



Original Article

# The Impact of Endoscopic Inflammation and Mucosal Healing on Health-related Quality of Life in Ulcerative Colitis Patients

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## Abstract

**Background:** Health-related quality of life [HRQoL] is impaired in ulcerative colitis and is correlated to clinical disease activity. The recent shift towards more objective treatment goals like mucosal healing generates a need for evaluating the association between endoscopic disease activity, mucosal healing and HRQoL.

**Methods:** In this cross-sectional study, patients with either active or inactive ulcerative colitis underwent sigmoidoscopy. Clinical disease activity was assessed by the Simple Clinical Colitis Activity Index [SCCAI], endoscopic inflammation by the Mayo Endoscopic Subscore [MES], and HRQoL by the Short Inflammatory Bowel Disease Questionnaire [SIBDQ] and Short Health Scale [SHS].

**Results:** A total of 110 patients, 71% with active disease, had a median SCCAI score of 3 and a median MES score of 1. Patients in clinical remission had a mean SIBDQ of 60 and SHS of 6. HRQoL decreased significantly with increasing clinical (SIBDQ [ $\chi^2 = 61.8$ ,  $p < 0.0001$ ] and SHS [ $\chi^2 = 63.4$ ,  $p < 0.0001$ ]) and endoscopic disease activity (SIBDQ [ $\chi^2 = 33.1$ ,  $p < 0.0001$ ] and SHS [ $\chi^2 = 40.3$ ,  $p < 0.0001$ ]). Mucosal healing was associated with a higher HRQoL than active inflammation (59/46,  $p < 0.0001$  [SIBDQ] and 7/20,  $p < 0.0001$  [SHS]). Decreased HRQoL was observed with more extensive disease. Linear regression revealed strong association between SIBDQ and SHS.

**Conclusions:** Not only clinical disease activity but also endoscopic inflammation and disease extent were associated with decreased HRQoL. Patients with mucosal healing had significant higher HRQoL, emphasising the importance of this treatment goal. Both SHS and SIBDQ are easy to use and to implement, and were strongly correlated.

**Keywords:** Inflammatory bowel disease; ulcerative colitis; health-related quality of life; patient-related outcome; mucosal healing;

## 1. Introduction

The disease course in ulcerative colitis consists of periods of both active and inactive disease, with medical treatment as the cornerstone of daily care. Even though the treatment options have improved during past decades, a substantial proportion of the patients do not achieve durable clinical remission, thus impairing their quality of

life.<sup>1,2</sup> The young age of disease onset and the unpredictable disease course further contribute to this impairment.<sup>3</sup>

Treatment goals have changed from achieving and maintaining steroid-free clinical remission towards the more objective goals: endoscopic and histological mucosal healing. When reaching these goals, the risk of relapse, treatment escalation and colectomy decreases.<sup>4,5,6</sup> Along with

this shift in treatment paradigm emerges a need for evaluation of the association between mucosal healing and health-related quality of life [HRQoL]. There is an increasing international interest and need for validated patient-reported outcomes in both clinical trials and daily care.<sup>7</sup>

Several different questionnaires for evaluating HRQoL have been designed. Some are primarily designed for clinical trials and other for daily clinical practice. The Inflammatory Bowel Disease Questionnaire [IBDQ]<sup>8</sup> is a comprehensive questionnaire mainly used in research. The IBDQ covers a broad range of quality measurements in 32 items divided in four categories: bowel symptoms, systemic symptoms, emotional functions, and social functions. A shortened version, the Short Inflammatory Bowel Disease Questionnaire [SIBDQ], is a validated 10-question tool measuring physical, social, and emotional status [score 10–70, low value equals low HRQoL].<sup>9</sup> The SIBDQ has been shown to accurately reflect clinical disease activity in ulcerative colitis [UC] patients<sup>10</sup> and a good correlation with the IBDQ has also been demonstrated.<sup>11</sup>

The SHS is a four-part visual analogue scale questionnaire measuring bowel symptoms, activities of daily life, worry, and general well-being [score 0–40, high value equals low HRQoL]. This score was originally designed and validated to simplify the measurement of HRQoL<sup>12</sup> in UC patients, and an acceptable association with the IBDQ was also shown. The SHS was later validated in patients with Crohn's disease<sup>13</sup> and in several languages.<sup>14,15</sup>

In UC, studies evaluating the association between HRQoL and endoscopic inflammation are lacking. Many patients may consider HRQoL far more important than the doctor's more objective measurements, and in order to justify these objective measurements in daily care, they have to be closely linked to HRQoL.

Therefore, the primary aim of this study was to assess the association between endoscopic inflammation, mucosal healing, and HRQoL. We also evaluated the association between clinical disease activity and HRQoL as well as the correlation between the two commonly used HRQoL assessment tools, the SIBDQ and the SHS. Possible differences between genders were evaluated.

2. Methods

2.1. Patients

In this cross-sectional study, 110 patients with either active or inactive ulcerative colitis were recruited from September 2012 to June 2014 at the Gastrounit, Medical Division, Copenhagen University Hospital Hvidovre, when they were to undergo sigmoidoscopy because of disease flare or regular surveillance of disease activity. All patients gave informed consent to the use of their medical data. The handling of data was approved by the Danish Data Protection Agency.

The inclusion criteria for this study were: [1] UC diagnosed by established criteria, and [2] disease extension > 10cm from the anus, with no intake of nonsteroidal anti-inflammatory drugs [NSAID] for > 4 weeks.

2.2. Evaluation of the clinical disease activity

Clinical disease activity was measured using the Simple Clinical Colitis Activity Index [SCCAI].<sup>16</sup> The SCCAI consists of six categories: stool frequency at day, stool frequency at night, urgency, rectal bleeding, general well-being, and extra-intestinal manifestations. Within each category, a value is assigned and added to a total score between 0 and 20 with increasing disease severity. We defined a value of 0–1 to equal inactive disease/remission, 2–4 mild activity, 5–8 moderate activity, and > 9 severe activity.

2.3. Evaluation of the disease extent and endoscopic inflammation

To ensure consistent evaluation of the endoscopic inflammation and disease extent, all patients underwent flexible sigmoidoscopy by the

same doctor [KT]. Extension was divided into proctitis, left-sided colitis, or extensive colitis according to the Montreal criteria.<sup>17</sup> An extensive colitis was diagnosed when no upper disease limit was found during sigmoidoscopy and a previous colonoscopy had revealed extensive colitis.

The endoscopic appearance was assessed using the Mayo Endoscopic Subscore [MES], which represents the endoscopic part of the total Mayo Score. MES divides inflammation into four categories of increasing severity: 0 equals inactive disease and 1–3 equals mild, moderate, or severe activity. In this study, we have chosen to define mucosal healing as MES = 0.

2.4. Evaluation of HRQoL

During their visit, all patients completed the Danish translations of the SIBDQ and the SHS.

2.5. Statistics

Data were analysed using non-parametric statistics. The Kruskal–Wallis test and Mann–Whitney test were used as appropriate in calculating differences in HRQoL in the different disease activity groups. The association between SIBDQ and SHS was assessed using linear regression. A *p* < 0.05 was considered statistically significant. All calculations and analyses were performed using SAS Enterprise Guide 6.1 [SAS Institute Inc., Cary, NC, USA].

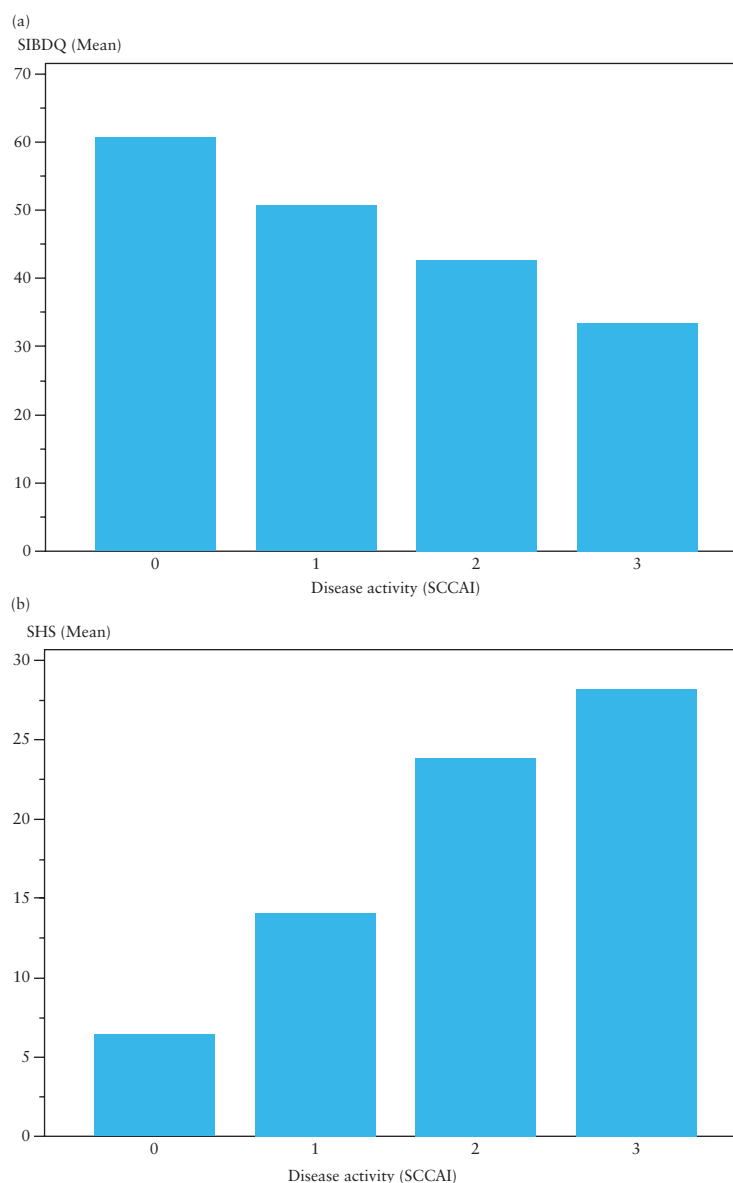
3. Results

A total of 110 patients were recruited. The median age was 37 years [19–80], and 56 % were female. The median disease duration was 4.5 years; 29% had mucosal healing, 20% active proctitis, 33% left-sided colitis, and 18% extensive colitis. According to the MES, 29% had mucosal healing, 26% had mild, 31% moderate, and 14%

Table 1. Patient characteristics.

Patient characteristics	
Characteristics	<i>n</i> = 110
Age [median, range]	37 years [19–80]
Gender [male/female]	48/62
Disease duration [median/range]	4.5 years [0.2–48.5]
Smoking	
• Never	48% [53]
• Former	36% [40]
• Current	15% [17]
Actual disease extent [% , <i>n</i> ]	
• Inactive	29% [32]
• Proctitis	20% [22]
• Left-sided colitis	33% [36]
• Extensive colitis	18% [20]
Clinical disease activity [median, IQR]	
• SCCAI	3 [1–7]
Mayo Endoscopic Score [% , <i>n</i> ]	
• 0	29% [32]
• 1	26% [29]
• 2	31% [34]
• 3	14% [15]
Medication	
• None	16% [18]
• Oral 5-ASA	58% [64]
• Topical 5-ASA	25% [27]
• Thiopurines	27% [30]
• Anti-TNFα	4% [4]
• Oral steroid	4% [4]

IQR, interquartile range; SCCAI, Simple Clinical Colitis Activity Index; 5-ASA, 5-aminosalicylic acid; TNF, tumour necrosis factor.



**Figure 1.** HRQoL grouped by clinical disease activity [SCCAI] [A: SIBDQ, B: SHS]. 0 = Remission [SCCAI 0–1] 1 = Mild [SCCAI 2–4] 2 = Moderate [SCCAI 5–8] 3 = Severe [SCCAI > 9]. HRQoL, Health Related Quality of Life; IBDQ, Inflammatory Bowel Disease Questionnaire; SHS, Short Health Scale; SCCAI, Simple Clinical Colitis Activity Index; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.

severe inflammation. According to the SCCAI, 35% were in clinical remission, 25% had mild, 25% moderate, and 15% severe disease activity. Their baseline characteristics are shown in Table 1.

### 3.1. The association between HRQoL and clinical disease activity

Patients in clinical remission have an average HRQoL of 60 [SIBDQ] and 6 [SHS]. Overall, we revealed significantly decreasing HRQoL with increasing clinical disease activity when assessed with both SIBDQ [ $\chi^2 = 61.8$ ,  $p < 0.0001$ ] and SHS [ $\chi^2 = 63.4$ ,  $p < 0.0001$ ], Figure 1a, b.

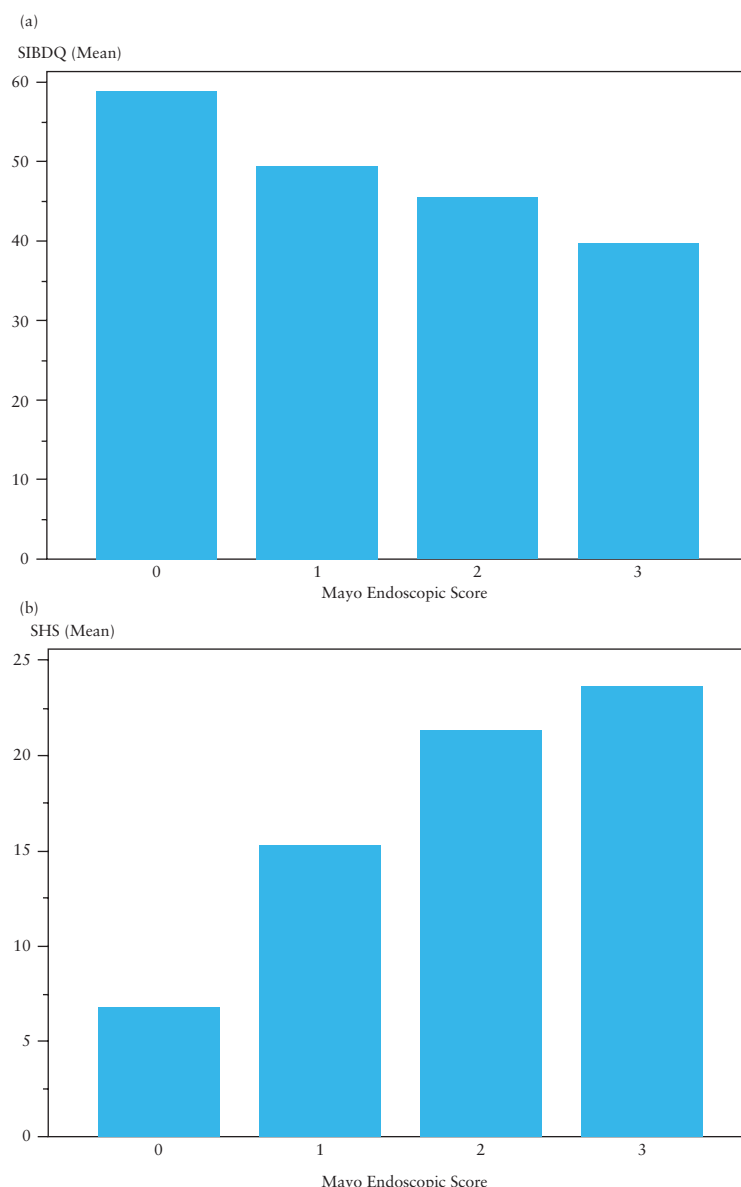
### 3.2. The association between HRQoL and endoscopic disease activity

We also found significantly decreased HRQoL with increasing endoscopic disease severity [MES] for both SIBDQ [ $\chi^2 = 33.1$ ,  $p < 0.0001$ ] and SHS [ $\chi^2 = 40.3$ ,  $p < 0.0001$ ], Figure 2a, b.

Overall, patients with mucosal healing [MES = 0] had a slightly decreased HRQoL compared with a moderately decreased HRQoL in patients with active inflammation [MES 1–3] (59 vs 46,  $p < 0.0001$  [SIBDQ] and 7 vs 20,  $p < 0.0001$  [SHS]), Figure 3a, b. In the group of patients in clinical remission [SCCAI  $\leq 1$ ], no difference in HRQoL was observed between patients with and without mucosal healing (63 vs 62 [SIBDQ],  $p = 0.66$  and 5 vs 7,  $p = 0.83$  [SHS]).

### 3.3. The association between disease extent and HRQoL

When we looked at disease extent, we found that the HRQoL decreased with more extensive disease when assessed with both SIBDQ and SHS ( $\chi^2 = 28.32$ ,  $p < 0.0001$ ) and SHS [ $\chi^2 = 33.64$ ,  $p < 0.0001$ ], Figure 4a, b. However, we do observe a slight increase in HRQoL in the case of extensive colitis evaluated by SHS.



**Figure 2.** HRQoL grouped by endoscopic disease activity [A: SIBDQ, B: SHS]. 0 = mucosal healing 1 = mild 2 = moderate 3 = severe. HRQoL, Health Related Quality of Life; SHS, Short Health Scale; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.

### 3.4. HRQoL and gender

Evaluating clinical disease activity [SCCAI], we did not find any difference between females and males [median SCCAI score 3 vs 3.5,  $p = 0.76$ ], and did not find any overall difference in HRQoL between females and males (49 vs 51,  $p = 0.49$  [SIBDQ] and 16 vs 15,  $p = 0.77$  [SHS]). Looking at endoscopic disease activity, we observed a difference in HRQoL between females and males but only in cases of mild inflammation (34 vs 56,  $p = 0.04$  [SIBDQ] and 20 vs 10,  $p = 0.02$  [SHS]). Comparing HRQoL between females and males, no differences were found in either mucosal healing (59 vs 60,  $p = 0.61$  [SIBDQ] and 7 vs 6,  $p = 0.23$  [SHS]) or endoscopic inflammation (43 vs 48,  $p = 0.12$  [SIBDQ] and 21 vs 18,  $p = 0.21$  [SHS]).

### 3.5. HRQoL and medication

We did not find any difference in HRQoL between patients receiving no medical therapy compared with patients receiving any monotherapy or combined therapy (49 vs 49,  $p = 0.96$  [SIBDQ], and 15

vs 15,  $p = 0.91$  [SHS]). Given the number of patients in this study and the number of treatment options, it was not possible to find any difference in HRQoL between different medical therapies.

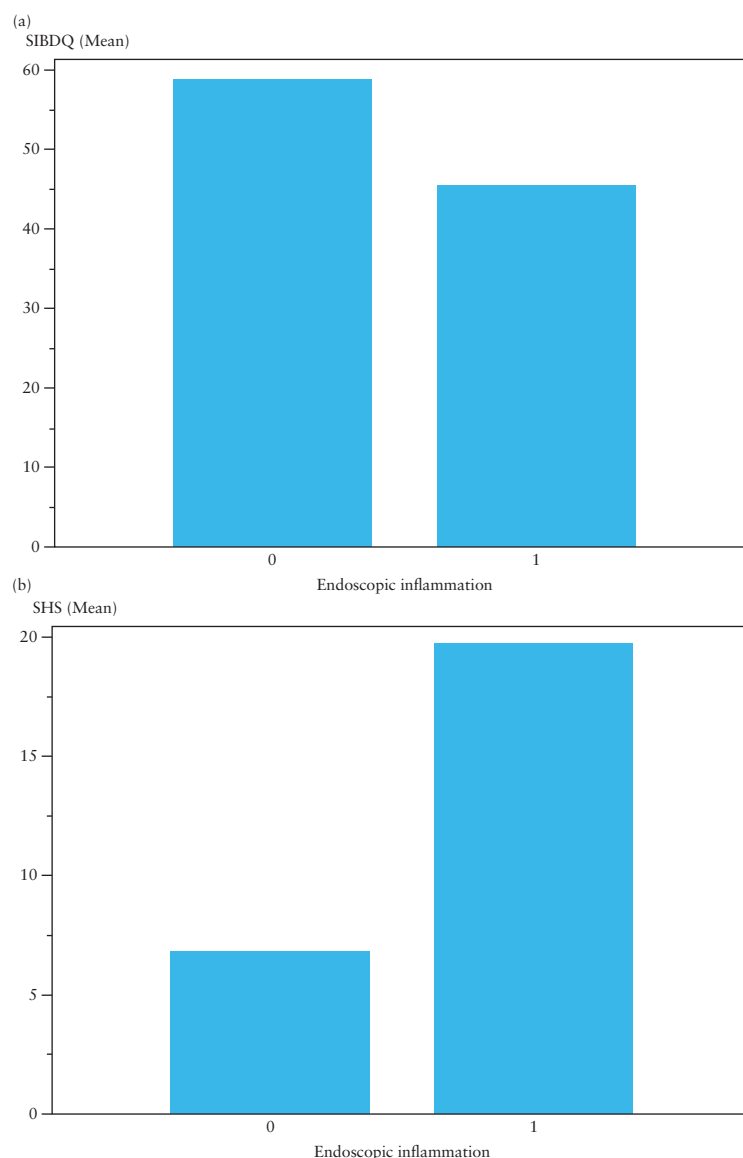
### 3.6. The association between SIBDQ and SHS

Testing the association between SIBDQ and SHS, we found a strong association using linear regression [ $\text{SHS} = -0.73 \times \text{SIBDQ} + 52.1$ ,  $p < 0.0001$ ] Figure 5.

## 4. Discussion

Increasing clinical disease activity evaluated by SCCAI was in this study associated with decreasing HRQoL regardless of SIBDQ or SHS scores.

The association between decreasing HRQoL with increasing clinical disease activity evaluated with the Partial Mayo Score has previously been reported in UC patients using both Assessment of Quality



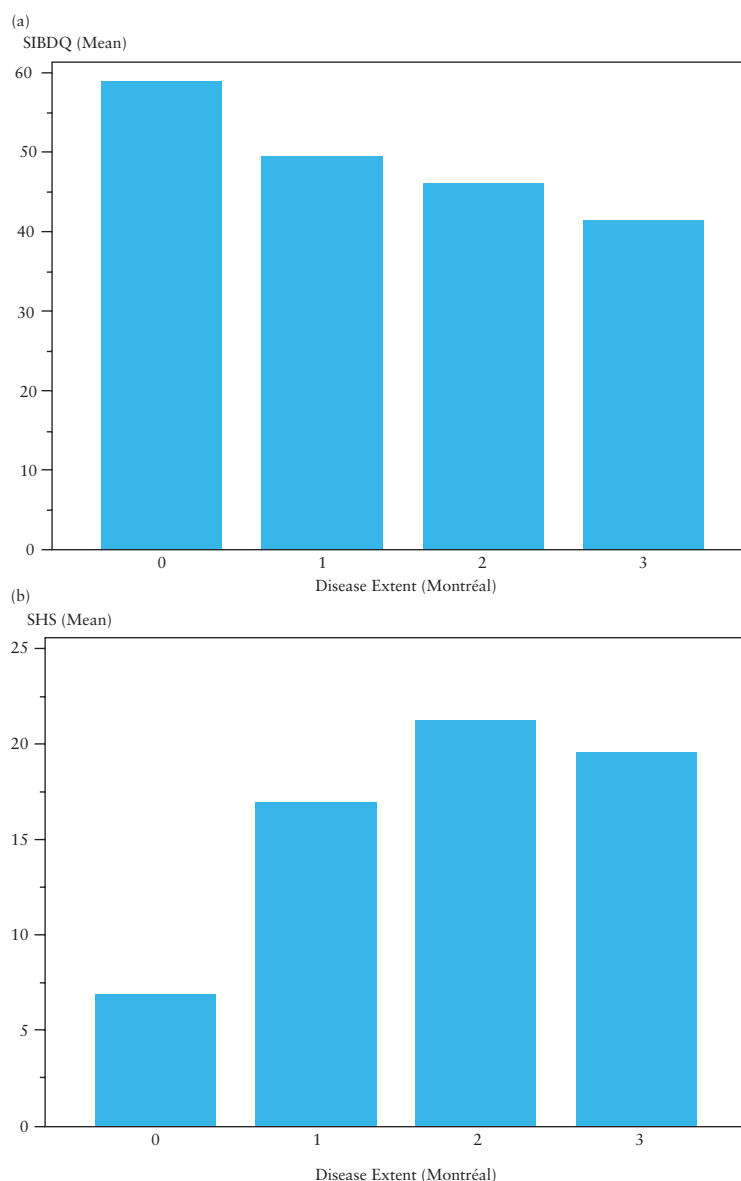
**Figure 3.** HRQoL in mucosal healing vs endoscopic inflammation [A: SIBDQ, B: SHS]. 0 = mucosal healing 1 = any inflammation. HRQoL, Health Related Quality of Life; SHS, Short Health Scale; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.

of Life-8-Dimension [AQoL-8D], Euro Quality of Life-5-Dimension 5-level [EQ-5D-5L], and IBDQ.<sup>2</sup> Three other studies similarly found significantly lower IBDQ or SIBDQ scores in patients with active UC compared with UC in remission.<sup>3,10,18</sup> Different clinical disease activity assessment tools were used [the Rachmilewitz Index, the Seo Index, and the Powell-Tuck Index, respectively]. We were not able to find any consistent difference in HRQoL between genders regarding clinical disease activity, despite the fact that male gender previously has been found to be associated with at better overall HRQoL.<sup>3,19</sup>

Even though the relationship between clinical disease activity and HRQoL seems to be consistent between several studies, the association between HRQoL and the endoscopic appearance of the mucosa is far less evaluated. In this study we found significantly decreasing HRQoL along with increasing endoscopic inflammation evaluated by the Mayo Endoscopic Score using both HRQoL assessment tools. This finding was the same for both genders.

Mucosal healing is a major goal in the treatment of IBD as it affects several important factors in the disease course, for example

need for medication, relapse rates, and risk for surgery. However, we know that achieving clinical remission is associated with better HRQoL,<sup>2</sup> and that when changing from clinical remission to mucosal healing as the treatment goal, the relationship with HRQoL needs to be re-evaluated. In our study we found significantly higher HRQoL in patients with endoscopic mucosal healing compared with endoscopically active disease. Casellas and colleagues have also recently found a near-normal HRQoL in UC patients with clinical remission and mucosal healing but applied a less restrictive definition of mucosal healing [MES 0–1].<sup>20</sup> The importance of mucosal healing is emphasised by these findings and by linking the doctor's objectives and the patient-reported outcomes together. However, in both males and females we found a slightly decreased HRQoL even in the presence of mucosal healing. This probably reflects the parts of the questionnaires that are non IBD-specific, such as fatigue and anxiety. We found a slightly decreased HRQoL in the patients with clinical remission, an observation also made by Lix *et al.*<sup>18</sup> who found a slightly decreased HRQoL [IBDQ] in inactive UC patients.



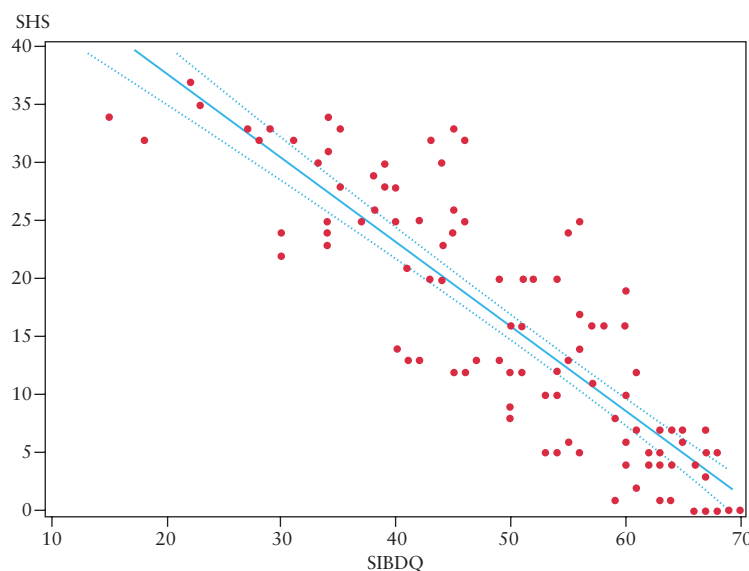
**Figure 4.** HRQoL grouped by disease extent [Montréal] [A: SIBDQ, B: SHS]. 0 = mucosal healing 1 = proctitis 2 = left-sided colitis 3 = extensive colitis. HRQoL, Health Related Quality of Life; SHS, Short Health Scale; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.

Furthermore, if patients were in clinical remission, we were not able to find any difference in HRQoL between those with and without mucosal healing [MH], but this might be due to the low number of patients in these subgroups.

We know that the symptoms of disease activity are influenced by the disease extent, and subsequently we observed a steadily decreasing HRQoL evaluated by SIBDQ along with more extensive disease. The minor increase in HRQoL in case of extensive disease evaluated by SHS is most likely due to a low number of patients. As we only performed sigmoidoscopy, the true disease extent could not be assessed and a clear distinction between left-sided and extensive colitis could not be made, so the distinction is based partly on the patient's previous disease extent.

The influence of medical therapy on HRQoL in IBD is not well described. We did not find any difference in HRQoL between patients receiving no or any treatment. This was also observed by Casellas and colleagues.<sup>20</sup> The IBSEN Study Group found a decreased

HRQoL in patients who had used corticosteroids during the past year.<sup>19</sup> This might be due to confounding by indication, and this issue makes it difficult to determine the influence of medical therapy in IBD patients. In 1996, Irvine and colleagues developed and validated a short version of the IBDQ in order to have a simple tool to measure HRQoL in both Crohn's disease and UC in clinical practice. A 10-question version with a 7-point scale was developed, and it explained 90% of the variance in the IBDQ in UC.<sup>9</sup> In 2000, Han *et al.* tried to develop a UC-specific SIBDQ but it turned out not to provide additional benefits compared with the original SIBDQ.<sup>11</sup> The SHS was developed by Hjortswang and colleagues in 2006 to provide a simple assessment tool to be used specifically in UC,<sup>12</sup> but it was later extended to be used [in different translations] in both Crohn's disease and UC.<sup>14,15</sup> The development and validation of the SHS was partly based on comparison with the IBDQ. No direct comparisons between the two short and easy to use HRQoL assessment tools have been made. In our study, all patients completed the



**Figure 5.** Association between SIBDQ and SHS using linear regression. [ $\text{SHS} = -0.73 \times \text{SIBDQ} + 52.1$ ,  $p < 0.0001$ ]. SHS, Short Health Scale; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.

two questionnaires and we found a very strong association between them, both in near-normal and in moderately to severely impaired HRQoL. This finding leads to the conclusion that both tools measure HRQoL in a reliable way, and that both can be implemented and used in daily clinical practice.

In conclusion, we found a strong relationship between HRQoL and both clinical and endoscopic disease activity in active as well as in inactive UC. More extensive and severe disease was associated with low HRQoL. Patients with MH had a significant higher HRQoL compared with patients with active endoscopic inflammation, emphasising the importance of MH as the treatment goal in UC. However, even in cases of MH, patients still have a slightly impaired HRQoL. We found no difference between genders. Finally, the SIBDQ and SHS were found to be strongly correlated and easily implementable. These observations link the important patient-related outcomes directly to major objective disease factors.

We hope that further prospective longitudinal trials will provide the answer as to whether MH will result in a sustained improvement in HRQoL in patients with UC. Moreover, a larger longitudinal study might be able to demonstrate whether MH can improve HRQoL in patients already in clinical remission.

## Conflict of Interest

KT: invited speaker AbbVie, MSD, Advisory board AbbVie. The other authors have no disclosures.

## Acknowledgments

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KT participated in design, enrolment, endoscopy, analysis, and interpretation of data and wrote the first draft. MK-K and IN-L participated in enrolment and interpretation of data, and AMN participated in design, enrollment, analysis, and interpretation of data. All authors have read and approved the final draft.

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