reduced stool frequency (69%), hard stools (43%), abdominal pain (40%), excessive flatus (29%), straining (24%), and sensation of incomplete emptying (14%). Proximal constipation was associated with female gender (OR 3.45 [1.45–8.24]), left-sided (OR 2.84 [1.14–7.11]) and concurrently active disease (OR 5.56 [1.96–16.67]), but not age, disease duration or therapy. A total of 88% had an increase in anti-inflammatory therapy, with the use of laxatives or fiber supplements in 63% compared with 1.4% of those without proximal constipation.

Conclusions: Proximal constipation is common, and its risk increases in active and distal disease, especially in women. Validation of its definition and evaluation of therapeutic strategies are needed. A new term “ulcerative colitis-associated constipation syndrome” is proposed to more accurately depict its nature.

Occasionally, proximal constipation may be detected as palpable colon distended by feces on abdominal examination, and it may be diagnosed using medical imaging techniques. Plain abdominal x-rays (AXR) detect fecal loading with a degree of subjectivity, and it may be difficult to relate this to functional fecal stasis.⁴ Abdominal computed tomography (CT) scanning can also detect right colonic loading. Transit time studies are more often used to investigate functional or slow transit constipation and have rarely been used in the setting of UC. In normal controls, colonic, rather than gastric or small intestinal, transit has a more clinically apparent effect on stool form, with rapid colonic transit resulting in looser stools and slow transit strongly correlated with hard stools.⁵

The aim of this study was to characterize proximal constipation in patients with UC in terms of prevalence, clinical features, and management. A cross-sectional observational study of a prospectively and consecutively recruited patient population was undertaken.

Materials and methods

Patient selection. Patients with UC consecutively seen in the Inflammatory Bowel Disease Clinic at Box Hill Hospital and in private clinics were identified. Their case notes were reviewed. The diagnosis was confirmed using standard clinical, endoscopic, and histopathological criteria through the careful review of source material. Patients with Crohn's disease, infective and indeterminate colitis, and those who had had a colectomy were excluded.

Definition of proximal constipation. As there was no pre-existing gold standard for defining proximal constipation, a definition using clinical criteria, shown in Table 1, was developed prior to data collection. Similar to the diagnosis of functional constipation,⁶ at least two criteria were required. The presence of active disease was not a diagnostic criterion. Symptoms needed to be present for at least 3 days per month during the previous 3 months. Investigations such as AXR or CT scans, reports by the radiologist as having fecal loading, or evidence of right-sided fecal loading at colonoscopy were recorded, but did not form part of the diagnostic criteria.

Patient assessment. As this was a cross-sectional, observational study, each participant was assessed at a single time point during the recruitment period (between 1/3/2007 and 1/3/2008) at a routine clinic visit. Patient characteristics, including age, gender, duration, and disease extent (using the Montreal classification⁷), were recorded. In this study, disease extent was determined from the most recent colonoscopy. Clinical activity was measured with the Rachmilewitz colitis activity index (CAI).⁸ Remission or quiescent disease has a score ≤ 4 , and disease was classified as active if the score was ≥ 5 . In the 6 months prior to the study visit, investigations for bowel-related symptoms were recorded, and medication use for colitis and use of laxatives or fiber supplements were evaluated. Change in medication was classified as: increased oral medication, increased rectal medication, addition of rectal medication, increased oral and rectal medication, addition of immunosuppression, no change, and decreased medication. The protocol was approved by the Eastern Health Research and Ethics Committee and by the Monash University Standing Committee on Ethics in Research Involving Humans.

Statistical analyses. All statistical analyses were performed using IBM-SPSS version 20 (Chicago, IL) or GraphPad Prism

Table 1 Definition of proximal constipation

Presence of at least two of the following criteria:

- Bloating
- Excessive or troublesome wind
- Abdominal cramping pain
- Reduced frequency of defecation compared with patient's own frequency
- Passage of hard or dry stool
- Straining at stool
- Sensation of incomplete defecation

5.0 (La Jolla, CA). Means or medians are presented in this study, with comparisons assessed with unpaired *t*-tests or Mann-Whitney *U* tests. In order to assess factors associated with proximal constipation, categorical variables were assessed using odds ratios initially in bivariate comparisons with proximal constipation. Subsequently, those factors with significant associations were included in the multivariate logistic regression analysis, along with other factors, including age and disease duration, as potential confounders of proximal constipation. In the multivariate analysis, a forced entry model was used, and continuous variables were maintained wherever possible. Exploratory models were performed prior to selection of variables in the final model based on goodness of fit. A *P* value ≤ 0.05 was considered statistically significant.

Results

Patient characteristics. A total of 125 consecutive patients with UC, 89 from the public hospital and 36 from private clinics, were recruited for this study. Mean age was 47 years (range 14–84), and 61 were men. The mean age of onset was 39 years (4.5–80), and the mean disease duration was 8.5 years (0.25–40); 38 patients had extensive disease, 41 had left-sided disease, and 43 had proctitis; in 3 patients, colitis extent could not be ascertained from the available information.

Medication was recorded for all patients as shown in Table 2. In the recent past or at the time of study visit, no patients were taking medications commonly associated with constipation (such as aluminum-based antacids; oral iron; and drugs with anticholinergic activity such as tricyclic antidepressants, cholestyramine, clozapine, opioids, or verapamil⁹). Seven patients were on no medication for colitis. Oral aminosaliculates were the medication most often used, followed by rectal mesalazine; 28% of patients were taking a single agent, 28% two, 28% three, 14% four, and 2% five agents for their colitis at the time of assessment.

Diagnosis of proximal constipation. A total of 58 of 125 patients (46%) had evidence of proximal constipation at either time of assessment or in the previous 6 months. Apart from difficulty with defecation, the most prevalent symptom was bloating (81%). The prevalence of other symptoms were as follows: reduced stool frequency (69%), hard stools (43%), pain and abdominal cramps (40%), excessive or troublesome wind or gas (29%), straining (24%), and a sensation of incomplete emptying (14%). Eighteen patients had two symptoms of proximal constipation, 25 had three, 10 had four, 3 had five, and two patients fulfilled all six criteria. AXR performed in 20 patients (34%) with proximal constipation was reported to demonstrate proximal colonic fecal loading. In two patients without proximal constipation who had AXR, fecal loading was not reported. No other imaging or transit studies were performed. Inclusion of abnormal imaging results as a diagnostic criterion did not change how patients were classified. Retained right colonic fecal material at colonoscopy was noted in four patients, all of whom had at least two other symptoms of proximal constipation.

Factors associated with proximal constipation. Characteristics of patients in whom proximal constipation had

Table 2 Patient characteristics according to presence or absence of proximal constipation at assessment visit

Index	Proximal constipation	No proximal constipation
Number studied	58 (46%)	67 (54%)
Number of men	20 (34%) [†]	41 (61%)
Mean age in years (range)	45 (20–74)	48 (14–84)
Mean age at diagnosis in years (range)	37 (15–72)	40 (4.5–80)
Disease duration in years (range)	1–25	0.25–40
Disease extent [‡]		
Extensive	10 (17%)	25 (37%)
Left-sided	17 (29%)	27 (40%)
Proctitis	29 (50%)	10 (15%)
Colectomy	NA	NA
Unknown	2 (3%)	1 (1%)
Therapy for colitis		
Oral 5-ASA	51 (88%)	55 (82%)
Rectal 5-ASA	41 (71%)	19 (28%)
Rectal corticosteroid	10 (17%)	11 (16%)
Oral prednisolone	14 (24%)	28 (42%)
Thiopurine	15 (26%)	16 (24%)
Methotrexate	4 (7%)	7 (10%)
Other [§]	5 (6%)	7 (9%)
Number of medications for colitis		
Nil	2 (3%)	5 (7%)
1	13 (22%)	22 (33%)
2	16 (28%)	20 (30%)
≥3	27 (47%)	20 (30%)

[†] $P = 0.004$; Fisher's exact test.

[‡] $P = 0.006$; Fisher's exact test.

[§]Infliximab, adalimumab, hydrocortisone, cyclosporine, clinical trial drug.

been documented at the study visit and were compared with those without are shown in Table 3. The majority of patients had active disease (CAI score ≥ 5) at the time of the study visit (93%). Proximal constipation was threefold more likely in women and was significantly associated with distal disease location; disease limited to the rectum was present in 50% of subjects with proximal constipation but only 15% of those without ($P < 0.001$, Fisher's exact test); and collectively, patients with left-sided colitis had a more than threefold risk. There was no difference between the two groups in terms of age (mean 45 vs 48 years), age at IBD diagnosis (mean 37 vs 40 years), or disease duration (8 vs 9 years respectively). Those with proximal constipation were more likely to be on concurrent rectal aminosalicylates and had higher CAI scores (median 4, range 0–11) compared to those without proximal constipation at the time of their study visit (0, 0–10), ($P < 0.0001$; Mann–Whitney U test).

The results of multivariate logistic regression analysis are shown in Table 4. Concurrently active disease (CAI ≥ 5), female gender, left-sided colitis, and rectal 5-ASA use were independent predictors of the presence of proximal constipation.

Therapy at time of proximal constipation. Use of anti-inflammatory medication was increased in 88% of patients at

Table 3 Bivariate analyses of factors (categorical variables, depicted with unadjusted odds ratios here) potentially associated with ever having proximal constipation

Variable	Unadjusted odds ratio [95% CI]	P value*
Age > 48 years [†]	0.97 [0.48, 1.96]	1.00
Female gender	2.99 [1.44, 6.21]	0.004
Disease duration ≥ 8 years [†]	0.79 [0.39, 1.60]	0.59
Active disease (CAI ≥ 5)	5.56 [1.96, 16.67]	0.001
Left-sided colitis only	3.07 [1.36, 6.94]	0.006
Positive test for proximal constipation [‡]	2.76 [2.14, 3.56]	<0.001
Use of a fiber supplement [§]	108 [13.98, 834.54]	<0.001
Rectal 5ASA added or dose increased	2.34 [1.002, 5.50]	0.046
Oral or rectal steroids added	1.20 [0.49, 2.91]	0.69
Oral 5ASA added or dose increased	0.85 [0.28, 2.59]	0.77
Other change in medical therapy	0.54 [0.17, 1.68]	0.28

*Statistically significant associations in bold.

[†]Mean for non-proximal constipation (PC) group used as cut-off value.

[‡]Where test (abdominal x-ray, computed tomography [CT] scan or other) suggestive of PC but not used in defining the condition.

[§]Artificially high OR as only one patient in the non-PC group was taking fiber.

the time of the study visit or within the previous 6 months. The most common change was an initiation or increase in rectal 5-ASA therapies, seen in 46% of these patients, with an OR of 2.34 (1.002–5.50, $P = 0.046$). Oral 5-ASA was started or the dose was increased in 18%. Steroid therapy was initiated or increased in 39%, comprising 11% given orally or intravenously, 14% rectally, and 11% both orally and rectally. In only 10% were there no changes made to medications. Apart from rectal 5-ASA, no changes in therapy were significantly different on bivariate analysis between the two groups.

Use of laxatives and fiber supplements was almost exclusively seen in patients with proximal constipation, occurring in 63% compared with one patient without who had occasionally

Table 4 Multivariate logistic regression analysis showing factors (depicted by adjusted odds ratios here) potentially associated with PC included in the final model¹

Variable	Adjusted odds Ratio [95% CI]	P value
Age (years)	0.99 [0.96, 1.02]	0.369
Disease duration (years)	0.98 [0.93, 1.04]	0.496
Female gender	3.45 [1.45, 8.24]	0.005
Left-sided colitis only	2.84 [1.14, 7.11]	0.026
Active disease (CAI ≥ 5)	8.70 [2.76, 27.78]	<0.001
Rectal 5-ASA used	2.99 [1.11, 8.06]	0.031

¹ Summary characteristics of final model: Omnibus test $\chi^2 = 37.0$, $P < 0.001$, Nagelkerke $R^2 = 0.34$, Hosmer & Lemeshow test $P = 0.89$.

used sterculia ($P < 0.001$). The most common laxative used was macrogol (33%), and the most commonly used fiber was sterculia (43%), and the combination of both was used in 10% of patients. There was occasional use of picosulfate (6%) magnesium sulfate (one patient), herbal laxatives (one patient), and psyllium (two patients). No dietary interventions were recorded in those with proximal constipation.

Discussion

Functional gastrointestinal symptoms are common, underrecognized, and probably undertreated in patients with IBD. In UC, the entity of proximal constipation is common, but it has received very little attention in the published literature, probably due to the lack of a widely accepted definition. Consequently, its true prevalence, associations and therapy are poorly defined. This cross-sectional, observational study aimed to address these deficiencies by first creating a definition and then applying it to a prospectively acquired group of patients with UC from both hospital and private clinics, thereby assessing its prevalence and associations. Nearly one in two had features of proximal constipation, and this was associated with distal disease extent, concurrently active disease and female gender, and was often treated with laxatives and insoluble fiber supplements.

The definition proposed in the current study is arbitrary, but serves the purpose of defining a patient group that has been poorly characterized or studied. Using this definition, proximal constipation in this cohort was more common than the 10–16% previously reported.^{2,13} Despite the consecutive nature of recruitment, the higher rates of constipation-related symptoms may be reflective of a population that undergoes more regular follow up because of such symptoms. Those patients who are completely symptom-free are less likely to attend follow ups. The addition of abdominal imaging or physiological markers to the diagnostic criteria may be appealing at first due to its perceived objectivity, but there are many aspects that severely limit their utility. The use of plain AXR to diagnose fecal loading in patients with constipation relies on a subjective assessment that has high interobserver variability and poor correlation with colonic transit and patient symptoms.¹⁰ There is a recommendation not to use AXR to diagnose constipation in children for similar reasons.¹¹ Therefore, it seems unjustified to expose patients to ionizing radiation (even when it delivers a dose of only 0.7 mSv or approximately equivalent to 25% of a year's background radiation¹²) for a test with low diagnostic possibilities. The use of CT scanning, without prior bowel preparation, cannot be supported due to its relatively high radiation exposure in a patient group that is already at risk of excessive exposure¹³ and impaired capacity of interpretation due to the lack of normal values. Physiological measurements of colonic transit using radio-opaque beads, capsule telemetry or scintigraphy would provide quantitative and objective data, but there is a wide variation of transit times, and these will not necessarily correlate with constipation or AXR findings.^{4,10} Transabdominal gastrointestinal ultrasound is a safe and noninvasive tool that permits the assessment of fecal loading within the colon. However, as with AXR and CT, there is no definition of normal, and assessment is subjective.

Identifying factors associated or not associated with proximal constipation is important both for identifying risk and protective factors and to assist in designing therapeutic strategies. Three factors were clearly demonstrated. First, women were affected thrice as often as men. This is consistent with findings in functional gastrointestinal disorders (FGID) where female preponderance may be even higher,^{14,15} a finding that has not been well explained. For example, gut transit time is often slower in women, but there are conflicting data regarding the effect of gender and the menstrual cycle on bowel function. Some studies show an increased transit time with increased tendency to constipation in women,^{16,17} particularly during the premenstrual phase,¹⁸ but these concepts have been refuted by other studies.¹⁹ However, constipation or slow transit alone is only one potential aspect of this syndrome. Second, proximal constipation was more likely to occur in the setting of active disease, especially in those with distal colitis (both independently associated with proximal constipation). This supports the published view that proximal constipation is a colonic dysmotility reaction to distal inflammation.² However, consistent with the small proportion of patients in the current study, it can persist in patients with inactive proctitis, but the duration of this effect is uncertain and may be prolonged.²⁰ Third, the syndrome was related to disease extent, with over three quarters of affected patients having left-sided or solely rectal disease. It is not surprising that it was uncommonly observed in patients with extensive colitis where inflammation would tend to increase propulsive motility throughout the colon²¹ and not allow fecal stasis to occur.

Colonic motility is variably abnormal in patients with active UC. Typically, in left-sided colitis, there is a slower transit of feces through the right colon^{3,6,7} and more rapid transit through the inflamed left colon, with distal irritability.^{8,9,11} Longitudinal motility testing in four patients indicated the normalization of transit time when remission was achieved, supporting the concept that PC is associated with active disease.⁴ Rectal inflammation can also have a functional impact, including hypersensitivity and hyperreactivity to distension and lack of compliance.^{9,12} Motility may also be abnormal in UC in remission, with prolonged transit times reported in both active and quiescent disease.¹³

Therapeutic actions that were taken when proximal constipation was present almost invariably involved intensification of anti-inflammatory medication and sometimes involved the use of therapy directed toward the functional bowel problem. Increasing anti-inflammatory therapy may not have been appropriate in some patients where symptoms were mislabeled as representing increased disease activity rather than being due to a functional disorder. While such an issue cannot be addressed in this cross-sectional study, it is worthy of prospective analysis in future studies. The evidence base for its management is poor, and high-quality clinical trials have not been performed.²² There are no data on, for example, the type of laxative approach, if any, that should be taken; which fiber supplements to use; or whether prokinetic agents have any place. Furthermore, dietary interventions are now more commonly being applied to patients with FGID, but few patients had dietary interventions attempted in the present cohort.

The slow passage of colonic luminal contents, likely in patients with this syndrome, has implications for the treatment of

patients with UC. The use of topically acting therapies, such as 5-ASA or budesonide,²³ is the preferred approach for a mildly to moderately active disease. Such drugs are mostly delivered to the large bowel following oral ingestion of preparations designed to be predominantly released in the large bowel lumen. Delay of transit through the proximal colon may result in reduced delivery to the distal inflamed colon, and resultant delayed or attenuated response to therapy was described for sulfasalazine over 30 years ago.²⁴

The strengths of the present study include the consecutive recruitment of the population studied, which should have limited selection bias, and its origin from both a secondary/tertiary referral specialized clinic and from a private practice setting, which limits the bias toward a more severe patient phenotype and course. The application of a predefined definition of proximal constipation and the rigorous attention to detail in the clinical information retrieved from extensive documentation that characterizes the recruiting clinics were additional strengths. However, the study has weaknesses. The first is the use of a definition that lacks validation or scrutiny by expert consensus (as outlined above). It may have been too inclusive, as shown by its higher prevalence than previously reported. Second, it suffers from the weaknesses associated with any observational study, including the reliance on the completeness of the records kept. Third, disease activity was assessed using a clinical index that includes abdominal pain or cramps as a variable. This might be more a reflection of constipation than active inflammatory disease and, indeed, was one of the criteria in the definition applied. Objective assessment of disease activity would have been preferable, but such is a limitation of retrospective studies.

The term “proximal constipation” is not completely accepted throughout the literature, and it may have misleading connotations. While “constipation” is accurate, the adjective “proximal” may limit the diagnosis to patients who have distal disease when it is noted that the syndrome can occur with any extent of UC. This may lead to underidentification and undertreatment of patients with this condition. Abandoning the old term and developing a more accurately descriptive name for this clinical syndrome may lead to more precise identification and improved treatments. It is proposed that the term “ulcerative colitis-associated constipation syndrome” (UCAC) more accurately describes the clinical scenario without the inherent biases or possible negative implications of the current term. Of importance, this term highlights *constipation* as the most important component, but *syndrome* indicates that other symptoms are also part of the condition, allows for the inclusion of patients with any extent of disease, makes no mention of disease activity, and indicates that it is *associated* with UC to reflect the relationship between the disorders rather than to define causality.

In conclusion, diagnostic criteria for the inadequately studied condition that has been variably termed proximal constipation have been described and applied to a consecutive population of patients with UC. The syndrome is common, affecting nearly half of patients at some time during their illness course. It is associated with, but not restricted to, women, active disease and distal colon involvement. Therapeutic response to its symptoms was variable but invariably involved intensification of anti-inflammatory therapy and, in many patients, the institution of laxative regimens that most often involve osmotic laxatives

and/or manipulation of fiber intake. The poor clinical characterization of this syndrome and the lack of an evidence base upon which therapeutic decisions can be rationally made indicate the need for further research. We propose that the new term “ulcerative colitis-associated constipation syndrome” be applied.

Acknowledgments

SLJ was in receipt of a postgraduate scholarship from the Gastroenterological Society of Australia. There was no other funding body associated with the development of this paper.

References

- Rao SSC, Holdsworth CD, Read NW. Symptoms and stool patterns in patients with ulcerative colitis. *Gut*. 1988; **29**: 342–5.
- Allison MC, Vallance R. Prevalence of proximal faecal stasis in active ulcerative colitis. *Gut*. 1991; **32**: 179–82.
- Rao SSC, Holdsworth B. Studies on the mechanism of bowel disturbance in ulcerative colitis. *Gastroenterology*. 1987; **93**: 934–40.
- Allison MC, Dick R, Pounder RE. A controlled study of faecal distribution in ulcerative colitis and proctitis. *Scand. J. Gastroenterol*. 1987; **22**: 1277–80.
- Degen LP, Phillips SF. How well does stool form reflect colonic transit? *Gut*. 1996; **39**: 109–13.
- Drossman D. AGA clinical symposium -- Rome III: New criteria for the functional GI disorders. *Program and Abstracts of Digestive Disease Week 2006*; Sp461–Sp469.
- Silverberg MS, Satsangi J, Ahmad T *et al.* Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 Montreal World Congress of Gastroenterology. *Can. J. Gastroenterol*. 2005; **19**(Suppl. A): 5–36.
- Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomized trial. *Br. Med. J*. 1989; **298**: 82–6.
- Group GE. Gastrointestinal therapeutic guidelines. *Therapeutic Guidelines*. 2006; **4**: 143–62.
- Cowlam S, Vinayagam R, Khan U *et al.* Blinded comparison of faecal loading on plain radiography versus radio-opaque marker transit studies in the assessment of constipation. *Clin. Radiol*. 2008; **63**: 1326–31.
- Reuchlin-Vroklage LM, Bierma-Zeinstra S, Benninga MA, Berger MY. Diagnostic value of abdominal radiography in constipated children: a systematic review. *Arch. Pediatr. Adolesc. Med*. 2005; **159**: 671–8.
- Hart D, Wall BF. *Radiation Exposure of the UK Population from Medical and Dental X-Ray Examinations*. Chilton, WI: National Radiation Protection Board, 2001.
- Newnham E, Hawkes E, Surendar A, James SL, Gearry R, Gibson PR. Quantifying exposure to diagnostic medical radiation in patients with inflammatory bowel disease: are we contributing to malignancy?. *Aliment. Pharmacol. Ther*. 2007; **26**: 1019–24.
- Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut*. 1999; **45**(Suppl. II): 1143–7.
- Chang L, Toner BB, Fukudo S *et al.* Gender, age, society, culture, and the patient's perspective in the functional gastrointestinal disorders. *Gastroenterology*. 2006; **130**: 1435–46.
- Stephen AM, Wiggins HS, Englyst HN, Cole TJ, Wayman BJ, Cummings JH. The effect of age, sex and level of intake of dietary fibre from wheat on large-bowel function in thirty healthy subjects. *Br. J. Nutr*. 1986; **56**: 349–61.
- Graff J, Brinch K, Madsen JL. Gastrointestinal mean transit times in young and middle-aged healthy subjects. *Clin. Physiol*. 2001; **21**: 253–9.

- 18 Degen LP, Phillips SF. Variability of gastrointestinal transit in healthy women and men. *Gut*. 1996; **39**: 299–305.
- 19 Kamm MA, Farthing MJ, Lennard-Jones JE. Bowel function and transit rate during the menstrual cycle. *Gut*. 1989; **30**: 605–8.
- 20 Lennard-Jones JE, Cooper GW, Newell AC, Wilson CWE, Avery Jones F. Observation in idiopathic ulcerative proctitis. *Gut*. 1962; **3**: 201–6.
- 21 Wells RW, Blennerhassett MG. Persistent and selective effects of inflammation on smooth muscle cell contractility in rat colitis. *Pflügers Arch*. 2004; **448**: 515–24.
- 22 Carter MJ, Lobo AJ, Travis SPL, on behalf of the IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. *Gut*. 2004; **53**(Suppl. 5): v1–v16.
- 23 Travis SPL, Danese S, Kupcinskas L *et al.* Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. *Gut*. 2014; **63**: 433–41.
- 24 Cowan GO, Das KM, Eastwood MA. Further studies of sulphasalazine metabolism in the treatment of ulcerative colitis. *Br. Med. J.* 1977; **2**: 1057–9.