CHAPTER 4

Total Soluble and Endogenous Secretory Receptor for Advanced Glycation Endproducts (RAGE) in IBD

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Abstract

Background Recruitment and activation of neutrophils, with release of specific proteins such as S100 proteins, is a feature of inflammatory bowel disease (IBD). Soluble forms of the receptor for advanced glycation endproducts (sRAGE), and variants such as endogenous secretory (esRAGE), can act as decoy receptors by binding ligands, including S100A12. The aims of this study were to determine total sRAGE and esRAGE concentrations in patients with IBD and correlate these with C-reactive protein (CRP), endoscopic scores and clinical disease activity scores.

Methods EDTA-plasma was collected from patients undergoing colonoscopy including those with Crohn's disease (CD: n = 125), ulcerative colitis (UC: n = 79) and control patients without endoscopic signs of inflammation (non-IBD: n = 156). Concentrations of sRAGE and esRAGE were determined by enzyme-linked immunosorbent assay and plasma CRP concentrations measured. Standard clinical disease activity and endoscopic severity scores were defined for all subjects.

Results Plasma sRAGE concentrations were lower in UC (but not CD) than non-IBD subjects ($P < 0.01$). Whilst sRAGE concentrations correlated negatively with endoscopic activity in UC ($P < 0.05$), this was not seen in CD. In contrast, esRAGE correlated negatively with disease activity in both UC ($P = 0.002$) and CD ($P = 0.0001$). Furthermore, sRAGE and esRAGE concentrations correlated inversely with CRP values ($P < 0.0001$).

Conclusions Although total sRAGE varied with activity in UC, esRAGE concentrations correlated inversely with endoscopic disease activity and CRP levels in both UC and CD. Additional studies are required to further define the significance of sRAGE and esRAGE in IBD.
Introduction
Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), are chronic incurable inflammatory conditions involving the gastrointestinal tract that result in significant morbidity and high rates of hospital admission. [1,2] The diagnosis of IBD relies upon histological examination of mucosal biopsies obtained endoscopically. [3] For example, ileocolonoscopy, a relatively invasive and expensive investigation, is currently undertaken to confirm or exclude IBD in individuals with suggestive symptoms. [4] Over recent years, researchers have been searching for sensitive and specific non-invasive biomarkers that may distinguish IBD from non-inflammatory conditions, such as irritable bowel syndrome (IBS). [5–10] Studies evaluating serum and fecal levels of one such biomarker, S100A12, have shown promising results. [11,12] S100A12, also known as EN-RAGE (Extracellular Newly identified Receptor for Advanced Glycation End-products binding protein) or Calgranulin C, is a pro-inflammatory protein predominantly secreted by neutrophils. [9,13] S100A12 is thought to bind RAGE (Receptor for Advanced Glycation End-products), resulting in the activation of intracellular signaling cascades and the production and release of pro-inflammatory cytokines (e.g. tumor necrosis factor (TNF)-α and interleukin (IL)-1β) that are linked to IBD pathogenesis. [14]

In addition to membrane-bound RAGE, soluble forms of this receptor (sRAGE) are now recognized. These circulating proteins may act as decoys, thereby preventing binding of ligands with membrane-bound RAGE. [15–17] Accordingly, one would hypothesize that levels of sRAGE would decrease in settings of active inflammation associated with increased production of S100A12 consequent to increased binding of sRAGE with S100A12. sRAGE negatively correlates with disease severity in various systemic conditions, such as coronary artery disease, [18] systemic lupus erythematosus, [19] atherosclerosis [20] and juvenile idiopathic arthritis. [21] However, imbalance between S100A12 and sRAGE could also lead to uninterrupted S100A12 activity. The total pool of sRAGE includes ectodomain-shed RAGE...
and a C-terminally truncated variant known as endogenous secretory (es) RAGE, which is secreted extracellularly. [19,20] By acting as a decoy receptor, esRAGE is able to neutralize the actions of advanced glycation end-products (AGEs) including S100A12. [22,23] Thus, the measurement of circulating esRAGE levels rather than total sRAGE levels may prove a more biologically relevant, and more sensitive, biomarker of disease activity in patients with IBD. To date, the patterns of circulating sRAGE have been evaluated in just three studies of patients with IBD. No relationship between disease activity of IBD and sRAGE levels was demonstrated in two studies, [6,24] whereas increased levels of sRAGE were shown in one study of 60 individuals with UC. [25] However, circulating levels of esRAGE have not yet been defined in the context of IBD. Thus, the aim of this observational study was to determine sRAGE and esRAGE concentrations in patients with endoscopically confirmed established or newly diagnosed IBD and correlate these results with endoscopic disease activity, clinical disease activity and plasma CRP concentration.

**Methods**

*Participants*

All patients undergoing colonoscopy to diagnose, evaluate or exclude IBD in 2010–2011 at the Department of Gastroenterology, Christchurch Hospital, Christchurch, New Zealand were invited to participate in this study. Informed consent was obtained from all patients or caregivers. The study was approved by the Upper South A Regional Ethics Committee.

The study group comprised patients with known or newly diagnosed CD or UC, based on standard endoscopic, histological or radiological criteria. [3] The non-IBD control group comprised patients in whom IBD was suspected on clinical grounds, but no evidence of bowel inflammation at colonoscopy or subsequent investigations was found. Patients with other gastrointestinal pathology, such as IBD unclassified (IBDu), colorectal polyps and colorectal cancer were excluded from the non-IBD control group.
Baseline demographic data including age, gender, current medical therapy and details of known gastrointestinal disease were collected at enrolment. GI symptoms in the week prior to colonoscopy were recorded.

**Disease assessment**
Disease activity was measured using a range of indices. Clinical disease indices included the Harvey Bradshaw index (HBI) for CD [26] and the simple clinical colitis activity index (SCCAI) for UC. [27] Mucosal scores were assessed using the Simple Endoscopic Score for Crohn's Disease (SES-CD) [28] and the Rachmilewitz score for UC. [29] For those with UC, inflammation was classified as inactive (score 0–3), mild (score 4–6), moderate (score 7–9) or severe (score 10–12) disease, as described previously. [30] For those with CD, SES-CD scores were defined as inactive (score 0–2), mild (score 3–6), moderate [7–15] or severe (score ≥16). [31]

**Sample collection**
Venous blood samples were collected in 4 ml EDTA-tubes prior to colonoscopy. After storage at 4°C overnight, samples were centrifuged for 5 min at 2,500 rpm. Plasma was collected in 1.7 ml Eppendorf tubes and stored at −80°C until used for analysis. In addition, fecal samples were obtained prior to colonoscopy and stored at −80°C and biopsies of inflamed and non-inflamed small and large intestine were taken during colonoscopy for histological examination and RNA expression analysis, although they were not used in the current study.

**Measurement of plasma sRAGE, esRAGE and CRP**
Plasma sRAGE and esRAGE concentrations were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MA, USA and B-Bridge International, Inc. Cupertino, CA, USA, respectively) following the manufacturer’s instructions. [6] Optical density was measured using an ELISA plate reader (Spectramax 190, Molecular Devices, Sunnyvale, CA, USA). Plasma concentrations of the two proteins were calculated using SoftMax Pro (version 5.3, October 1998; Molecular Devices, Sunnyvale, CA, USA). The lower detection limit of the sRAGE ELISA
was 78 pg/ml, whereas the esRAGE assay detected 50 pg/ml. Results outside the standard range were repeated in higher or lower dilutions respectively. CRP was measured using a standard analyzer (Abbott C8000, Libertyville, IL, USA) after vigorous shaking and centrifuging of the tubes at 13,000 rpm for one minute.

Statistical analysis
Data was analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5.0c (GraphPad Inc., San Diego, CA, USA). Mann–Whitney U-tests were used to compare sRAGE and esRAGE concentrations between inactive, mild, moderate and severely active mucosal inflammation. Spearman's correlation was used to determine correlation coefficients and significance. Results are presented as mean ± standard error of the mean (SEM), unless otherwise specified. Normal probability plot and histograms of raw data showed violation of normality and thus the appropriate non-parametric tests were used. The level of significance was set as a two-tailed \( P < 0.05 \).

Results
Patient characteristics
The study group comprised 125 patients (3 children) with established or newly diagnosed CD and 79 patients with established or newly diagnosed UC. The remaining cohort consisted of 254 patients, of which 156 (23 children) were included as non-IBD controls. Excluded were patients with significant intestinal pathology, other than inflammation (e.g. polyps and cancer). Patient baseline characteristics did not differ between groups (Table 1).

Plasma C-reactive protein concentrations
Plasma CRP concentrations were higher in IBD (12.5 ± 1.98 mg/l; \( P < 0.0001 \)), CD (13.3 ± 2.1 mg/l; \( P < 0.0001 \)) and UC (11.2 ± 3.94 mg/l; \( P < 0.001 \)) than non-IBD controls (5.31 ± 1 mg/l). Within the CD group, CRP was higher in those with moderate (20.7 ± 4.47 mg/l; \( P < 0.001 \)) and severe
(45.2 ± 12.9 mg/l; P < 0.0001) endoscopic inflammation, than in the inactive group (6.27 ± 1.2 mg/l). However, CRP values were not elevated in mildly active disease (11.22 ± 3.73 mg/l; P = 0.06) compared to those with inactive disease. Within the UC group, higher concentrations of CRP were seen in patients with moderate (41.3 ± 31.5 mg/l; P < 0.01) and severe (11.2 ± 3 mg/l; P < 0.05) endoscopic inflammation, than in those with inactive disease (4.18 ± 0.6 mg/l). Again, those with mild disease did not have higher CRP concentrations than those with inactive disease (16.1 ± 7.1 mg/l; P = 0.168) (Fig. 1A–C).

Table 1 Clinical characteristics of CD, UC and non-IBD patients according to endoscopic severity scores.

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>CD</th>
<th>non-IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (% )</td>
<td>N (% )</td>
<td>N (%)</td>
</tr>
<tr>
<td>Total</td>
<td>79 (100)</td>
<td>125 (100)</td>
<td>156 (100)</td>
</tr>
<tr>
<td>Male</td>
<td>44 (55.7)</td>
<td>62 (49.6)</td>
<td>55 (35.3)</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>53.5 ± 14.4</td>
<td>44.6 ± 15.1</td>
<td>36.9 ± 18.7</td>
</tr>
<tr>
<td>Newly diagnosed</td>
<td>7 (8.9)</td>
<td>20 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Disease activity (endoscopic scores a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>50 (63.3)</td>
<td>55 (44.0)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>16 (20.2)</td>
<td>42 (33.6)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>9 (11.4)</td>
<td>17 (13.6)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>4 (5.1)</td>
<td>11 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Disease activity (HBI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>-</td>
<td>71 (56.8)</td>
<td></td>
</tr>
<tr>
<td>5-10</td>
<td>-</td>
<td>36 (28.8)</td>
<td></td>
</tr>
<tr>
<td>11-19</td>
<td>-</td>
<td>16 (12.8)</td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>-</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Disease activity (SCCAI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>64 (81.0)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>11 (13.9)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>4 (5.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Disease location (CD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileitis</td>
<td>-</td>
<td>60 (48.0)</td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>-</td>
<td>34 (27.2)</td>
<td></td>
</tr>
<tr>
<td>Ileocolitis</td>
<td>-</td>
<td>31 (24.8)</td>
<td></td>
</tr>
<tr>
<td>Disease extent (UC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>13 (16.5)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>35 (44.3)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pancolitis</td>
<td>31 (39.2)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IBD, inflammatory bowel disease; CD, Crohn’s disease; UC, ulcerative colitis; HBI, Harvey-Bradshaw index. [22]; SCCAI, simple clinical colitis index. [23]

**Plasma soluble RAGE concentrations**

Plasma sRAGE concentrations were lower in UC than non-IBD controls (1,173 ± 68.2 pg/ml vs 1,455 ± 62 pg/ml; *P* < 0.01). However, sRAGE concentrations in CD (1,447 ± 72 pg/ml) or IBD (1,341 ± 52 pg/ml) were not different to non-IBD control values (*P* > 0.05 for both comparisons). Within the UC group, sRAGE concentrations were lower in severe (616 ± 85 pg/ml) compared with inactive (1276 ± 89 pg/ml) endoscopic inflammation (*P* < 0.05). Differences between mild (*P* = 0.32) and moderate (*P* = 0.12) endoscopic inflammation did not differ from that of the inactive group. In contrast, no differences were found between those with mild (*P* = 0.20), moderate (*P* = 0.46) or severe endoscopic CD (*P* = 0.10) and those with inactive disease (Fig. 2A and B).

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**Figure 1** Plasma CRP in patients with and without inflammatory bowel disease. CRP was elevated in Crohn’s disease, ulcerative colitis and in the combined IBD group compared to control subjects without IBD (A). In both CD (B) and UC (C), CRP values increased with disease severity.
Plasma endogenous secretory RAGE concentrations

In contrast to the findings for sRAGE, esRAGE concentrations differed between UC, CD and the control group. In the CD cohort, esRAGE concentrations were highest in those with inactive disease (449.3 ± 24.95 pg/ml) and lowest in those with severe disease activity (181.8 ± 23.11 pg/ml).
Furthermore, concentrations of esRAGE were also lower in patients with active UC (83.5 ± 14.1 pg/ml) compared to those in remission (402.0 ± 30.7 pg/ml, \( P = 0.001 \); Fig. 3B).

**Relationship between esRAGE and sRAGE**

In the UC and CD cohorts, the percent contribution of esRAGE levels to the total circulating RAGE concentration (sRAGE) was defined for each level of disease activity. The contribution of esRAGE to the total sRAGE varied in a disease activity dependent fashion for both UC (inactive 33.0 ± 1.78%; mild 23.2 ± 2.11%; moderate 22.6 ± 2.38% and severe 13.5 ± 0.75%; \( P = 0.0004 \)) and CD (inactive 32.3 ± 1.68%; mild 26.4 ± 1.37%; moderate 24.8 ± 3.50% and severe 14.9 ± 1.26%; \( P = 0.0002 \)) (Fig. 4A and B).

**Figure 4** The relationship between esRAGE and sRAGE in patients with CD and UC. The percentage contributions of measured esRAGE to the total sRAGE were calculated in individuals with CD (A) and UC (B), according to disease activity scores.

**Correlation between disease markers**

The Harvey–Bradshaw index (HBI) scores correlated with the endoscopic disease activity scores \( (r = 0.227, P < 0.05) \) in the patients with CD, as did CRP \( (r = 0.393; P < 0.0001) \) (Table 2). In contrast, there was no correlation between sRAGE concentrations and endoscopic activity \( (P = 0.97) \). However, there was a weak negative correlation between esRAGE and endoscopic disease activity \( (r = -0.2356; P < 0.01) \). In patients with UC, the simple clinical colitis activity index (SCCAI) correlated with endoscopic disease activity \( (r = 0.343, p < 0.01) \) (Table 3).
Correlations between CRP and endoscopic activity ($r = 0.384; P < 0.001$) and between sRAGE ($r = -0.231; P < 0.05$) and endoscopic activity were also evident. In addition, there was a moderate negative correlation between esRAGE and the Rachmilewitz index ($r = -0.4220; P < 0.0001$) (Table 3). There was a negative correlation between CRP and both sRAGE and esRAGE in the total study group ($r = -0.251$ and $r = -0.249$ respectively, both $P < 0.0001$).

**Discussion**

The current study demonstrated a significant relationship between circulating RAGE and disease activity in IBD, especially for the endogenous secretory variant of this protein. Although total sRAGE values correlated inversely with endoscopic disease activity in UC, esRAGE values correlated with disease activity in both UC and CD. In addition, CRP values were negatively correlated with total sRAGE concentrations in patients with IBD.

**Table 2** Correlation of the simple endoscopic score for Crohn’s disease (SES-CD) subgroups with the HBI, plasma sRAGE and CRP.

<table>
<thead>
<tr>
<th>Endoscopic activity</th>
<th>Inactive (0–3)</th>
<th>Mild (4–6)</th>
<th>Moderate (7–9)</th>
<th>Severe (10–12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>55</td>
<td>42</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>HBI</td>
<td>4.55 ± 0.59</td>
<td>4.14 ± 0.66</td>
<td>7.53 ± 1.69</td>
<td>7.73 ± 0.94</td>
</tr>
<tr>
<td>sRAGE (pg/ml)</td>
<td>1616 ± 122.4</td>
<td>1310 ± 92.6</td>
<td>1438 ± 241.9</td>
<td>1133 ± 150.5</td>
</tr>
<tr>
<td>esRAGE (pg/ml)</td>
<td>449.3 ± 24.95</td>
<td>340.7 ± 26.64</td>
<td>333.4 ± 54.65</td>
<td>181.8 ± 23.11</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>6.27 ± 1.18</td>
<td>11.22 ± 3.73</td>
<td>20.74 ± 4.72</td>
<td>45.17 ± 12.9</td>
</tr>
</tbody>
</table>

Abbreviations: HBI, Harvey Bradshaw index [22]; CRP, C-reactive protein; sRAGE, soluble receptor for advanced glycation endproducts; esRAGE, endogenous secretory RAGE.

Numbers are presented as mean ± SEM.

*Activity scored by the simple endoscopic score for Crohn’s Disease (SES-CD). [24]

**Table 3** Correlation of the Rachmilewitz index for ulcerative colitis with the SCCAI, plasma sRAGE and CRP.

<table>
<thead>
<tr>
<th>Endoscopic activity</th>
<th>Inactive (0–3)</th>
<th>Mild (4–6)</th>
<th>Moderate (7–9)</th>
<th>Severe (10–12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>50</td>
<td>16</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>SCCAI</td>
<td>2.24 ± 0.31</td>
<td>4.63 ± 0.92</td>
<td>5.33 ± 1.46</td>
<td>5.00 ± 1.47</td>
</tr>
<tr>
<td>sRAGE (pg/ml)</td>
<td>1276 ± 89.4</td>
<td>1117 ± 145.7</td>
<td>948.4 ± 149.3</td>
<td>616.2 ± 84.8</td>
</tr>
<tr>
<td>esRAGE (pg/ml)</td>
<td>402.0 ± 30.7</td>
<td>311.1 ± 31.7</td>
<td>218.6 ± 36.1</td>
<td>83.5 ± 14.1</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>4.18 ± 0.64</td>
<td>16.1 ± 7.12</td>
<td>41.3 ± 31.47</td>
<td>11.23 ± 3.00</td>
</tr>
</tbody>
</table>

Abbreviations: SCCAI, simple clinical colitis activity index [23]; CRP, C-reactive protein; sRAGE, soluble receptor for advanced glycation endproducts; esRAGE, endogenous secretory RAGE.

Numbers are presented as mean ± SEM.

*Activity scored by the Rachmilewitz index for ulcerative colitis. [25]
and controls. These data suggest that RAGE production and consumption may contribute to the complex inflammatory events seen in IBD.

This is the first study describing the relationship between sRAGE concentration and endoscopic disease activity in IBD. To date, three other studies describe the patterns of sRAGE in IBD. In 2007, Leach et al. [6] determined serum sRAGE concentrations in 39 children with IBD. sRAGE concentrations in this group did not differ from those in the non-IBD controls (median 1,661 [range 555 – 3,613] pg/ml vs 2001 [777 – 2,915] pg/ml), or between CD, UC and IBD. The study by Leach and colleagues [6] differs from the current study in that it included solely pediatric patients at the time of diagnosis of IBD and included a smaller number of subjects. Malickova et al. [24] measured serum sRAGE concentrations in 29 adult patients with long-standing IBD prior to biological treatment and compared these to the levels in gender and age-matched control serum samples from 30 healthy blood donors. Again, there was no difference between IBD patients and healthy donors (mean ± SD; 772 ± 274 pg/ml vs 720 ± 107 pg/ml, respectively, $P = 0.159$). Three-quarters of the patients in this study were diagnosed with CD.

These data are consistent with the findings seen in the CD population in the current study, together suggesting that variations in sRAGE concentrations may be less relevant in CD than in the setting of UC. The most recent study investigating total sRAGE concentrations in IBD included 60 adult patients with UC. [25] Increased serum sRAGE was seen in this group, in comparison to a group of 113 healthy controls (median [interquartile range]; 740 [640 – 820] pg/ml vs 580 [470 – 770] pg/ml, respectively, $P < 0.05$). The differences between the findings in this Turkish study and those seen in the UC cohort included in the current study may be explained by methodological differences, including the ELISA kits utilized and variations in the control groups. Furthermore, ethnic differences may also be relevant. A recent study showed wide variations in sRAGE expression across different ethnic groups. [32]
The patterns of sRAGE expression have previously been defined in several other inflammatory states. For instance, much lower levels of sRAGE were seen in a group of children with Kawasaki’s disease (an acute vasculitis with potential long-term cardiac complications) than in a control group of children. [33] This finding was seen despite very elevated levels of S100A12 in the children with Kawasaki’s disease, suggesting an imbalance between S100A12 and sRAGE. The relationship between sRAGE and S100A12 was also determined in a group of adults with end-stage renal disease. [20] Levels of sRAGE negatively correlated with several key vascular findings in this study, with inverse relationships to S100A12 levels. In addition, lower levels of sRAGE are associated with increased severity of chronic lung disease in adults [34] and increased risk of sepsis in preterm infants. [35]

Most of these studies, including the current study, evaluated plasma sRAGE concentrations rather than serum levels. The impact of this is not clear at present. The collection method does, however, affect the measurement of S100A12, [36] meaning that concurrent measurement of S100A12 was not possible in the current study. esRAGE concentrations have been assessed in several other disease states, such as vascular disease and diabetes. [23, 37–39] Low levels of esRAGE are associated with increased risk of developing renal complications in individuals with Type 1 Diabetes. [37] Furthermore, strong correlations between esRAGE and oxidative stress have been established in Type 2 Diabetes. [38] One study evaluated esRAGE mRNA levels in peripheral blood mononuclear cells in a small group of 13 patients with CD. [39] This study focused upon esRAGE expression in a larger group of individuals with joint disease and included the subjects with CD as a disease control group. esRAGE expression was downregulated in CD (76%) compared to healthy controls (100%), but not to the same level seen in the patients with joint disease (54%). Levels of esRAGE protein were not measured in this study.
The current study describes the patterns of sRAGE in the largest group of patients with IBD and non-inflammatory controls to date, and provides the first observations of changes in esRAGE concentrations in IBD. A further strength of the current study is that endoscopic activity is used as a reference, instead of clinical disease scores as used in other studies. Clinical disease scores may not always reflect endoscopic inflammation due to the presence of non-inflammatory symptoms in many patients. Although a large number of patients were included, the smaller sizes of sub-groups with moderate and severe disease activity limited further analysis. In addition, the current study was not able to measure levels of RAGE ligands, such as S100A12, in this population. In conclusion, the current study has demonstrated disease activity dependent variations of esRAGE in UC and CD, whilst also showing a similar relationship for total sRAGE in the UC cohort alone. These data indicate either consumption of sRAGE or decreased systemic production in the context of this chronic gut disease.

Currently available evidence does not indicate that measurement of circulating RAGE would permit one to distinguish between IBD and non-inflammatory conditions in patients with gastrointestinal symptoms. However, the current study supports esRAGE as a marker of disease activity in the context of IBD. Further studies are now required to substantiate these findings and to elucidate the further clinical roles of sRAGE and esRAGE (and related ligands) in IBD.
References


Total soluble and endogenous secretory receptor for advanced glycation endproducts (RAGE) in IBD