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Validation of a Simple, Patient Directed, Symptom based Index for Intestinal Inflammation

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Abstract

Objective: Optimal management of the Inflammatory Bowel Diseases (IBD) aims for low levels of inflammation to reduce complication rates and disease burden. Scoring systems have been developed to monitor disease but most have not been validated or have shortcomings that limit their practical use. Our aim was to compare two patient related outcome scoring systems with established and validated tools to estimate disease severity in patients with IBD.

Material and Methods: Consecutive patients with either Crohn's disease or ulcerative colitis were recruited from outpatient clinics. Depending on their disease, patients were ask to complete the Crohn's Disease Activity Index (CDAI), short Crohn's Disease Activity Index (sCDAI), Simple Chronic Colitis Activity Index (SCCAI) and the Dudley Intestinal Symptom Questionnaire (DISQ). All patients had bloods taken for a full blood count and a faecal sample for measurement of faecal calprotectin (FCP).

Results: Ninety-one patients (47 CD, 44 UC) were recruited for this prospective analysis. In CD, the CDAI, sCDAI and IBDQ correlated well with each other. Limited agreement was demonstrated with the DISQ. Neither scoring system correlated well with faecal calprotectin. In UC patients there was limited agreement between the SCCAI and the DISQ but better correlation with the IBDQ. No correlation was seen with faecal calprotectin.

Conclusion: There was some correlation between the clinical indices, more so in UC than CD but neither correlated with FCP. It remains difficult to use patient-reported outcomes to measure mucosal inflammation and determine remission.

Keywords

CDAI, Crohn's disease, Faecal calprotectin, IBDQ, Patient reported-outcomes, sCDAI, SCCAI, Ulcerative colitis, Scoring systems, Management

Background

Inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn's disease are lifelong chronic intermittent diseases characterised by periods of increased inflammatory activity (flare-ups) and periods of relative quiescent disease (remission) [1]. These diseases affect mainly young people in their productive years. Optimal management of the IBDs aims for low levels of inflammation or even mucosal healing which in turn will reduce complication rates and disease burden [2-4]. It is widely accepted that monitoring of these chronic, often debilitating conditions needs to be multidimensional, including severity of inflammation and quality of life but this is often difficult to achieve, especially in the clinical setting [4-6].

The gold standard for assessing disease severity is colonoscopy with biopsy and histological assessment [7]. However, this is not always readily available, costly, time consuming, invasive and unpleasant. For this reason, measuring levels of calprotectin (FCP), an abundant neutrophil protein released during inflammation, in faeces has emerged as a useful surrogate disease marker [8]. Good correlation between FCP and colonoscopic findings have been reported [9].

Over the last decades, clinicians have aimed to design non-invasive, clinically useful instruments, to accurately measure and monitor disease activity. To-date, multiple indices exist, some of which have been validated. For Crohn's disease, as the gold standard, however not without criticism, is the Crohn's Disease Activity Index (CDAI), developed in 1975 [10,11]. This requires patients to monitor symptoms daily over a seven day period and also requires objective measures such as weight and haematocrit. It furthermore requires an abdominal examination. This makes a CDAI difficult to use in daily clinical practice. To address some of the shortcomings of the CDAI, a short CDAI (sCDAI) was developed retrospectively by Thia *et al.* using patient-level data from four budesonide clinical trials to select variables from the full CDAI which best predicted health-related quality of life as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) [12]. The sCDAI was found to be a valid, reliable, and responsive tool for the measurement of CD activity.

For years, several indices were developed for UC but most were not validated [13]. In 1998, the Simple Clinical Activity

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Index (SCCAI) was designed by Walmsley *et al.* as a simpler, easier alternative to the Powell-Tuck Index [14]. By reducing the number of symptoms from six to five, discarding clinician dependent clinical signs such as abdominal tenderness, temperature, faecal blood and sigmoidoscopy, the SCCAI is simple enough to be used in the routine outpatient setting.

It has to be noted though that there are indications that the Food and Drug Administration (FDA) is moving away from the Crohn's Disease Activity Index more towards patient-reported outcomes (PROs) and objective measures of disease, such as findings from endoscopy [3]. PROs can be assessed for example by the IBDQ [15]. Inflammatory Bowel Diseases are known to impair quality of life no matter whether Crohn's disease or ulcerative colitis [16]. The IBDQ is a patient-reported measure of health related quality of life. It lists 32 most common disease-related problems and asks patients to grade severity of each problem in their life from one (not a problem) to seven (a very severe problem). This tool is well validated and used most commonly in clinical trials. It correlates well with disease activity indices [16].

However, most of the above mentioned tools are validated in Inflammatory Bowel Disease but other diseases, for instance rheumatological disorders have gastrointestinal manifestations that are difficult to evaluate. A lesser known tool for symptom assessment is the Dudley Intestinal Symptom Questionnaire (DISQ), a brief questionnaire which asks the patient to grade the severity of fifteen common symptoms on a five point scale. The DISQ is fast to complete without physicians input and was designed in 1994 for point-of-care symptom monitoring in both Crohn's disease and ulcerative colitis patients [17]. The DISQ was shown in an early study to correlate well with the CDAI (R = 0.894; p = 0.000) [17,18]. This was confirmed in a later study and also the DISQ has recently been validated for monitoring bowel symptoms in patients with spondyloarthropathies [19].

The aim of this prospective study was therefore to evaluate the correlation between the established but in some cases difficult to apply scoring systems CDAI, sCDAI, SCCAI, with the simple DISQ in patients with Crohn's disease and ulcerative colitis. As a gold standard, we used faecal calprotectin measurements and the IBDQ.

Materials and Methods

Participants

For this prospective observational assessment, patients with confirmed diagnosis of either Crohn's Disease or ulcerative colitis were recruited consecutively from the outpatient clinic at the Gastroenterology Unit at Dunedin Hospital, New Zealand in 2013 and 2014. Following consent, the patients were given the relevant questionnaires for completion; for patients with CD this was the IBDQ, CDAI, DISQ and for patients with UC, the SCCAI, IBDQ and DISQ. All patients were asked to complete a demographic questionnaire and provide a faecal sample for faecal calprotectin quantification. In CD patients a blood sample was obtained to analyse for a full blood count. An abdominal examination was part of the clinic appointment (performed by the primary consultant).

Questionnaires

As described elsewhere, the CDAI consists of 8 values, weighted differently to calculate a score (Appendix). The number of liquid stools, abdominal pain and general well-being need to be collected over the preceding 7 days. Scores range from 0 to over 450. It has been determined that values of < 150 reflect remission, between 150-220 mild disease, 220-450 moderate to severe disease and > 450 severe disease [10]. The short CDAI (sCDAI) was calculated from the CDAI proforma using the following formula: sCDAI = 44 + (2 x number of liquid or soft stools each day for 7 days) + (5 × sum of seven daily abdominal pain ratings) + (7 × sum of seven general well-being ratings).

The SCCAI for UC asks patients to estimate frequency of bowel motions in a typical day and typical night (concerning the last three days), urgency of defecation, presence of blood in stool, rank of their general wellbeing and the clinician notes any extra colonic features of disease. A cut-off < 2.5 has been shown to correlate with remission.

The DISQ lists 15 IBD symptoms which the patients rate the severity of over the past week, from zero (not present) to 5 (most severe).

The IBDQ consists of 32 questions that asks patients to grade the level of disability the IBD causes in their life, from 1 (low disability) to 7 (high disability). The CDAI requires patients to record the number of loose bowel motions over a week, and their daily general level of well-being and abdominal pain over 7 days. Patients are also required to note whether any fevers occurred or antidiarrheal medications were required over the preceding week.

Patients were asked to complete the questionnaires at home and were give a return envelope. The faecal specimens were collected by the participants themselves, and dropped off at the local laboratory and analysed by Canterbury Health Laboratories using a single step enzyme linked immunosorbent assay (ELSIA) using antibodies against six epitopes on the calprotectin protein. The assay produced a value for the faecal calprotectin ranging from 0 to > 500 ug/g. A value of > 50 ug/g is the considered to signify active bowel inflammation. Blood tests were collected by phlebotomists at Southern Community Laboratories. All questionnaires were evaluated by HJK.

Statistical analysis

Correlations were analysed using the Spearman's correlation coefficient. Differences between the groups were tested using a student t-test. A $p \leq 0.05$ was regarded significant. Data analysis was performed with SPSS 17.0 (Chicago, IL).

The study was conducted with the approval of Lower South Ethics Committee (#LRS/09/06/022).

Results

In total, 149 patients were approached to participate in this study. Ninety one (61%) patients were recruited for this prospective analysis. Most participants who declined enrolment cited time constraints and/or a lack of interest. Some patients did not provide a complete dataset. For patients with Crohn's disease, this was mainly an incomplete CDAI (not all seven days were recorded), for all patients, the IBDQ was sometimes not completed due to the length of the questionnaire. Forty-two (89%) of 47 Crohn's disease patients and 37 (84%) of 44 Ulcerative Colitis patients provided a complete response. The two disease groups did not differ in age but slightly more women were recruited in the CD group. This difference was not statistically significant (Table 1).

Table 1: Patient demographics.

	CD	UC	p
Number of patients	47	44	
Female	22 (46.8%)	17 (38.6%)	0.5651
Age (years): mean ± SD (range)	52.6 ± 16.33 (19-85)	52.5 ± 14.3 (22-82)	0.9753
CDAI/SCCI: Mean ± SD (range)	128.10 ± 125.15 (10.5-447.1)	3.0 ± 2.1 (1-8)	
Faecal Calprotectin (µg/g)	269.84 ± 193.72 (24-500)	220.6 ± 197.3 (6-500)	0.233
DISQ	21.96 ± 11.96 (5-48)	23.1 ± 10.4 (2-45)	0.6297
IBDQ	167.34 ± 37.16 (60-219)	174 ± 34.8 (58-218)	0.3807

Table 2: Correlation of indices and faecal calprotectin in Crohn's disease.

	DISQ	Calprotectin	IBDQ	sCDAI
CDAI	R = 0.323, p = 0.020, n = 43	R = 0.164, p = 0.298, n = 42	R = -0.717, p < 0.001, n = 42	R = 0.786, p < 0.001, n = 44
DISQ		R = -0.090, p = 0.559, n = 44	R = -0.428, p = 0.003, n = 45	R = 0.368, p = 0.012, n = 43
Calprotectin			R = -0.156, p = 0.311, n = 44	R = 0.099, p = 0.519, n = 42
IBDQ				R = -0.595, p < 0.001, n = 43

Table 3: Correlation of indices and faecal calprotectin in ulcerative colitis.

	Calprotectin	DISQ	IBDQ
SCCI	R = 0.300	R = 0.538	R = -0.646
	P = 0.090	P < 0.001	P < 0.001
	N = 33	N = 41	N = 40
Faecal Calprotectin		R = -0.158	R = -0.026
		P = 0.373	P = 0.882
		N = 34	N = 34
DISQ			R = -0.592
			P < 0.001
			N = 41

Correlation varied between the different scoring systems. In CD, the CDAI correlated well with the sCDAI and with the IBDQ. Only limited agreement was demonstrated with the DISQ. The DISQ itself showed limited correlation with the IBDQ and the sCDAI. Neither scoring system correlated well with faecal calprotectin (Table 2).

In UC patients there was limited agreement between the SCCAI and the DISQ but better correlation with the IBDQ. No correlation was seen with faecal calprotectin. There was no correlation between faecal calprotectin and the IBDQ or the DISQ (Table 3).

Discussion

We evaluated the correlation of two short, patient focussed and suitable for point-of-care testing indices, namely the DISQ and the sCDAI to assess disease severity in IBD. The Dudley Intestinal Symptom Questionnaire (DISQ) showed only limited correlation with the established Crohn's disease activity index (CDAI) and the sCDAI and the IBDQ but did not correlate with faecal calprotectin. In UC, the DISQ correlated with the IBDQ and the Simple Chronic Colitis Activity Index (SCCAI) but again no correlation was established with faecal calprotectin. In contrast, in Crohn's disease, as shown earlier, the sCDAI correlated well with the longer version, the CDAI [12] but not as good with the IBDQ and not with faecal calprotectin.

Certainly since the advent of mucosal healing as the treatment target in IBD, but probably well before then, has it become obvious that clinical indices do not correlate well with endoscopic findings [20-22]. The gold standard of assessing disease activity in IBD remains a colonoscopy [7]. However, this is invasive and not readily available. As an alternative, faecal calprotectin measurements have shown good correlation with endoscopic disease activity in both CD and UC [23,24]. Point-of-care devices are being established but handling faeces might be a barrier for patients [25].

Several disease activity indices have been developed for both IBDs since their first description. In Crohn's disease, the CDAI is most often used in clinical trials but due to the requirement of collecting information over 7 days as well as necessary physician input and blood testing has not been accepted in daily clinical practice [10]. The remedy some of these inconveniences, the sCDAI was developed [12]. However, still a 7 day assessment is necessary although no blood test or examination was seen to be a requirement for disease activity assessment. In our prospective analysis, the sCDAI correlated well with the longer version (R = 0.786; p < 0.001), the CDAI but not so good with the IBDQ (R = 0.595; p < 0.001). These results are in agreement with previous reports. Irvine *et al.* found a highly significant correlation between the CDAI and the IBDQ (r = -0.67; P < 0.0001) [26]. Not surprisingly, in our study there was no correlation with faecal calprotectin (R = 0.099; p < 0.519) however that result was not significant.

The DISQ was developed as a patient-completed, quick and simple point-of-care instrument to assess severity of symptoms [17]. In a previous study, we found this to be a reliable tool, easy to use by patients and physicians alike to assess intestinal symptoms in patients with spondyloarthropathies. We were able to demonstrate significant correlations between the DISQ and the IBDQ ($r^2 = 0.45$, p < 0.001) and between the DISQ and the CDAI ($r^2 = 0.46$; p < 0.0001) in patients with CD [19]. We were unable to repeat these findings in the current study. In CD there was only a very limited correlation between the DISQ and the CDAI, sCDAI, IBDQ but no correlation with FCP while in UC, there was acceptable correlation between the DISQ and the SCCAI (R = 0.538; p < 0.001) and the IBDQ (R = 0.592; p < 001) and again no correlation with FCP.

Furthermore, our study suggests that both physician-led (CDAI) and patient guided (DISQ and SCCAI) disease indices correlate better with measures of health related quality of life (IBDQ) than markers of inflammation (FCP). In fact, there was no correlation FCP and IBDQ in either disease. This is in line with previous studies showing clinical assessment does not correlate with endoscopic assessment [27,28]. It is known however, that markers of inflammation, such as faecal calprotectin are better correlated to endoscopic disease [29] and are more reliable at predicting disease relapse [30].

There are limitations to this study. First of all, the small sample size was due to time constraints and the analysis of more participants might have demonstrated a clearer picture. The discrepancy between a previous study using the DISQ and this study warrants further investigations to determine the role of this short and simple, patient-focussed instrument to assess disease severity. The sCDAI seems well suited to replace the longer version, however, the 7 day assessment period will continue to limit its use.

Acknowledgements

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Appendix

Appendix 1. Crohn's Disease Activity Index	
Clinical or laboratory variable	Weighting factor
Number of liquid or soft stool each day for seven days	×2
Abdominal pain (graded from 0-3 on severity) each day for seven days	×5
General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days	×7
Presence of complications. One point each for: arthralgia or arthritis; iritis or uveitis; erythema nodosum, pyoderma gangrenosum or aphthous ulcers; anal fissures, fistulae or abscesses; other fistulae; fever during the previous week.	×20
Taking loperamide or opiates for diarrhoea	×30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	×10
Haematocrit points under 47 in men and 42 in women	×6
Percentage deviation from standard weight	×1

Appendix 2. Simple Clinical Colitis Activity Index	
Symptom	Score
Bowel frequency (day)	
1-3	0
4-6	1
7-9	2
>9	3
Bowel frequency (night)	
1-3	1
4-6	2
Urgency of decaecation	
Hurry	1
Immediately	2
Incontinence	3
Blood in stool	
Trace	1
Occasionally frank	2
Usually frank	3
General well being	
Very well	0
Slightly below par	1
Poor	2
Very poor	3
Terrible	4
Extracolonic features, such as arthritis, pyoderma gangrenosum, erythema nodosum and uveitis.	1 per manifestation

Appendix 3. Dudley IBD Symptom Questionnaire
Answer the following, using the five point scale below to describe frequency and intensity of possible symptoms, selecting the number that best corresponds to your symptoms this week.
1 = non (never) 2 = mild (occasionally) 3 = moderate 4 = severe 5 = incapacitating

1. Frequent stools

2. Loose stools (diarrhoea)

3. Blood in your stool

4. Waking up at night to have a bowel movement

5. Urgency to evacuate bowels

6. A strong and persistent desire to evacuate your bowels after defaecation

7. A continual need to evacuate your bowels accompanied by straining (tenesmus)

8. Accidental soiling of your underwear (incontinence)

9. Soreness or itiching of your anus (rectum)

10. Passage of gas

11. Pain or cramping in abdomen (stomach)

12. Loss of appetite (anorexia)

13. Nausea

14. Tiredness (fatigue)

15. Fever