

# Soluble syndecan-1 as marker of intestinal inflammation: A preliminary study and evaluation of a new panel of biomarkers for non-invasive prediction of active ulcerative colitis

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## Abstract

**Background.** Syndecan-1 (Sdc1) is a heparin sulfate proteoglycan expressed in intestinal epithelium, which plays a crucial role in inflammation and epithelial repair. Sdc1-knockout mice have a deteriorated course of dextran sulfate sodium-induced colitis as compared to controls. Syndecan-1 is also shed into the serum during inflammation of the epithelium. We hypothesized that an increased serum level of soluble Sdc1 is a biomarker of intestinal inflammation in ulcerative colitis (UC).

**Objectives.** To evaluate serum soluble Sdc1 as a biomarker of intestinal inflammation in UC.

**Materials and methods.** This is a proof-of-concept study. Patients were recruited by the University Hospital Münster and HELIOS Albert Schweitzer Klinik Northeim (Germany). Blood samples were collected from UC patients actively suffering from this condition and those in remission. The levels of Sdc1 were measured with Diaclone CD 138 ELISA kit (Diaclone Research, Besançon, France) and routine clinical data were collected (C-reactive protein (CRP) levels, calprotectin in stool samples). Data were analyzed using SPSS software.

**Results.** Soluble Sdc1 levels were significantly elevated in the active UC group as compared to the inactive UC group ( $94.5 \pm 68.1$  ng/mL compared to  $28.3 \pm 12.6$  ng/mL,  $p = 0.0020$ ). The levels of Sdc1 also significantly correlated with the severity of UC as measured with the Mayo score ( $p = 0.0248$ ). Receiver operating characteristic (ROC) analysis showed a good correlation of Sdc1 with an endoscopic Mayo score  $\geq 2$ , with a value of 0.7747 (95% confidence interval (95% CI) = 0.5775–0.9718). A cutoff value of 37.1 ng/mL of Sdc1 showed a sensitivity of 78% and a specificity of 77%. A panel of biomarkers including CRP, hemoglobin, hematocrit, and Sdc1 was able to precisely predict active UC with an area under the curve (AUC) = 0.9395 (95% CI = 0.8509–1.0000).

**Conclusions.** Serum soluble Sdc1 correlates significantly with mucosa inflammation and Mayo score in UC. Clinical trials No. NCT 02333526.

**Key words:** inflammatory bowel disease, biomarker, CD138, syndecan-1, ulcerative colitis

## Background

Syndecan-1 (CD138, Sdc1) is a heparin sulfate proteoglycan that plays an important role in inflammation and wound healing.<sup>1,2</sup> Physiologically, there is a high concentration of Sdc1 in the intestinal epithelium. Sdc1-knockout mice exhibit impaired wound healing of the skin and show a higher mortality rate in an experimental model of colitis induced with dextran sulfate sodium.<sup>3,4</sup> Likewise, in ulcerative colitis (UC) patients, a lack of Sdc1 has been observed in histological specimens of ulcers.<sup>5,6</sup> In addition, a shedding of Sdc1 into the bloodstream during inflammation has been observed.<sup>7,8</sup> Furthermore, Sdc1 has been shown to play a role in autoimmune diseases like psoriasis.<sup>9</sup>

Guidelines recommend that the therapeutic aim of UC treatment should be both clinical and endoscopic remission.<sup>10,11</sup> In particular, the therapeutic goal is to achieve mucosal healing.<sup>12</sup> Therefore, it would be advantageous to identify non-invasive assessments, such as biomarkers or a panel of biomarkers, that indicate endoscopic remission. Presently, C-reactive protein (CRP), sedimentation rate and stool calprotectin are established biomarkers for intestinal inflammation, but none of these markers are specific to inflammatory bowel disease (IBD),<sup>13</sup> nor are any of these markers used as an alternative to endoscopic remission.<sup>14</sup> For example, stool calprotectin is most frequently used in studies of IBD, but the cutoff levels have been difficult to determine.<sup>15</sup> Other fecal markers like lactoferrin have not proven to be superior to stool calprotectin.<sup>14</sup> C-reactive protein is a long-standing marker for inflammation in general, but its ability to distinguish between mucosal healing and moderate-to-severe colitis is controversial due to poor accuracy and the use of different cutoff values.<sup>15</sup> Cytokines and downstream proteins have been evaluated as markers for UC, but they also have not been shown to be superior to stool calprotectin in its ability to distinguish between active and inactive colitis.<sup>16</sup> A wide range of markers connected to the immune response has also been evaluated.<sup>14</sup> However, none have proven superior if used as a single marker for active UC. A relatively new approach is to evaluate biomarker panels for the detection of mucosal healing. For example, Hosomi et al. evaluated a combination of presepsin and CRP for Crohn's disease activity, which showed a sensitivity of nearly 100%.<sup>17</sup> Therefore, identifying biomarkers specific to IBD is worthy of investigation.

## Objectives

Based on previous research, we considered the possibility that soluble Sdc1 levels in blood serum may correlate with the presence of colonic inflammation in UC and may be useful as a specific biomarker. Thus, the aim of this study was to examine the correlation between Sdc1 levels and the presence of inflammation with respect to disease activity, medication and other biomarkers of inflammation.

## Materials and methods

### Study design

This study was designed as proof of concept study. We hypothesized that Sdc1 is a suitable indicator of intestinal inflammation. The main outcome parameter was serum soluble Sdc1 levels from blood samples collected during routine outpatient visits from patients diagnosed with UC.

### Setting

This study was performed in accordance with the Declaration of Helsinki. The trial involved human participants, was approved by the local ethics committee at the University of Göttingen, Germany (approval No. 25/8/14) and was registered (Clinical trials No. NCT 02333526).

The study was conducted at the Helios Albert-Schweitzer-Hospital in Northeim, Germany and the University Hospital in Münster, Germany from 2015 to 2018. Routine outpatient visits were used to recruit patients, and all participants signed informed consent for blood collection and data storage. All data were collected in a Microsoft Excel table (Microsoft Office 2013; Microsoft Corp., Redmond, USA), immediately anonymized and processed according to the European Union law. A follow-up examination was not performed.

### Participants

Patients older than 18 years with a history of UC and signed informed consent were considered eligible for the study. Exclusion criteria included a history of Crohn's disease, infectious intestinal disease, an age under 18 years, pregnancy, and lack of informed consent.

### Variables

Secondary parameters were age, sex, active UC, UC in remission, Mayo score for UC, extent of UC, medication, leucocyte count, CRP, thrombocyte count, hemoglobin, hematocrit, and fecal calprotectin.

### Data sources and management

All blood samples were collected according to good clinical practice. The samples were labeled with a code and brought to the laboratory. Samples were centrifuged at 3000 × g for 10 min and serum was obtained. The serum samples were stored at -70°C until processing. A commercially available enzyme-linked immunosorbent assay (ELISA) kit was used to measure soluble Sdc1 (Diacclone Research, Besançon, France). Material that was not used was discarded.

To avoid bias, all patients with UC had their diagnosis confirmed by endoscopy and histologic examination of gut specimens.

## Study size

As this was a proof of concept study, the patients were divided into 2 groups: 13 patients with UC and a Mayo score <2, and 14 patients with UC and a Mayo score ≥2. Patient recruitment was considered complete after attaining a strong and significant signal for our main outcome parameter, and when statistical power 1-beta surpassed 0.8 (80%).

## Quantitative variables

We chose the endoscopic Mayo score for the discrimination of active and inactive UC as this methodology has been well established in literature. Patients with a Mayo score <2 (inactive or mild disease) were considered as inactive, while patients with a Mayo score ≥2 (moderate-to-severe) were considered as active. A Mayo score of 2 was chosen due to the significant signal of Sdc1 detected using an unpaired t-test.

## Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows, v. 27 (IBM Corp., Armonk, USA). Values are displayed as mean and standard deviation (SD), or n. To test for significance, unpaired t-tests (to compare means) or Pearson's  $\chi^2$  tests (to compare n in contingency tables) were used, and an alpha level of a  $p < 0.05$  was considered significant. To examine the correlation between the complete Mayo score and Sdc1, the Kruskal–Wallis test was used, and a  $p < 0.05$  was considered statistically significant. To examine the correlations of CRP and stool calprotectin with Sdc1, bivariate correlation (Pearson's  $r$ ) was used. A receiver operator characteristic (ROC) curve analysis was performed to check for the discrimination threshold of Sdc1 (discrimination of colonoscopic Mayo score <2 compared to ≥2). Points on the ROC curve nearest the upper left corner were chosen for cutoff values as this resulted in optimal sensitivity and specificity. Logistic regression analysis was performed to determinate the regression coefficients of CRP, hemoglobin, hematocrit, and Sdc1 since these parameters were proven to be significant in t-test analyses. Based on these data, a model (see results) was created to improve the prediction of active UC. This model was again analyzed using ROC curve analysis.

## Results

Twenty-seven patients with UC were eligible for this study and provided informed consent. All of the recruited patients were included. Among these, 13 were considered inactive and 14 were considered active, as indicated by the Mayo score. For those with active UC, the distribution of colonic inflammation was as follows: 50% pancolitis, 31.5% left-sided UC, 12.5% ulcerative proctitis, and 6% right-sided UC.

Blood was drawn and samples underwent Sdc1 analysis. As outlined above, 2 groups were differentiated based on a Mayo score <2 and ≥2. In these 2 groups, no significant differences in age, duration of disease, gender, mesalazine usage, comorbidities, tumor necrosis factor (TNF) blocker usage, and azathioprine usage were observed. It was found that drugs like vedolizumab, steroids or other immunomodulatory drugs were used more often in the active UC group than in the inactive UC group. Significant differences were also found between the active and inactive UC groups in the level of CRP, leucocyte count, hemoglobin, hematocrit level, and fecal calprotectin.

The Sdc1 was also significantly elevated in the active UC group as compared to the inactive UC group ( $94.5243 \pm 68.0518$  ng/mL compared to  $28.3423 \pm 12.5921$  ng/mL,  $p = 0.0020$ ; Table 1). The Kruskal–Wallis test showed a significant correlation between Sdc1 values and the extent of UC as measured with the complete Mayo score (degrees of freedom (df) = 8,  $p = 0.0248$ ; Fig. 1). In addition, ROC analysis showed an area under curve (AUC) of 0.7747 (95% confidence interval (95% CI) = 0.5775–0.9718; Fig. 1), indicating a pretty good correlation of Sdc1 with the activity of UC (according to the endoscopic Mayo score). As a result of the ROC analysis, it was determined that a cutoff value of 37.1 ng/mL of Sdc1 was associated with a sensitivity of 78% and a specificity of 77%.

Based on these data, we were able to model a panel of biomarkers for improved prediction of active UC. First, we performed a logistic regression analysis identifying CRP, hemoglobin, hematocrit, and soluble Sdc1 as parameters for the prediction of active colitis as defined with an endoscopic Mayo score of 2 or above. Next, we calculated the x-value where

$$x = 4.078 * [\text{CRP [mg/dL]}] - 1.961 * [\text{hemoglobin [g/dL]}] + 0.466 * [\text{hematocrit [\%]}] + 0.040 * [\text{Sdc1 [ng/mL]}] + 2.900.$$

The probability (P) that the patients suffers from active UC was estimated using x in this mathematical term (1):

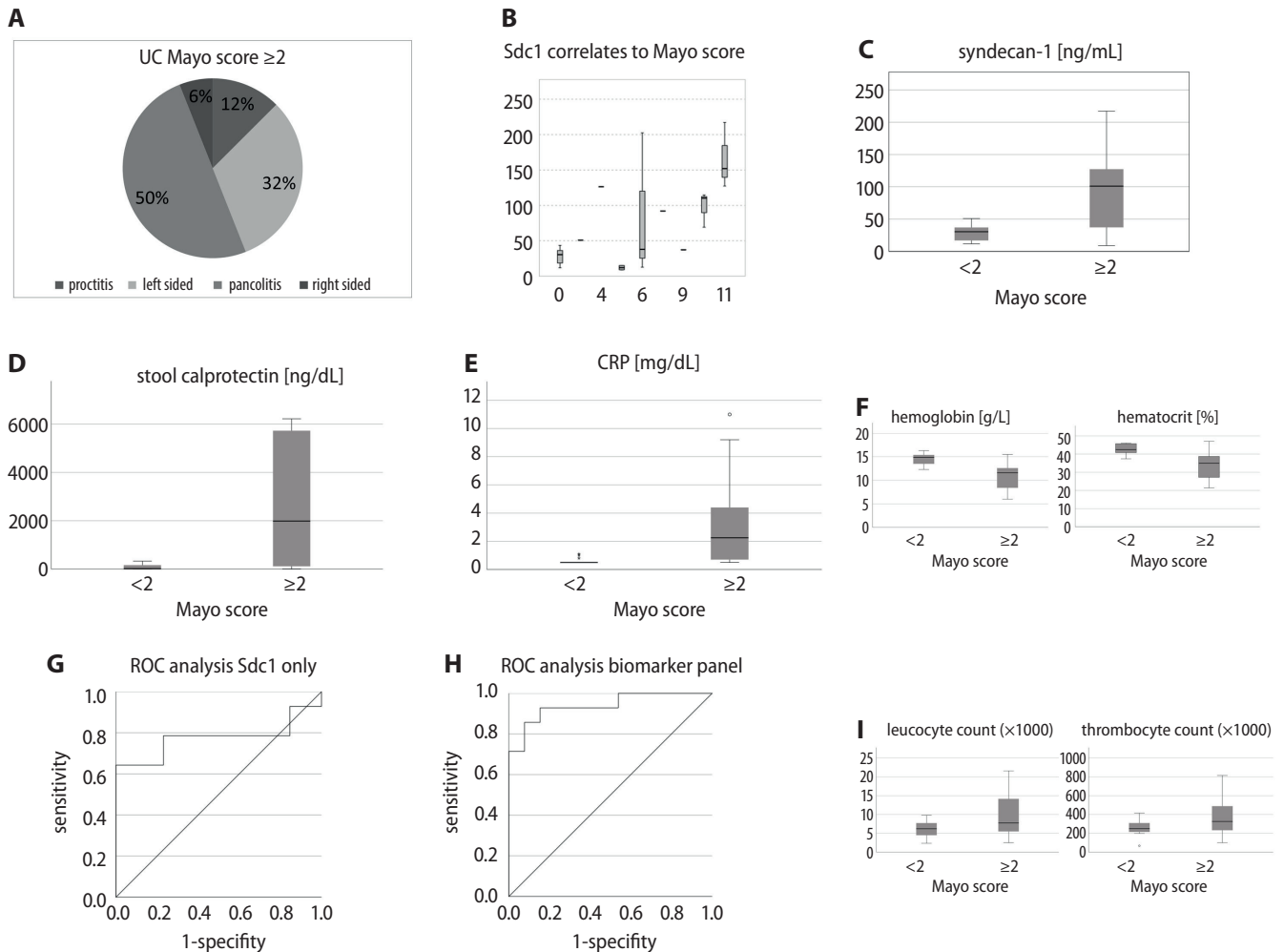
$$P = \frac{1}{1 + e^x} \quad (1)$$

ROC analysis of this predictive model revealed an AUC of 0.9395 (95% CI = 0.8509–1.0000; Fig. 1).

Finally, a significant correlation between Sdc1 and CRP was observed ( $r = 0.6061$ ,  $p = 0.0008$ ). The correlation between Sdc1 and fecal calprotectin was positive but non-significant ( $r = 0.3381$ ,  $p = 0.2001$ ).

## Discussion

Our data suggest that soluble Sdc1 is a marker of activity for UC, indicating the possibility of a strong biomarker signal that should be validated in a larger multicenter study. It is known that level of Sdc1 can be influenced by other non-inflammatory states. For example, acute exercise



**Fig. 1.** A. Ulcerative colitis infestation pattern; B. Kruskal–Wallis diagram: positive correlation of Sdc1 with the complete Mayo score ( $p = 0.0248$ ); C. Sdc1 is elevated in active UC,  $p = 0.002$ ; D. Stool calprotectin is elevated in UC ( $p = 0.0179$ ); E. CRP is higher in active UC ( $p = 0.0080$ ); F. Hemoglobin and hematocrit are significantly altered as compared to inactive UC (for  $p$ -values see Table 1); G. Receiver operation characteristic for Sdc1 only. X-axis is 1-specificity, Y-axis is sensitivity. AUC is 0.7747 (95% CI = 0.5775–0.9718). Best discriminative cutoff value is 37.1 ng/mL Sdc1 (sensitivity of 78% and a specificity of 77%); H. Receiver operation characteristic for a biomarker panel including Sdc1, CRP, hematocrit, and hemoglobin. X-axis is 1-specificity, Y-axis is sensitivity. This panel enables sharp discrimination of inactive and active UC beyond a Mayo score of 2; AUC is 0.9395 (95% CI = 0.8509–1.0000); I. Leucocyte and thrombocyte count. Leucocyte count is significantly higher in active UC ( $p = 0.0429$ ). A nonsignificant elevation of the thrombocyte count in active UC was observed

is able to raise Sdc1.<sup>18</sup> The Sdc1 is also elevated after trauma, especially after polytrauma, where it is a quantitative marker of endotheliopathy.<sup>19</sup> In arterial hypertension, elevated Sdc1 levels are also observed.<sup>20</sup> Furthermore, Sdc1 is a biomarker for sepsis and sepsis survival after abdominal surgery.<sup>21</sup> Previous studies have also associated Sdc1 with breast cancer. For example, Sdc1 levels correlate with the tumor size of breast cancers.<sup>22</sup> Aside from the different roles of Sdc1 in human biology, the role of Sdc1 in IBD is apparent. In UC, the amelioration of intestinal inflammation and neutrophil migration is well described.<sup>23</sup> Soluble Sdc1 is elevated in IBD,<sup>24</sup> which is also confirmed by our results. In contrast to the abovementioned publication, we found a higher level of Sdc1 in active UC. Other forms of IBD, such as Crohn's disease<sup>25</sup> and acute colonic diverticulitis,<sup>26</sup> are also associated with elevated soluble Sdc1 levels. Additionally, Sdc1 levels are elevated in acute neuromyelitis optica<sup>27</sup> and in children with celiac disease.<sup>28</sup>

All of these conditions suggest that Sdc1 alone is likely insufficient as a biomarker for colon inflammation.<sup>29</sup> Therefore, we established a biomarker panel to include CRP, hemoglobin, hematocrit, and Sdc1, all of which can be easily obtained from patient blood samples. Our calculations revealed that active UC, as defined by an endoscopic Mayo score  $\geq 2$ , can be identified using this panel. The accuracy of this panel (93%) exceeds that of stool calprotectin (89%),<sup>30</sup> which is the best-established marker for UC activity to date. Stool calprotectin serves as a good marker to discriminate severe UC from mild-to-moderate UC,<sup>31</sup> but its ability to detect mucosal healing is less sensitive (sensitivity is only 79%).<sup>32</sup> Stidham et al. described a neuronal network evaluation of UC videos that was able to predict the endoscopic Mayo score with an accuracy of 96%, as compared to human review which had an accuracy of 89%.<sup>33</sup> Therefore, our panel has the potential to be as good as the human eye to predict active UC.

**Table 1.** Demographic data, comorbidities, medication, and results

Parameter	UC Mayo score <2	UC Mayo score ≥2	p-value	df
n	13	14	n/a	
Age [years] ±SD	44.69 ±16.849	38.86 ±13.722	0.3316 (t-test)	25
Patients with comorbidities, n	7	6	0.5680 ( $\chi^2$ test)	1
Arterial hypertension, n	3	1	0.2442 ( $\chi^2$ test)	1
PSC, n	2	3	0.6862 ( $\chi^2$ test)	1
Other comorbidities, n	3	3	0.9180 ( $\chi^2$ test)	1
Duration of disease [years] ±SD	15.23 ±13.755	19.71 ±12.035	0.0849 (t-test)	25
Female, n	7	6	0.5679 ( $\chi^2$ test)	1
Mesalazin, n	7	6	0.5680 ( $\chi^2$ test)	1
TNF blocker, n	6	4	0.3445 ( $\chi^2$ test)	1
Azathioprin, n	3	2	0.5568 ( $\chi^2$ test)	1
Other medication, n	0	3	0.0766 ( $\chi^2$ test)	1
CRP [mg/dL] ±SD	0.608 ±0.2139	3.386 ±3.4678	0.0080 (t-test)	25
Leucocyte count [ $\times 1000/\mu\text{L}$ ] ±SD	6.2531 ±2.2982	10.3171 ±6.4863	0.0426 (t-test)	25
Thrombocyte count [ $\times 1000/\mu\text{L}$ ] ±SD	255.62 ±85.243	375 ±202.951	0.0607 (t-test)	25
Hemoglobin [g/L] ±SD	14.508 ±1.2945	10.936 ±2.9209	0.0004 (t-test)	25
Hematocrit [%] ±SD	42.792 ±3.0674	33.993 ±7.7225	0.0007 (t-test)	25
Stool calprotectin [ng/mL] ±SD	86.75 ±118.705	2734.38 ±2792.978	0.0179 (t-test)	14*
Sdc1 [ng/mL] ±SD	28.3423 ±12.5921	94.5243 ±68.0518	0.0020 (t-test)	25

All values as mean and standard deviation (SD) or n. Bold digits denote significant result ( $p < 0.05$ ); \*stool calprotectin was not available in all cases; PSC – primary sclerosing cholangitis; TNF – tumor necrosis factor; CRP – C-reactive protein; Sdc1 – syndecan-1; n/a – not applicable; df – degrees of freedom.

Our results prove to be very important as they demonstrate a non-invasive way to identify a treat to target strategy (especially mucosal healing) in UC that is coupled with a better disease management outcome. Therefore, non-invasive detection of active UC using blood sample would be of value.<sup>34</sup> The Sdc1, as part of a biomarker panel, has the potential to be a simple non-invasive way for disease management. Treatment could then be modified or individually dosed without repeated endoscopy.

## Limitations

Our study has some important limitations. There were nonsignificant differences between both groups regarding comorbidities, duration of disease and age, which might have contributed to our results. We also cannot exclude that use of a TNF blocker like infliximab influenced the results, as these agents likely downregulate Sdc1 in UC.<sup>35</sup> In addition, only 2 centers contributed to this study. Our post hoc power analysis showed an effect size of  $d = 1.37$  and a 1-beta error of 0.88, which means that the power of this study was sufficient to draw conclusions. Nevertheless, due to the low numbers of patients included and study centers, we fear that the data available here cannot be generalized. However, we do think that we accomplished a proof of principle. It is possible that disruptive factors may also have influenced our results (e.g., inflammation of other origins, undetected cancer or trauma before blood collection). Additionally, we were

not able to correlate our data to histology patterns as described using the Riley score.

## Conclusions

Finally, we would like to suggest validating the presented panel of biomarkers in a larger cohort of patients. As previously described, the traditional panel with the inclusion of Sdc1 might be useful for treat-to-target strategies in UC.

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