Pain in IBD patients: very frequent and frequently insufficiently taken into account

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Abstract: BACKGROUND Pain is a common symptom related to inflammatory bowel disease (IBD). In addition to abdominal pain, pain can also be an extraintestinal manifestation of IBD. Pain treatment is challenging and a substantial part of IBD patients are treated with opioids. Therefore, a better knowledge on pain symptoms is crucial for a better therapeutic approach to this clinical problem. METHODS Patients of the Swiss IBD Cohort Study (SIBDCS) (n = 2152) received a questionnaire regarding pain intensity, pain localization and impact of pain on daily life and social activities. Furthermore, the questionnaire investigated the use of pain-specific medication. RESULTS A vast majority of patients (71%) experienced pain during the disease course. For a substantial part of patients (49% in UC and 55% in CD) pain is a longstanding problem (>5 years). Pain in UC was of shorter duration compared to CD (p < 0.01). Abdominal pain (59.5%) and back pain (38.3%) were the main pain localizations. 67% of patients took pain medication; 24% received no pain treatment. The general quality of life was significantly lower in patients suffering of pain compared to those without pain (38 vs. 77; (-100 very bad; 100 very good) p<0.0001). CONCLUSIONS Prevalence of pain is high in patients of the SIBDCS. It is a longstanding problem for the majority of the patients affected. Pain was found to be undertreated in the SIBDCS and was significantly associated with health-related quality of life. Thus, an increased awareness is mandatory to address this frequent complication in the course of IBD.

DOI: https://doi.org/10.1371/journal.pone.0156666

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-134506
Journal Article
Published Version

Originally published at:
Zeitz, Jonas; Ak, Melike; Müller-Mottet, Séverine; Scharl, Sylvie; Biedermann, Luc; Fournier, Nicolas; Frei, Pascal; Pittet, Valerie; Scharl, Michael; Fried, Michael; Rogler, Gerhard; Vavricka, Stephan; Swiss IBD Cohort Study Group (2016). Pain in IBD patients: very frequent and frequently insufficiently taken into account. PLoS ONE, 11(6):e0156666.
DOI: https://doi.org/10.1371/journal.pone.0156666
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Background

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Methods

Patients of the Swiss IBD Cohort Study (SIBDCS) (n = 2152) received a questionnaire regarding pain intensity, pain localization and impact of pain on daily life and social activities. Furthermore, the questionnaire investigated the use of pain-specific medication.

Results

A vast majority of patients (71%) experienced pain during the disease course. For a substantial part of patients (49% in UC and 55% in CD) pain is a longstanding problem (>5 years). Pain in UC was of shorter duration compared to CD (p < 0.01). Abdominal pain (59.5%) and back pain (38.3%) were the main pain localizations. 67% of patients took pain medication; 24% received no pain treatment. The general quality of life was significantly lower in patients suffering of pain compared to those without pain (38 vs. 77; (-100 very bad; 100 very good) p<0.0001).

Conclusions

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significantly associated with health-related quality of life. Thus, an increased awareness is mandatory to address this frequent complication in the course of IBD.

Introduction

Abdominal pain is a common symptom related to Crohn’s disease (CD) and ulcerative colitis (UC), also collectively known as inflammatory bowel disease (IBD). During disease flares pain is present in 50–70% of IBD patients[1, 2]. Pain can also be caused by extraintestinal manifestations (EIM) of IBD or can be an extraintestinal manifestation by itself and more than 40% of IBD patients suffer from EIM[3–5] With a prevalence in the literature of 1–46%, arthropathies are the most common EIM of IBD[4, 6–16].

Pronounced severe impact of pain on health related quality of life (HRQOL) is known for various diseases[17–20]. Longstanding pain leads to a significant decrease in HRQOL, increase in pain medication intake and comorbidities including depression, anxiety and addiction [21–23]. Lower HRQOL also has been shown to result in an increased healthcare utilization among youth with IBD[24]. Furthermore, pain attacks severely interfere with social and working habits [25–27]. In an analysis of the data from the SIBDCS it could be shown that EIM were one of the most important predictors for temporary work disability in patients with CD[28].

In a German study including some 300 patients using a specifically designed questionnaire regarding pain and HRQOL 87.9% of IBD patients reported pain and showed a significantly reduced HRQOL. Surgery reduced pain and patients on analgesics reported more pain and lower HRQOL than patients not on analgesics [29].

Pain may directly be caused by inflammation as inflammatory cytokines and mediators have been shown to sensitize primary afferent neurons[30]. But ongoing inflammation does not fully explain pain in many IBD patients: about 20% of patients in complete clinical and endoscopic remission continue to experience pain. Pain treatment is complex and challenging. Pain perception in IBD patients may be influenced by multiple factors; peripheral, central, and environmental (stress) factors [31]. Pain treatment is challenging. NSAIDs can be very effective medications for arthralgia, arthritis or other rheumatic diseases, but their use in IBD is limited due to the risk of disease exacerbation and disease flares[32–38]. Even up to one-sixth of IBD patients in USA are chronically treated with opioids[39, 40]. Furthermore, pain in IBD was identified as the most common cause (48% of cases) for readmission 4 weeks after discharge from the hospital[41].

Here, we evaluated the well-characterized patient collective of the SIBDCS regarding pain, its impact of pain on daily life and social activities and the use of pain-specific medication. With 1’263 IBD patients included we present, to our best knowledge, the most extensive analysis of pain in IBD up to date.

Methods

Study Design

In the nationwide Swiss IBD Cohort Study (SIBDCS) patients with IBD from all regions of Switzerland have prospectively been included since 2006. In the SIBDCS at inclusion retrospective data is collected and afterwards patients are followed-up on a yearly basis. The cohort study is supported by the Swiss National Science Foundation and approved by the local ethical committees (IRB approval number: EK-1316, approved on 05.02.2007 by the Cantonal Ethics Committee of the Canton Zürich, Switzerland). As a participant of the SIBDCS the patients...
gave written informed consent for their clinical records to be used in this study. The cohort goals and methodology are described elsewhere[42].

2152 adult patients of the SIBDCS received a questionnaire regarding pain localization, impact of pain on daily life, how the surrounding responds to the patients’ pain and how activities of daily life are influenced. Furthermore, the questionnaire investigated the use of pain-specific medication. To develop the questionnaire, we used the validated German pain questionnaire[43]. Out of the 25 items in the German pain questionnaire 16 items were taken into our questionnaire (we used items 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 18, 20, 21, 22, A1). Within these questions the patients were asked to mark their pain localizations in a body scheme and define the duration of the occurrence of pain (differentiating less than a month, 1 month–½ year, ½ year–1 year, 1–2 years, 2–5 years and >5 years). Furthermore, they had to define the pain attacks regarding duration, frequency, intensity and quality and the patients were questioned about medical and non-medical treatment of pain and the impact of pain on their duties of daily life and work. We used a German and a French version of the questionnaire. The questionnaires are included in the supporting information (S1 and S2 Files).

Statistical Analysis

Clinical data were retrieved from the data center of the SIBDCS at the University of Lausanne. These data and additional data obtained from a review of the patients’ files were entered into a database (Access 2000; Microsoft Switzerland Ltd Liab. Co., Wallisellen, Switzerland).

A descriptive statistical analysis was performed. Categorical variables were summarized as frequencies and percentages, whereas quantitative variables as median and range. Differences in categorical data distribution between groups were assessed using the Chi-squared test, or the Fisher’s exact test in case of insufficient sample size. The general wellbeing was analyzed by student’s t-test. For the analysis of the disease duration the Wilcoxon-Mann-Whitney ranksum test was used. A p-value < 0.05 was considered statistically significant. All statistical analyses were carried out using GraphPad Prism 5.04 for Windows (GraphPad Software Inc.).

Results

Patient’s characteristics

We received 1263 completed questionnaires (response rate 59%). 599 from 1263 of the patients were male (47%) and 664 were female (53%). The median age was 47 years. 679 patients had the diagnosis of CD (54%), 556 UC (44%), 28 indeterminate colitis (IC) (2%). EIM of IBD were present in 699 patients (55%). The median disease duration was 15 years (0–57 years) (Table 1). The mean disease duration of all IBD patients was 15 years (0–57 years). In a subgroup analysis the mean disease duration of CD patients was longer (16 years (0–57 years)) than in UC (14 years (0–49) which was statistically significant (p = 0.002). The last disease location can be seen in Table 1.

Prevalence of pain in IBD

A total of 1263 completed questionnaires was analyzed regarding pain. The vast majority of patients (894, 71%) reported having experienced pain in general during the course of the disease. Only 369 (29%) of the patients that sent back the questionnaire reported no pain (Table 1). There was no statistical difference when comparing CD and UC regarding the occurrence of pain (P = 0.5726) (Table 1). When comparing the prevalence of pain in patients with any extraintestinal manifestation (EIM) and without, slightly more patients with EIM (73%;
508 of 699 patients with EIM versus 68%; 386 of 564 patients without EIM) reported pain, but this did not reach statistical significance (p = 0.1058).

### Duration and evolution of pain in IBD

Pain was a longstanding problem for the majority of the patients with 52% (469 patients) of patients experiencing pain >5 years. Fifteen patients (2%) reported pain since <1 month, 57 patients (6%) suffered from pain since 1 month—½ year, 59 patients (7%) since ½ year—1 year, 79 patients (9%) since 1–2 years and 215 (24%) since 2–5 years (Table 2). When comparing CD and UC 388 (70%) of the 556 UC patients reported pain in general. Of these the majority (191 patients, 49%) reported to suffer from pain more than 5 years. The 679 CD patients on the other hand also reported about pain in 71% (484 patients); of these a majority (265 patients, 55%) also suffered from pain >5 years. When comparing the duration of pain statistically more UC patients (47 patients; 12%) only suffered from pain in the last 1–2 years compared to CD (30 patients, 6%; p = 0.0026). For the other durations of pain there was no statistical difference (Table 2).
When characterizing the pain of all 894 IBD patients reporting of pain in general, 493 patients (55%) had pain attacks with no pain in between and 111 patients (12%) had pain attacks without being completely free of pain in between. 162 patients (18%) had a constant pain with slight fluctuations, 80 patients (9%) had constant pain with strong fluctuation. 48 patients (5%) did not specify (Table 3). When analysing the 484 CD patients who reported pain 268 patients (55%) reported about pain attacks with no pain in between, 67 (14%) had pain attacks without being completely free of pain in between. 91 (19%) had a constant pain with slight fluctuation, while 44 (9%) had a constant pain with strong fluctuation. When analysing the 556 UC patients 209 patients (54%) reported about pain attacks with no pain in between, 41 (11%) had pain attacks without being completely free of pain in between. 69 (18%) had a constant pain with slight fluctuation, while 34 (9%) had a constant pain with strong fluctuation. There was no statistically difference in the evolution of pain between CD und UC (Table 3).

### Frequency of pain in IBD

When characterizing the pain attacks of the 894 patients reporting pain in general, 173 patients (19%) had pain multiple times a day, 50 (6%) once daily, 137 (15%) multiple times per week, 38 (4%) once per week, 138 (15%) multiple times per month with only 73 patients (8%) reporting of pain once a month and 155 patients (17%) less than monthly. 130 patients (15%) did not specify (Table 4).

When comparing CD and UC patients in the group of CD patients presenting with pain 104 patients (21%) had pain multiple times a day, 26 (5%) once daily, 86 (14%) multiple times per week, 19 (4%) once per week, 66 (14%) multiple times per month, 36 (7%) once per month.

### Table 2. Period suffering from pain.

| Pain period | Total IBD N(%) | Crohn's Disease N(%) | Ulcerative colitis N(%) | p-value |
|-------------|----------------|----------------------|-------------------------|---------|
| <1 month    | 15 (2)         | 6 (1)                | 9 (3)                   | p = 0.2956 |
| 1 month—½ year | 57 (6)    | 34 (7)               | 20 (5)                  | p = 0.4006 |
| ½ year-1 year | 59 (7)    | 30 (6)               | 27 (7)                  | p = 0.6807 |
| 1–2 years   | 79 (9)         | 30 (6)               | 47 (12)                 | p = 0.0026 |
| 2–5 years   | 215 (24)       | 119 (25)             | 93 (24)                 | p = 0.8739 |
| >5 years    | 469 (52)       | 265 (55)             | 191 (49)                | p = 0.1166 |
| No pain     | 369 (29.2)     |                      |                        |         |

doi:10.1371/journal.pone.0156666.t002

### Table 3. Pain characterization.

| Pain character                  | Total IBD N(%) | Crohn's Disease N(%) | Ulcerative colitis N(%) | p-value |
|---------------------------------|----------------|----------------------|-------------------------|---------|
| Constant pain w. slight fluctuation | 162 (18)       | 91 (19)              | 69 (18)                 | p = 0.7253 |
| Constant pain w. strong fluctuation | 80 (9)         | 44 (9)               | 34 (9)                  | p = 0.9054 |
| Pain attacks w. pain free intervals | 493 (55)       | 268 (55)             | 209 (54)                | p = 0.6815 |
| Pain attacks w. constant pain   | 111 (12)       | 67 (14)              | 41 (11)                 | p = 0.1492 |
| Not specified                   | 48 (5)         | 14 (3)               | 34 (9)                  | p = 0.0002 |

doi:10.1371/journal.pone.0156666.t003
and 82 (17%) less than monthly. 65 (13%) did not specify. In the analysis of the UC patients 66 patients (17%) had pain multiple times a day, 21 (5%) once daily, 49 (13%) multiple times per week, 19 (5%) once per week, 64 (16%) multiple times per month, 36 (9%) once per month and 69 (18%) less than monthly. 64 patients (16%) did not specify. More CD patients (86 patients, 18%) reported of pain multiple times per week compared with UC (49 patients, 13%; p = 0.0385 (Table 4).

### Duration and intensity of pain episodes in IBD

The pain attacks most often had a duration of minutes (229 patients, 26%) to hours (244 patients, 27%), in 11% (102 patients) the pain duration was seconds and in 10% (93 patients) up to 3 days with only 73 patients (8%) reporting pain over more than 5 days. 153 patients (17%) did not specify the pain attacks (Table 5). In the subgroup analysis in the group of CD patients similar results were found with a pain duration of minutes (130 patients, 27%) to hours (124 patients, 26%), in 13% (63 patients) the pain duration was seconds and in 11% (55 patients) up to 3 days with 8% (38 patients) reporting pain over more than 5 days. 74 patients (15%) did not specify. In the group of UC patients there was a pain duration of minutes (92 patients, 24%) to hours (114 patients, 29%), in 10% (37 patients) the pain duration was seconds and in 9% (35 patients) up to 3 days with 8% (32 patients) reporting pain over more than 5 days. 78 patients (20%) did not specify. There was no statistically difference between CD und UC (Table 5).

The median pain intensity in the past 4 weeks was 2/10. 235 patients (26%) had no pain in the previous 4 weeks. The greatest pain intensity in the last 4 weeks was a median of 3/10.
Pain localization

Most of the 894 patients who reported pain suffered from abdominal pain (532 patients, 59.5%), followed by back pain in 342 patients (38.3%), knee pain in 258 patients (28.9%) and hip pain in 231 patients (25.8%). 220 patients (24.6%) reported headaches, 132 patients neck pain (14.8%), 204 patients (22.8%) pain in the hand and finger joints, 90 patients (10.1%) reported pain in the elbows, 192 patients (21.5%) shoulder pain and 16.6% (148 patients) reported pain in the feet/ankles. 312 patients (34.9%) did not specify (Table 6).

In the subgroup analysis there was no relevant difference in the pain localization in the CD and UC patients (Table 6).

Treatment of pain

The majority of the 894 patients reporting of pain (600 patients, 67%), received pain medication. Only 116 patients (13%) had physiotherapy. 216 patients (24%) received no pain treatment.

When accessing the kind of medical pain treatment, the majority of 37% (333 patients) used Acetaminophen. Only 112 patients (13%) used NSAID and COX-2 inhibitors were used seldom (3%, 22 patients). Opioids or Metamizole were used in 16% (142 patients) while 239 patients (27%) did not specify (Table 7). In a subgroup analysis of the CD and UC patients reporting pain slightly more CD patients used Acetaminophen (39%, 189 patients) compared to UC (34%, 131 patients), but this was not statistically significant (p = 0.2918). For NSAIDs, COX-2 inhibitors, opioids and Metamizole there was no statistical difference when comparing CD and UC (Table 7).

| Table 6. Pain localization. | Total IBD | Crohn’s Disease | Ulcerative colitis | p-value |
|-----------------------------|----------|-----------------|-------------------|--------|
| Pain localization           | N(%)     | N(%)            | N(%)              |        |
| Head                        | 220 (24.6) | 123 (25)       | 92 (24)           | p = 0.5807 |
| Neck                        | 132 (14.8) | 75 (16)        | 56 (14)           | p = 0.7033 |
| Hand/finger                 | 204 (22.8) | 121 (25)       | 79 (20)           | p = 0.1235 |
| Elbow                       | 90 (10.1)  | 52 (11)        | 36 (9)            | p = 0.4991 |
| Shoulder/arm                | 192 (21.5) | 114 (24)       | 75 (19)           | p = 0.1374 |
| Back                        | 342 (38.3) | 195 (40)       | 139 (36)          | p = 0.1836 |
| Hip/thigh                   | 231 (25.8) | 132 (27)       | 95 (25)           | p = 0.3931 |
| Knee/ lower leg             | 258 (28.9) | 143 (30)       | 113 (29)          | p = 0.9404 |
| Ankle/foot                  | 148 (16.6) | 84 (17)        | 61 (16)           | p = 0.5831 |
| Abdomen                     | 532 (59.5) | 293 (61)       | 224 (58)          | p = 0.4062 |
| Not specified               | 312 (34.9) | 166 (34)       | 141 (29)          | p = 0.5683 |

Table 7. Treatment of pain.

| Treatment of pain           | Total IBD | Crohn’s Disease | Ulcerative colitis | p-value |
|-----------------------------|----------|-----------------|-------------------|--------|
| Acetaminophen               | 333 (37) | 189 (39)        | 131 (34)          | p = 0.1199 |
| NSAID                       | 112 (13) | 63 (13)         | 45 (12)           | p = 0.5370 |
| Opioid/Metamizole           | 142 (16) | 83 (17)         | 50 (13)           | p = 0.0884 |
| COX-2 inhibitor             | 22 (3)   | 16 (3)          | 6 (2)             | p = 0.1283 |
| Other                       | 156 (17) |                 |                   |        |
| Not specified               | 239 (27) | 114 (24)        | 119 (31)          |        |
Impact of pain on quality of life

When assessing the impact on quality of life, 528 patients (59%) of the patients had an impact on the duties of daily life, with a median of 3/10 (0: no impact, 10: very strong impact), 329 (37%) had no impact and 37 (4%) did not specify. 513 patients (57%) had an impact on their work with a median of 4/10 (0: no impact, 10: very strong impact), 344 (39%) had no impact on work, 37 (4%) did not specify. The general quality of life was significantly lower in patients suffering of pain compared to those without pain (38 vs. 77; (-100 very bad; 100 very good) p < 0.0001).

Discussion

Using data from 1,263 SIDBCS patients we showed prevalence of pain in IBD patients was high. With 71% of our patients reporting pain, pain is present in many more patients than generally assumed. This is consistent with data from Germany were a high prevalence of pain (87.9%) was found in a much smaller cohort of 334 patients[29]. When comparing CD and UC patients separately we could find no significant difference in the occurrence of pain. This is in line with the study by Schirbel et al. and also Heikenen et al. who evaluated presenting symptoms of IBD in a children cohort[29, 44].

For a significant number of patients with IBD chronic pain is a growing problem and has a large impact on quality of life. Due to its frequency and possible direct relation to a hypersensitivity state due to the inflammatory process, it has even been proposed to add chronic pain to the list of extraintestinal manifestations of IBD[39, 45].

Furthermore, we showed that pain is a longstanding problem for the majority of the patients affected. 52% of patients experiencing pain > 5 years with only 2% reporting pain since less than 1 month. In a subgroup analysis comparing CD and UC, statistically more UC patients only suffered from pain in the last 1–2 years compared to CD (p = 0.0026). This reflects that pain in UC may be of shorter duration compared to CD. A possible explanation for this could be that CD patients, due to its higher prevalence of EIM, suffer more frequently of longer a duration of pain in comparison to UC [46]. In an evaluation of EIM in the SIBDCS by our group 43% of CD compared to 31% of UC patients had one to five EIMs[7]. Even though we could find that the disease duration in the UC patients was shorter than in the CD disease patients (14 years versus 16 years, p = 0.002), we don’t see this difference as relevant for the interpretation of the pain duration, especially regarding pain in the last 1–2 years.

The main pain localization was abdominal pain (59.5%), but a large proportion of patients also suffered from back pains, joint pains and headaches. Back pain was reported in 38.3% and 28.9% of patients suffered of knee pain. Furthermore 22.8% of IBD patients had pain in the hand and finger joints and 21.5% reported shoulder pain. This is in line with the literature showing that arthropathies are the most common extraintestinal manifestations in IBD[4, 6–16]. Of note the recognition of EIM is of great importance, since we could show that in one quarter of patients with IBD, EIMs appeared before the time of IBD diagnosis[47]. In a study by van der Have et al. IBD patients with back/joint pain reported a significantly lower quality of life and work productivity compared with IBD patients without back/joint pain[48]. In our cohort pain also had a strong impact on the health related quality of life (HRQOL). 59% of patients reported an impact on the HRQOL. Furthermore, HRQOL was significantly lower in patients suffering of pain as compared to those without pain (38 vs. 77; (-100 very bad; 100 very good) p < 0.05.

When characterizing pain, the majority of patients reported pain attacks with no pain in between (55%). On the other hand, a substantial part of patients (40%) reported not being pain free between the pain attacks or even having a constant pain.
Notably, we show that pain is undertreated: one fourth of the patients reporting pain did not receive pain treatment. Given the high prevalence of joint and back pain and the known efficacy of physiotherapy it is surprising that only 13% of the patients received physiotherapy[49]. When accessing the different kinds of pain treatment, the majority received acetaminophen. However, a substantial part of patients was treated with NSAIDS despite that there is substantial evidence that there is a risk of exacerbation of IBD after treatment with NSAIDs. In a study by Takeuchi et al. nonselective NSAIDs were associated with a 17%-28% relapse rate within 9 days of ingestion[32–34].

Our study has strengths, but also limitations. A clear strength is the large cohort that we studied with 1263 completed questionnaires, making it, to our best knowledge, the largest study on this topic in IBD up to date.

The limitations of our study however, include that, due to the study design and the fact that we did not control unreturned questionnaires we can face a reporting bias. Patients who actually suffer from pain due to IBD might want to share their feelings, while patients that do not suffer would be more enticed to completely discard the questionnaire. This would result in overestimation of pain prevalence in our study. Against this limitation speaks, that compared to the German study by Schirbel et al. with 387 IBD patients, which had a response rate of 96.8%, our prevalence of pain was not higher[29].

In summary, using a nationwide patient cohort of IBD patients we have demonstrated that prevalence of pain in IBD patients is high and that it is present in many more patients than generally assumed. Further more pain has a substantial impact on the HRQOL. Thus, an increased awareness is mandatory to address this frequent complication in the course of IBD. Furthermore, it underlines the importance of pain management in IBD.

Supporting Information

S1 File. German SIBDCS Pain Questionnaire. Pain questionnaire sent to the patients of the Swiss IBD Cohort Study (SIBDCS) in German.

(SDOCX)

S2 File. French SIBDCS Pain Questionnaire. Pain questionnaire sent to the patients of the Swiss IBD Cohort Study (SIBDCS) in French.

(SDOCX)

Acknowledgments

The authors thank all the patients for their collaboration and the members of the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) for their contribution. Members of the SIBDCS: Claudia Anderegg; Peter Bauerfeind; Christoph Beglinger; Stefan Begré; Dominique Belli; José Bengoa; Luc Biedermann; Janek Binek; Mirjam Blattmann; Nadia Blickenstorfer; Stephan Boehm; Jan Borovicka; Christian Braegger; Patrick Bühr; Bernard Burand; Emmanuel Burri; Sophie Buyse; Matthias Cremer; Dominique Criblez; Philippe de Saussure; Lukas Degen; Joaakim Delarive; Christopher Dörig; Barbara Dora; Gian Dorla; Tobias Ehmann; Ali El Wafa; Mara Egger; Matthias Engelman; Christian Felley; Markus Flieglner; Nicolas Fournier; Montserrat Fraga; Alain Frei; Pascal Frei; Remus Frei; Michael Fried; Florian Froehlich; Raoul Furlano; Suzanne Gallot-Lavallée; Martin Geyer; Marc Girardin; Delphine Golay; Tanja Grandinetti; Beat Gysi; Horst Haack; Johannes Haarer; Beat Helbling; Peter Hengstler; Denise Herzog; Cyrill Hess; Klaas Heyland; Thomas Hinterleitner; Philippe Hiroz; Claudia Hirsch; Petr Hruz; Pascal Juillerat; Rosmarie Junker; Christina Knellwolf; Christoph Knoblauch; Henrik Köhler; Rebekka Koller; Claudia Krieger; Gerd A. Kullak-Ublick; Markus Landolt; Frank
Lehmann; Valérie McLin; Philippe Maerten; Michel Maillard; Christine Manser; Andrew Macpherson; Michael Manz; George Marx; Rémy Meier; Christa Meyenberger; Jonathan Meyer; Pierre Michetti; Benjamin Misselwitz; Darius Moradpour; Patrick Mosler; Christian Mottet; Christoph Müller; Pascal Müller; Beat Mullhaupt; Claudia Münger; Leilla Musso; Andreas Nagy; Cristina Nichita; Jan Niess; Natacha Noël; Andreas Nydegger; Maliza Nzabonimpa; Nicole Obialo; Carl Oneta; Cassandra Oropesa; Céline Parzanese; Laetitia-Marie Petit; Fränziska Piccoli; Julia Pilz; Gaëlle Pittet; Valérie Pittet; Bruno Raffa; Ronald Rentsch; Sophie Restellini, Jean-Pierre Richterich; Silvia Rihs; Jocelyn Roduit; Daniela Rogler; Gerhard Rogler; Jean-Benoît Rossel; Markus Sagmeister; Gaby Saner; Bernhard Sauter; Mikael Sawatzki; Michael Scharl; Sylvie Scharl; Nora Schaub; Martin Schelling; Susanne Schibli; Hugo Schlaub; Daniela Schmid; Sybille Schmid; Jean-François Schnegg; Alain Schoepfer; Christiane Sokollik; Frank Seibold; Gian-Marc Semadeni; Mariam Seirafi; David Semela; Arne Senning; Marc Sidler; Johannes Spalinger; Holger Spangenberg; Philippe Sadler; Volker Stenz; Michael Steuerwald; Alex Straumann; Michael Sulz; Alexandra Suter; Michela Tempia-Caliera; Joël Thorens; Sarah Tiedemann; Radu Tutuian; Ueli Peter; Stephan Vavricka; Francesco Viani; Roland Von Känel; Alain Vonlaufen; Dominique Vouillamoz; Rachel Vulliamy; Helene Werner; Paul Wiesel; Reiner Wiest; Tina Wylie; Jonas Zeitz; Dorothee Zimmermann. The main 6 centers of the SIBDCS in Switzerland include Clinic Barmelweid, University Hospital Bern, University Hospital Geneva (HUG), Hôpital Neuchâtelois, Kantonsspital Olten, Kantonsspital St. Gallen, Centre Hospitalier Universitaire Vaudois Lausanne (CHUV), Gastro-entérologie — La Source-Beaulieu Lausanne and University Hospital Zurich. Head of the SIBDCS is Prof. Dr. med. Dr. phil. Gerhard Rogler (E-mail: info@ibdcohort.ch).

**Author Contributions**

Conceived and designed the experiments: JZ SV GR. Analyzed the data: JZ MA NF SS VP MF MS PF SV GR LB. Contributed reagents/materials/analysis tools: SM. Wrote the paper: JZ MA.

**References**

1. Wagtmans MJ, Verspaget HW, Lamers CB, van Hogezand RA. Crohn’s disease in the elderly: a comparison with young adults. J Clin Gastroenterol. 1998; 27(2):129–33. PMID: 9754773.

2. Aghazadeh R, Zali MR, Bahari A, Amin K, Ghahghaie F, Firooz F. Inflammatory bowel disease in Iran: a review of 457 cases. J Gastroenterol Hepatol. 2005; 20(11):1691–5. doi:10.1111/j.1440-1746.2005.03905.x PMID: 16246187.

3. Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. J Clin Gastroenterol. 1996; 23(1):29–34. PMID: 8835896.

4. Lakatos L, Pandur T, David G, Balogh Z, Kuronya P, Tollas A, et al. Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: results of a 25-year follow-up study. World journal of gastroenterology: WJG. 2003; 9(10):2300–7. PMID: 14562397; PubMed Central PMCID: PMCPMC4656482.

5. Vavricka SR, Schoepfer A, Scharl M, Lakatos PL, Navarini A, Rogler G. Extraintestinal Manifestations of Inflammatory Bowel Disease. Inflammatory bowel diseases. 2015; 21(8):1982–92. PMID: 26154136; PubMed Central PMCID: PMCPMC4511685.

6. Salvarani C, Vlachonikolis IG, van der Heijde DM, Fornaciari G, Macchioni P, Beltrami M, et al. Musculoskeletal manifestations in a population-based cohort of inflammatory bowel disease patients. Scandinavian journal of gastroenterology. 2001; 36(12):1307–13. PMID: 11761022.

7. Vavricka SR, Bruun L, Ballabeni P, Pittet V, Prinz Vavricka BM, Zeitz J, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011; 106(1):110–9. doi: 10.1038/ajg.2010.343 PMID: 20806297.

8. Palm O, Bernklev T, Moun B, Gran JT. Non-inflammatory joint pain in patients with inflammatory bowel disease is prevalent and has a significant impact on health related quality of life. The Journal of rheumatology. 2005; 32(9):1755–9. PMID: 16142874.
9. D’Inca R, Podsiadlew M, Ferronato A, Punzi L, Salvagnini M, Stumiolo GC. Articular manifestations in inflammatory bowel disease patients: a prospective study. Dig Liver Dis. 2009; 41(8):565–9. doi: 10.1016/j.dld.2009.01.013 PMID: 19278908.

10. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol. 2001; 96(4):1116–22. doi: 10.1111/j.1572-0241.2001.03756.x PMID: 11316157.

11. Lanna CC, Ferrari Mde L, Rocha SL, Nascimento E, da Cunha AS. A cross-sectional study of 130 Brazilian patients with Crohn’s disease and ulcerative colitis: analysis of articular and ophthalmologic manifestations. Clin Rheumatol. 2008; 27(4):503–9. doi: 10.1007/s10067-007-0797-5 PMID: 18097711.

12. Turkcapar N, Toruner M, Soykan I, Aydintug OT, Cetinkaya H, Duzgun N, et al. The prevalence of extraintestinal manifestations and HLA association in patients with inflammatory bowel disease. Rheumatology international. 2006; 26(7):663–8. doi: 10.1093/rheumatology/ken195 PMID: 16136311.

13. de Vlam K, Mielants H, Cuvelier C, De Keyser F, De Vos M. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. The Journal of rheumatology. 2000; 27(12):2860–5. PMID: 1128677.

14. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. Gut. 1998; 42(3):387–91. PMID: 9577346; PubMed Central PMCID: PMC1727027.

15. Brynskov J, Binder V. Arthritis and the gut. Eur J Gastroenterol Hepatol. 1999; 11(9):997–9. PMID: 10503836.

16. van Erp SJ, Brakenhoff LK, van Gaalen FA, van den Berg R, Fidder HH, Verspaget HW, et al. Classifying Back Pain and Peripheral Joint Complaints in Inflammatory Bowel Disease: A Prospective Longitudinal Follow-up Study. Journal of Crohn's & colitis. 2015. doi: 10.1093/ectccc/jjv195 PMID: 26512134.

17. Kukreja M, Bryant AS, Cleveland DC, Dabal R, Hingorani N, Kirklin JK. Health-Related Quality of Life in Adult Survivors After the Fontan Operation. Semin Thorac Cardiovasc Surg. 2015; 27(3):299–306. doi: 10.1053/j.semtcvs.2015.08.007 PMID: 26708372.

18. Hussain KB, Fontana RJ, Moyer CA, Su GL, Sneed-Pee N, Lok AS. Comorbid illness is an important determinant of health-related quality of life in patients with chronic hepatitis C. Am J Gastroenterol. 2001; 96(9):2737–44. doi: 10.1111/j.1572-0241.2001.00413.x PMID: 11569704.

19. Naliboff BD, Kim SE, Bolus R, Bernstein CN, Mayer EA, Chang L. Gastrointestinal and psychological mediators of health-related quality of life in IBS and IBD: a structural equation modeling analysis. Am J Gastroenterol. 2012; 107(3):451–9. doi: 10.1038/ajg.2011.377 PMID: 22085819; PubMed Central PMCID: PMC3854577.

20. Luo J, Hendryx M, Safford MM, Wallace R, Rossom R, Eaton C, et al. Newly Developed Chronic Conditions and Changes in Health-Related Quality of Life in Postmenopausal Women. J Am Geriatr Soc. 2015; 63(11):2349–57. doi: 10.1111/j.1572-0241.2015.03795.x PMID: 26503931.

21. Padua L, Aprile I, Frusciante R, Iannaccone E, Rossi M, Renna R, et al. Quality of life and pain in patients with facioscapulohumeral muscular dystrophy. Muscle Nerve. 2009; 40(2):200–5. doi: 10.1002/mus.21308 PMID: 19609906.

22. Jakobsson U, Hallberg IR. Pain and quality of life among older people with rheumatoid arthritis and/or osteoarthritis: a literature review. J Clin Nurs. 2002; 11(4):430–43. PMID: 12100639.

23. Fujimura T, Takahashi S, Kume H, Takeuchi T, Clinical Study Group of Tokyo University Affiliated H, Kitamura T, et al. Cancer-related pain and quality of life in prostate cancer patients: assessment using the Functional Assessment of Prostate Cancer Therapy. Int J Urol. 2009; 16(5):522–5. doi: 10.1111/j.1444-2242.2009.02291.x PMID: 19383037.

24. Ryan JL, Mellon MW, Junger KW, Hente EA, Denson LA, Saeed SA, et al. The clinical utility of health-related quality of life screening in a pediatric inflammatory bowel disease clinic. Inflammatory bowel diseases. 2013; 19(12):2666–72. doi: 10.1097/MIB.0b013e3182a82b15 PMID: 24051932; PubMed Central PMCID: PMCPMC3863996.

25. Blondel-Kucharski F, Chiroop C, Marquis P, Cortot A, Baron F, Gendre JP, et al. Health-related quality of life in Crohn's disease: a prospective longitudinal study in 231 patients. Am J Gastroenterol. 2001; 96(10):2915–20. doi: 10.1111/j.1572-0241.2001.14681.bx PMID: 11693326.

26. Casellas F, Lopez-Vivancos J, Badia X, Vilaseca J, Malagelada JR. Influence of inflammatory bowel disease on different dimensions of quality of life. Eur J Gastroenterol Hepatol. 2001; 13(5):567–72. PMID: 11396538.

27. Irvine EJ. Quality of life in inflammatory bowel disease and other chronic diseases. Scand J Gastroenterol Suppl. 1996; 221:26–8. PMID: 9110394.
28. Siebert U, Wurm J, Gothe RM, Arvandi M, Vavricka SR, von Kanel R, et al. Predictors of temporary and permanent work disability in patients with inflammatory bowel disease: results of the Swiss inflammatory bowel disease cohort study. Inflammatory bowel diseases. 2013; 19(4):847–55. doi: 10.1097/MIB.0b013e31827278e PMID: 23446333.

29. Schirbel A, Reichert A, Roll S, Baumgart DC, Buning C, Wittig B, et al. Impact of pain on health-related quality of life in patients with inflammatory bowel disease. World journal of gastroenterology: W.J.G. 2010; 16(25):3168–77. PMID: 20593502; PubMed Central PMCID: PMC2896754.

30. Bielefeldt K, Ozaki N, Geohart GF. Experimental ulcers alter voltage-sensitive sodium currents in rat gastric sensory neurons. Gastroenterology. 2002; 122(2):394–405. PMID: 11832454.

31. Srinath A, Young E, Szigethy E. Pain management in patients with inflammatory bowel disease: translational approaches from bench to bedside. Inflammatory bowel diseases. 2014; 20(12):2433–49. doi: 10.1097/MIB.0000000000000170 PMID: 25208108.

32. Ananthakrishnan AN, Higuchi LM, Huang ES, Khalili H, Richter JM, Fuchs CS, et al. Aspirin, nonsteroidal anti-inflammatory drugs in exacerbations of inflammatory bowel disease. J Clin Gastroenterol. 2015. doi:10.1097/MCG.0000000000000421 PMID: 26485106.

33. Bielefeldt K, Davis B, Binion DG. Pain and inflammatory bowel disease. Inflammatory bowel diseases. 2009; 15(4):778–88. doi: 10.1002/ibd.20848 PMID: 19130619; PubMed Central PMCID: PMC3180862.

34. Kefalakes H, Stylianides TJ, Amanakis G, Kolios G. Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality? European journal of clinical pharmacology. 2009; 65(10):963–70. doi: 10.1007/s00228-009-0719-3 PMID: 19711064.

35. Bielefeldt K, Davis B, Binion DG. Pain and inflammatory bowel disease. Inflammatory bowel diseases. 2009; 15(4):778–88. doi: 10.1002/ibd.20848 PMID: 19130619; PubMed Central PMCID: PMC3180862.

36. Kaufmann HJ, Taubin HL. Nonsteroidal anti-inflammatory drugs activate quiescent inflammatory bowel disease. Ann Intern Med. 1987; 107(4):513–6. PMID: 3498419.

37. Miner PB Jr. Factors influencing the relapse of patients with inflammatory bowel disease. Am J Gastroenterol. 1997; 92(12 Suppl):4–8S. PMID: 9395345.

38. Kefalakes H, Stylianides TJ, Amanakis G, Kolios G. Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality? European journal of clinical pharmacology. 2009; 65(10):963–70. doi: 10.1007/s00228-009-0719-3 PMID: 19711064.

39. Bielefeldt K, Ozaki N, Geohart GF. Experimental ulcers alter voltage-sensitive sodium currents in rat gastric sensory neurons. Gastroenterology. 2002; 122(2):394–405. PMID: 11832454.

40. Rath HC, Andus T, Caesar I, Scholmerich J. [Initial symptoms, extra-intestinal manifestations and course of pregnancy in chronic inflammatory bowel diseases]. Med Klin (Munich). 1998; 93(7):395–400. PMID: 9711052.

41. Hazratjee N, Agito M, Lopez R, Lashner B, Rizk MK. Hospital readmissions in patients with inflammatory bowel disease. Am J Gastroenterol. 2013; 108(7):1024–30. doi: 10.1038/ajg.2012.343 PMID: 23820989.

42. Pittet V, Juillerat P, Mottet C, Felley C, Ballabeni P, Burnand B, et al. Cohort profile: the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). International journal of epidemiology. 2009; 38(4):238–51. doi: 10.1093/ije/dyp045 PMID: 18782896.

43. Hagge T, Brumme C, ebner S, Menold D. Development and evaluation of the multidimensional German pain questionnaire. Schmerz. 2002; 16(4):263–70. doi: 10.1007/s00482-002-0162-1 PMID: 12192435.

44. Heikenen JB, Werlin SL, Brown CW, Balint JP. Presenting symptoms and diagnostic lag in children with inflammatory bowel disease. Inflammatory bowel diseases. 1999; 5(3):315–21. PMID: 10453370.

45. Siegel CA, MacDermott RP. Is chronic pain an extraintestinal manifestation of IBD? Inflammatory bowel diseases. 2009; 15(5):769–71. doi: 10.1002/ibd.20844 PMID: 19107773.

46. Zippi M, Corrado C, Pica R, Avallone EV, Cassieri C, De Nittio D, et al. Extraintestinal manifestations in a large series of Italian inflammatory bowel disease patients. World journal of gastroenterology: W.J.G. 2014; 20(46):17463–7. doi: 10.3748/wjg.v20.i46.17463 PMID: 25516659; PubMed Central PMCID: PMC4265606.

47. Vavricka SR, Rogler G, Gantenbein C, Spoerri M, Prinz Vavricka M, Navarini AA, et al. Chronological Order of Appearance of Extraintestinal Manifestations Relative to the Time of IBD Diagnosis in the
Swiss Inflammatory Bowel Disease Cohort. Inflammatory bowel diseases. 2015; 21(8):1794–800. doi: 10.1097/MIB.0000000000000429 PMID: 26020601.

48. van der Have M, Brakenhoff LK, van Erp SJ, Kaptein AA, Lenders M, Scharloo M, et al. Back/joint pain, illness perceptions and coping are important predictors of quality of life and work productivity in patients with inflammatory bowel disease: a 12-month longitudinal study. Journal of Crohn's & colitis. 2015; 9(3):276–83. doi: 10.1093/ecco-jcc/jju025 PMID: 25547976.

49. Sveaas SH, Berg IJ, Provan SA, Semb AG, Hagen KB, Vollestad N, et al. Efficacy of high intensity exercise on disease activity and cardiovascular risk in active axial spondyloarthritis: a randomized controlled pilot study. PloS one. 2014; 9(9):e108688. doi: 10.1371/journal.pone.0108688 PMID: 25268365; PubMed Central PMCID: PMCPMC4182541.