Increased fatigability of external anal sphincter in inflammatory bowel disease: Significance in fecal urgency and incontinence

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KEYWORDS
Fecal incontinence; Inflammatory bowel disease; Fatigue rate index; Endoanal ultrasound

Abstract

Background and aims: Fatigability of external anal sphincter (EAS) has not been studied in inflammatory bowel disease (IBD) patients. We evaluated EAS fatigability in IBD patients with and without fecal incontinence (FI) and urgency, and correlated fatigability with demographic and clinical factors, and EAS endosonography.

Methods: Fifty-eight consecutive IBD cases and 14 healthy volunteers completed Bristol stool form and a FI severity scale. Groups I, II and III included 27 patients with urgency including 13 with concomitant FI, 31 patients without FI or urgency, and 14 controls, respectively. We performed stationary pull-through manometry with an 8-channel water-perfused catheter. Fatigue rate (FR) was calculated by linear regression during a 20-s anal squeeze, and fatigue rate index (FRI) as the ratio of squeeze pressure increment to FR. EAS thickness and deficits were evaluated with an endoanal 10-MHz probe. Patients underwent sigmoidoscopy.

Results: Group I demonstrated a higher Bristol score, more frequent defecations, and more EAS deficits compared to group II. Resting, peak squeeze pressures and EAS thickness did not differ between groups. FR was increased in group I versus II, and in group II versus III; FRI was decreased in group I versus II and in group II versus III (p<0.001, adjusting for age and BMI). Gender, oral glucocorticoids, presence of proctitis, perianal disease and EAS defects did not interact with group membership on FR or FRI.

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; BMI, body mass index; CD, Crohn’s disease; CDAI, Crohn’s disease activity index; EAS, external anal sphincter; EAUS, endoanal ultrasound; FISS, fecal incontinence severity scale; FR, fatigue rate; FRI, fatigue rate index; HPZ, anal sphincter high pressure zone; IBD, inflammatory bowel disease; IQR, interquartile range; PDAI, perianal disease activity index; rs, Spearman’s rank correlation coefficient; UC, ulcerative colitis.

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1. Introduction

Among the multiple factors involved in the complex mechanism of anal continence, fatigueability of the external anal sphincter (EAS) is perhaps the least studied. Although the role of EAS in anal continence is indisputable, most reports of anal physiology have focused on the maximum force of EAS contraction, reflected in the parameter of maximum squeeze pressure.

EAS is normally subject to fatigue, being a striated muscle. However, compared to other skeletal muscles, EAS demonstrates a higher percentage of slow-twitch fibers (Type I), which renders EAS more resistant to fatigue. Early studies have demonstrated a higher percentage of slow-twitch fibers muscle. However, compared to other skeletal muscles, EAS demonstrates a higher percentage of slow-twitch fibers (Type I), which renders EAS more resistant to fatigue. Early studies have demonstrated a higher percentage of slow-twitch fibers (Type I), which renders EAS more resistant to fatigue. Early studies have demonstrated a higher percentage of slow-twitch fibers (Type I), which renders EAS more resistant to fatigue.

In 1998, Marcello et al. introduced fatigue rate index (FRI), a calculated predictor of the time needed for EAS to fatigue from maximum contraction to baseline pressure. The method and its modification by Telford et al. in part rely on the estimation of fatigue rate (FR) by linear regression analysis over a 40 or 20-second squeeze period; FRI thus permits comparisons between studies performed by different groups employing different manometric methodologies (e.g., perfused, balloon mini-probe, and solid-state manometry). Despite the detected FRI differences between continent and control groups in these studies, and the incorporation of FRI methodology in modern manometric analysis packages, few subsequent reports have further defined the clinical value of FRI in fecal incontinence (FI).

Several clinical phenotypes in inflammatory bowel diseases (IBD) may affect the function of anal sphincter complex: anorectal inflammatory involvement is a constant feature of ulcerative colitis and has been reported in 15–80% of patients with Crohn’s disease (CD). Perianal fistulizing CD frequently threatens the integrity of external anal sphincter due to direct invasion by fistulae, and sometimes due to aggressive surgical treatment, especially in undiagnosed cases. Reduced peak squeeze pressures have been reported in CD patients with overt FI. However, external sphincter fatigability has not been previously studied in IBD.

Our aim was to compare FR and FRI between IBD patients with and without fecal urgency and incontinence and healthy individuals. We also sought to correlate these endpoints with demographic and clinical parameters that potentially impact EAS function, and with the sonographic appearance of EAS.

2. Materials and methods

2.1. Participant selection and group allocation

Fifty-eight patients with histologically-proven UC (n=20, 10 female) or CD (n=38, 8 female) participated in the study. All were prospectively recruited between June 2007 and September 2008, during consecutive visits at an IBD reference center in north-western Greece. Patients 15–70 years old in ambulatory regimen were eligible. We excluded patients with significant comorbidities, medications other than IBD regimen, uncontrolled perianal sepsis, patulous anus, a history of three or more vaginal deliveries, or forceps–vacuum delivery, obstetric perineal laceration, and abdominal surgery (other than cholecystectomy). Patients who were operated for anal surgery were eligible in lack of obvious tear or stenosis.

Fourteen healthy volunteers (7 female) were recruited during the same period by a public advertisement. Screening history and examination were insignificant for chronic conditions, gastrointestinal disease, perianal surgery, obstetric anorectal damage and medications.

Participants were allocated in 3 groups. Twenty-seven patients could not defer defecation for more than 5 min after the first call to stool (group I). In addition to reporting urgency, 13 out of the 27 patients in group I also responded affirmatively to the lead question: “Have you had problems with leakage of stool (accidents or soiling) during the last 3 months?”

Severity of FI was further graded according to the validated, self-reported Fecal Incontinence Severity Scale (FISS) as: minor underwear staining and gas incontinence (n=8), small-to-moderate amount of liquid stool (n=3) and overt incontinence (n=2). Thirty-one patients denied fecal urgency or incontinence (group II). Fourteen healthy volunteers comprised group III.

2.2. Protocol

The study protocol was approved by the ethics committee of Ioannina University Hospital, and included 3 subsequent visits.

2.2.1. Screening visit

All subjects provided informed consent. A review of medical history, IBD and continence status and general, perianal and rectal examinations were performed by one of the investigators (KK). Perianal disease severity was graded in CD according to perianal disease activity index (PDAI). A questionnaire encompassing Crohn’s disease activity index (CDAI), simple activity index for UC, Bristol stool form scale and a daily bowel diary was provided, and patients instructed to complete during the following week.

2.2.2. Anorectal testing visit

All subjects returned after 7–10 days, having fasted overnight and abstained from smoking on the same day. IBD medications were withheld for 12 h. Anorectal manometry and anal sphincter fatigue assessment were performed 60 min after rectal cleansing with 2 phosphate enemas, followed by the endoanal ultrasound study (EAUS). All

Conclusions: IBD is associated with increased fatigue rate and decreased fatigue rate index. These differences were even more striking in patients with incontinence or urgency. © 2010 European Crohn’s and Colitis Organisation. Published by Elsevier B.V. All rights reserved.
procedures were conducted by a single, experienced investigator (AP), who was blinded to patient history.

2.2.3. Endoscopic visit

Five to ten days later, patients underwent flexible sigmoidoscopy (performed by DC) after an oral polyethylene glycol cleansing regimen. The endoscopic appearance of anorectal mucosa was defined as normal in the presence of mild, localized erythema and no additional findings, and as proctitis in the presence of more severe erythema, oedema, erosions or ulcerations.

2.3. Anorectal manometry: procedure and analysis

Water-perfused manometry (rate: 0.5 mL min⁻¹) was performed with a polyvinyl catheter (diameter 4.8 mm) incorporating 8 manometric channels; these ended in respective radial ports, evenly arranged at 4 cm from catheter tip. Pressure signals were back-transmitted to transducers, digitized and imported for analysis to computerized software (Medtronic, Innova, Athens, Greece).

Subjects were examined in the left lateral position. After calibration, the catheter was inserted so that the ports were located at a distance of 6 cm from the anal verge. Following a 5-minute run-in period, resting anal pressures were measured for 60 s at each of 6 stations 1 cm apart during a stationary pull-through, allowing 20 s for pressure equilibrium at each step. Squeeze pressures were then registered for 5 s at each of 6 stations, during a second stationary pull-through. Mean resting pressure, mean maximum squeeze pressure, and high pressure zone (HPZ) at rest were thus defined.

After 5 min the catheter was reinserted, so that the ports were positioned at the level of maximum recorded squeeze pressure. Subjects were asked to squeeze maximally for 20 s, trying to maintain an effort of stable intensity, instead of alternating contraction and relaxation. Subjects were verbally motivated during the entire squeeze period.

The analysis software combines pressure values from all 8 radial channels to generate an average squeeze tracing (Fig. 1). The average peak squeeze pressure (Ppeak) and baseline pressure values (Pbaseline, 8-channel mean during the 10-s period preceding squeeze) were registered. A linear regression line was then fitted to the tracing; the negative slope of the line represented EAS fatigability rate (FR). A segment starting at the squeeze threshold (10 mm Hg over Pbaseline) and ending at the end of squeeze effort was selected for regression analysis. Fatigue rate index (FRI), a predicted measure of maximum squeeze time, was calculated according to the function:

\[ FR = \frac{P_{\text{peak}} - P_{\text{baseline}}}{FR} \]

2.4. Endoanal ultrasound

Participants were examined in the left lateral position. A 360°-rotating, 10-MHz radial probe was used (type 1850, BK Medical, Herlev, Denmark), covered by a water-filled sonolucent cone; after insertion to puborectalis level, the full anal length was scanned during gradual withdrawal. EAS defects were diagnosed as any disruption of muscle fiber continuity in the transverse plane. Circumferential extend (measured by the angle of extension from the center of the probe) was recorded for every EAS tear. Fragmentation of EAS due to multiple defects was also registered.

2.5. Statistical analyses

We calculated percentages to describe binary and categorical variables and median with interquartile range (IQR) to describe continuous variables. We used χ² and Kruskal–Wallis tests for comparisons among groups. For pair-wise comparisons we used Mann–Whitney test. To investigate whether differences in certain characteristics among groups may potentially confound the results, we also performed ANCOVA to compare FR and FRI among groups after adjustment for age, body mass index (BMI) and mean resting and mean maximum anal pressures. To examine whether there is any interaction that may affect the main outcomes (FR, FRI), we performed two-way analysis of variance (ANOVA). Interaction with group membership was investigated for the following parameters: gender, disease, orally administered glucocorticoids, proctitis, perianal disease, EAS defects, and EAS fragmentation. Correlations between continuous variables were assessed with Spearman’s rank coefficient (rs). Continuous variables were log-transformed and the assumptions of normality and equal variances were verified, in order to apply ANOVA.

All p values were two-tailed and were considered as statistically significant when p<0.05.

3. Results

3.1. Participants’ characteristics

Participant demographics did not differ between the 3 groups. Among the clinical parameters summarized in Table 1, simple clinical colitis index, PDAI, and patient
percentage with a positive history of perianal surgery were all increased in group I compared to group II. In addition, group I demonstrated a higher weekly number of bowel movements and increased Bristol scale score, compared to other groups. In 13 symptomatic patients with a history of anal surgery, onset of urgency or incontinence was recent and not associated with the time of surgery; anal surgery preceded diagnosis of IBD in 6 of them.

### 3.2. Tolerability of study procedures

All procedures were well tolerated; the durations of anorectal manometry and ultrasound procedures were 15.4±3.2 and 8.3±4.6 min, respectively. During office visits 5–10 days after completion of the evaluation, no patient reported any adverse events, defecatory alterations or new perianal symptoms.

### 3.3. Comparison of anal sonographic parameters between study groups

There were no significant differences in mean EAS thickness between groups (Table 2). No sphincteric defects were demonstrated in group III. In total, 13 patients were diagnosed with EAS defects; these were more common in group I compared to group II. The mean circumferential extend of EAS defects did not differ between groups I and II. EAS fragmentation by multiple defects was diagnosed only in 4 patients of group I (3 incontinent and one with urgency); in the remaining 9 patients with EAS defects, these were single.

### 3.4. Comparison of anal manometric parameters between study groups

Anal pressure profiles did not differ between groups. In contrast, a significant intergroup difference was demonstrated for FR and FRI (Table 3). Mean FR was increased in group II compared to controls, and was also increased in group I compared to group II. On the contrary, mean FRI was decreased in groups I and II as compared to controls, and in group I as compared to group II.

These differences remained significant after adjustment for body mass index (BMI) and age (ANCOVA: p<0.001 both for FR and FRI). Certain incontinent patients had abnormally low mean resting and mean maximum squeeze pressures. However, intergroup differences of log-transformed FRI remained significant after adjustment for mean resting and mean maximum squeeze pressures (ANCOVA p<0.001).

### 3.5. Role of demographic, clinical, and sonographic characteristics on the observed intergroup fatigability differences

The two-way ANOVA demonstrated significantly lower FR, FRI and peak anal pressure in female patients for each

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**Table 1 Demographics and clinical profile of participants.**

<table>
<thead>
<tr>
<th></th>
<th>Group I (N=27)</th>
<th>Group II (N=31)</th>
<th>Group III (N=14)</th>
<th>p value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median, IQR)</td>
<td>37 (31, 55)</td>
<td>39 (30, 53)</td>
<td>43.5 (34, 55)</td>
<td>0.717</td>
</tr>
<tr>
<td>Female (N)</td>
<td>6</td>
<td>12</td>
<td>7</td>
<td>0.172</td>
</tr>
<tr>
<td>Parity, N (median, IQR)</td>
<td>2 (0, 3)</td>
<td>1 (0, 2)</td>
<td>2 (0, 2)</td>
<td>0.493</td>
</tr>
<tr>
<td>BMI, kg/m² (median, IQR)</td>
<td>23.1 (21.7, 28.1)</td>
<td>25.6 (23.2, 28.3)</td>
<td>25 (23.5, 25.5)</td>
<td>0.613</td>
</tr>
<tr>
<td>CD/UC (N)</td>
<td>18/9</td>
<td>20/11</td>
<td>–</td>
<td>1.000</td>
</tr>
<tr>
<td>Duration of IBD history, months (median, IQR)</td>
<td>108 (66.5, 163.8)</td>
<td>67 (20, 123)</td>
<td>–</td>
<td>0.053</td>
</tr>
<tr>
<td>CDAI (median, IQR)</td>
<td>88.3 (48.3, 130.9)</td>
<td>62.7 (25.9, 84)</td>
<td>–</td>
<td>0.212</td>
</tr>
<tr>
<td>Simple activity index (median, IQR)</td>
<td>5 (1.75, 6.25)</td>
<td>2.5 (0, 3)</td>
<td>–</td>
<td>0.048</td>
</tr>
<tr>
<td>Glucocorticoids per os (N) b</td>
<td>12</td>
<td>9</td>
<td>–</td>
<td>0.278</td>
</tr>
<tr>
<td>Duration of glucocorticoid administration (weeks)</td>
<td>24 (2, 37)</td>
<td>16 (6, 44)</td>
<td>–</td>
<td>0.540</td>
</tr>
<tr>
<td>Weekly number of bowel movements (median, IQR)</td>
<td>16 (12, 23)c, d</td>
<td>9 (7, 12)</td>
<td>7 (5, 8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bristol stool form scale (weekly median, IQR)</td>
<td>5 (5, 6)c, d</td>
<td>4 (3, 4)</td>
<td>3 (3, 4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Active proctitis (N)</td>
<td>13</td>
<td>7</td>
<td>–</td>
<td>0.055</td>
</tr>
<tr>
<td>Active perianal disease (N)</td>
<td>9</td>
<td>6</td>
<td>–</td>
<td>0.247</td>
</tr>
<tr>
<td>PDAI (median, IQR)</td>
<td>3 (0, 6)</td>
<td>0 (0, 0.5)</td>
<td>–</td>
<td>0.0078</td>
</tr>
<tr>
<td>Perianal surgery (N)</td>
<td>14</td>
<td>4</td>
<td>–</td>
<td>0.0018</td>
</tr>
</tbody>
</table>

BMI, body mass index; CD, Crohn’s disease; CDAI, Crohn’s disease activity index; EAS, external anal sphincter; IQR, interquartile range; PDAI, perianal disease activity index.

a χ² and Kruskal–Wallis tests.

b In all cases methylprednisolone was administered at a dose of 4–24 mg per day, excluding 2 male CD patients from group I, which were treated with oral budesonide.

c Significantly different from group III (p<0.001).

d Significantly different from group II (p<0.001).
group as compared to the corresponding male participants (Table 4). However, there was no significant interaction to confirm this potential effect among the subgroups. In addition, there were no significant interactions between group membership and disease type, oral glucocorticoid use, proctitis, perianal disease, perianal surgery, and sonographic EAS defects (Table 4). Notably, 3 CD patients in group II (one male) with proximal muscle weakness attributable to glucocorticoid-induced myopathy, demonstrated further FR increase (range: 1.6–2.6 mm Hg s\(^{-1}\)) and FRI decrease (range: 47–88 s).

### 3.6. Correlation of symptom severity with stool form, frequency, anal sphincter function and sonography

In group I, FISS score correlated with weekly number of bowel movements (Fig. 2), mean weekly Bristol stool score (\(r_s=0.678, p<0.001\)), and mean anal resting pressure (\(r_s=0.414, p=0.043\)). In contrast, there was no correlation between FISS score and squeeze pressure (\(r_s=-0.129, p=0.555\)), FR (\(r_s=-0.174, p=0.337\), or FRI (\(r_s=-0.286, p=0.167\)).

In the 13 patients with EAS defects, there was no correlation between the circumferential extend of defects and either FR (\(r_s=0.301, p=0.787\)) or FRI (\(r_s=-0.082, p=0.441\)). However, the 4 patients with fragmented EAS demonstrated decreased peak anal pressures (mean 93, range 56–165 mm Hg) and a further decrease in FRI (mean 23, range 17–29 s), in association with more severe symptoms (FISS range: 7–10). Given the small patient number, we did not analyze statistically the effect of EAS fragmentation.

### 4. Discussion

In this study we investigated the fatigability of external anal sphincter in healthy volunteers and IBD patients with or without fecal urgency and incontinence. Our findings suggested that EAS fatigability increased in IBD patients, especially in patients who also presented with urgency or incontinence as compared to healthy controls. This was indicated by an incremental trend for FR and a decrease in FRI. Our results remained unchanged after adjusting for BMI, age, mean resting and mean maximum squeeze pressure. We found no significant interaction with IBD status in our exploratory analyses that included factors such as disease type, oral administration of glucocorticoids, proctitis, perianal disease, perianal surgery, and sonographic EAS defects.

Our symptomatic IBD group demonstrated similar baseline and peak anal pressures, but increased FR and decreased FRI relative to the asymptomatic continent group. Sonographic EAS defects and history of perianal surgery were more common in the former group. However, increased EAS fatigability in incontinent IBD patients appeared to be independent of the presence or size of EAS defects and may probably reflect a specific functional abnormality of this patient group.

On the other hand, the observed FRI decrease in group I was overall the result of increased FR, and not of changes in basal or peak anal pressures. Only the 4 patients with EAS fragmentation furthermore demonstrated abnormally low peak squeeze pressure, which resulted in a greater decrease of FRI. Thus, irrespective of EAS defects, our data suggested the presence of a dysfunctional, easily fatigable EAS in IBD with urgency and incontinence. When disruption of sphincteric mechanical integrity supervened (as evidenced by

### Table 2 Intergroup comparisons of anal sonographic findings.

<table>
<thead>
<tr>
<th></th>
<th>Group I (N=27)</th>
<th>Group II (N=31)</th>
<th>Group III (N=14)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAS thickness, mm (median, IQR)</td>
<td>4.93 (3.75, 5.55)</td>
<td>5.1 (3.56, 5.64)</td>
<td>4.56 (3.03, 4.77)</td>
<td>0.113</td>
</tr>
<tr>
<td>Cases with single EAS defects, N</td>
<td>10</td>
<td>3</td>
<td>–</td>
<td>0.0248</td>
</tr>
<tr>
<td>Extend of EAS defect, ° (median, IQR)</td>
<td>39 (28, 61)</td>
<td>32 (25, 46)</td>
<td>–</td>
<td>0.398</td>
</tr>
<tr>
<td>Cases with fragmented EAS, N</td>
<td>4</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

EAS, external anal sphincter; IQR, interquartile range.

### Table 3 Intergroup comparisons of anal sphincter pressure and fatigability.

<table>
<thead>
<tr>
<th></th>
<th>Group I (N=27)</th>
<th>Group II (N=31)</th>
<th>Group III (N=14)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting HPZ, cm (median, IQR)</td>
<td>2.7 (2.3, 3.4)</td>
<td>3 (2.52, 3.45)</td>
<td>2.9 (2.27, 3.67)</td>
<td>0.653</td>
</tr>
<tr>
<td>MRP, mm Hg (median, IQR)</td>
<td>76 (43, 85)</td>
<td>72 (61, 82)</td>
<td>65 (54, 80)</td>
<td>0.520</td>
</tr>
<tr>
<td>MMSP, mm Hg (median, IQR)</td>
<td>212 (178, 246)</td>
<td>217 (167, 264)</td>
<td>161 (139, 313)</td>
<td>0.859</td>
</tr>
<tr>
<td>BAP, mm Hg (median, IQR)</td>
<td>84 (50, 109)</td>
<td>80 (75, 89)</td>
<td>75 (69, 92)</td>
<td>0.707</td>
</tr>
<tr>
<td>PAP, mm Hg (median, IQR)</td>
<td>228 (183, 285)</td>
<td>234 (154, 294)</td>
<td>169 (131, 338)</td>
<td>0.874</td>
</tr>
<tr>
<td>FR, s (median, IQR)</td>
<td>1.5 (1.3, 2.5)</td>
<td>0.90 (0.52, 1.55)</td>
<td>0.5 (0.3, 0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FRI, s (median, IQR)</td>
<td>80 (48.9, 117.6)</td>
<td>158.9 (82.8, 277.7)</td>
<td>277.5 (206.3, 362)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BAP, baseline anal pressure; FR, fatigue rate; FRI, fatigue rate index; HPZ, high pressure zone; IQR, interquartile range; MMSP, mean maximum squeeze pressure; MRP, mean resting pressure; PAP, peak anal pressure.

\(^a\) Significantly different from group III (p<0.001).
\(^b\) Significantly different from group II (p<0.001).
\(^c\) Significantly different from group III (p<0.01).
sonographic EAS fragmentation by multiple defects), peak squeeze pressure was also affected, contributing to a further reduction of maximum squeeze duration. However, this later finding needs to be replicated in larger studies including more patients with sphincteric defects of varying severity.

We observed decreased FRI in the asymptomatic IBD group compared to control group, despite similar basal and peak anal pressures. Thus, the difference should be most likely attributed to the increased FR of the former group. The underlying mechanism leading to increased FR in continent IBD patients is unclear. EAS defects were present in only 3 patients of group II and therefore, their effect could not be evaluated. Although previous reports have suggested gender and age-related differences in skeletal muscle fatigability, these effects did not significantly impact on EAS fatigability differences among our study groups. Although the effect of local inflammatory processes (e.g. proctitis and fistulae) on EAS contractile properties is largely unknown, increased EAS fatigability appeared to be unrelated to local inflammation, based on our data.

In theory, pudendal neuropathy may present as part of a symmetric polyneuropathy, a well-established extraintestinal manifestation of IBD. However, lack of associated symptoms, risk factors for pudendal stretch injury, and normal squeeze pressures and EAS thickness in group II, all argue against neuropathic damage. There is a growing body of evidence for significant effects of nutritional deficiencies and pro-inflammatory cytokines on myocyte apoptosis and atrophy, leading to generalized muscle dysfunction in IBD. Reduced muscular mass was reported in recently diagnosed IBD patients. A high prevalence of sarcopenia was similarly demonstrated in CD patients in remission, in correlation with BMI. Our IBD cohort overall demonstrated normal BMI and EAS thickness, making an atrophic EAS change less likely. However, depletion of arm muscular mass was recently reported in patients with active IBD and normal BMI. Therefore, the contribution of mild sarcopenia in the enhanced EAS fatigability of our group is still possible.

The chronic form of glucocorticoid-induced proximal myopathy is well characterized in the literature. It is more frequently diagnosed in women after prolonged administration of fluorinated steroids, in daily oral doses equivalent to 40 mg of prednisone. Facial, respiratory and hand muscles are usually spared, however data on sphincteric muscles are scarce. In our cohort, low-to-moderate doses of glucocorticoids did not overall impact anal pressures or fatigability. Nevertheless, the 3 identified patients with symptoms compatible with steroid myopathy demonstrated increased FR and decreased FRI. Thus, although the reported preferential atrophy of the fast-twitch glycolytic myosin fibers (type IIB) would not conceptually lead to increased muscle fatigability in steroid myopathy, larger studies are warranted to address this possibility.

A histological study of 13 steroid-free patients with active CD reported a shift of gastrocnemius myosin chains from the slow, aerobic to the fast, anaerobic phenotype. Pro-inflammatory cytokines and enhanced gut permeability were implicated. Other studies have correlated myosin phenotype with muscle fatigability behavior. If these histochemical alterations were confirmed in EAS, they would provide a potential mechanism of EAS fatigability, independent of glucocorticoid effects.

Stool frequency and consistency represent 2 key factors of the fecal continence mechanism, in the general population and in IBD. Accelerated transit, exudation due to

<p>| Table 4 | Two-way analysis of variance of fatigue rate and fatigue rate index across study groups and several clinical categories. | p | values of individual and interaction effects are provided for each one of the analyzed clinical factors. |</p>
<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on BAP&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Effect on PAP&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Effect on FR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Effect on FRI&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Individual</td>
<td>Interaction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Individual</td>
<td>Interaction&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gender</td>
<td>0.228</td>
<td>0.514</td>
<td>&lt;0.001</td>
<td>0.418</td>
</tr>
<tr>
<td>Disease</td>
<td>0.122</td>
<td>0.688</td>
<td>0.622</td>
<td>0.517</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>0.541</td>
<td>0.859</td>
<td>0.350</td>
<td>0.670</td>
</tr>
<tr>
<td>Proctitis</td>
<td>0.388</td>
<td>0.187</td>
<td>0.644</td>
<td>0.766</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>0.964</td>
<td>0.850</td>
<td>0.891</td>
<td>0.849</td>
</tr>
<tr>
<td>Anal surgery</td>
<td>0.825</td>
<td>0.425</td>
<td>0.285</td>
<td>0.317</td>
</tr>
<tr>
<td>EAS defect</td>
<td>0.739</td>
<td>0.773</td>
<td>0.289</td>
<td>0.455</td>
</tr>
</tbody>
</table>

BAP, baseline anal pressure; EAS, external anal sphincter; FR, fatigue rate; FRI, fatigue rate index; PAP, peak anal pressure.
<sup>a</sup> All parameters were log-transformed.
<sup>b</sup> With group membership.
inflammation, and bile acid malabsorption may all cause increased stool frequency and liquidity in IBD. The latter two may in turn reveal subclinical anorectal dysfunction and threaten continence, as a tighter and more sustained seal of the anal lumen is essential in this setting. Our findings support a direct association of frequent, loose stools with increased fatigue rate. These alterations were exaggerated in IBD. However, we perceive that the evaluation of FR and FRI is clinically relevant, given the key importance of assessing stool frequency and consistency in the management of FI and urgency, along with anal functional testing.

The lack of correlation between incontinence severity and motility endpoints (excluding anal resting tone) is not surprising, as the pathogenesis of FI and urgency appears to be multifactorial in IBD. However, we believe that the evaluation of FR and FRI is clinically relevant, given the observed intergroup differences; we further believe that the value of baseline FR and FRI in predicting future continence status may also be evaluated in future prospective studies of continent IBD patients.

In conclusion, our study showed that IBD was associated with decreased fatigue rate index of the EAS as a result of increased fatigue rate. These alterations were exaggerated in IBD patients with fecal urgency or incontinence. The clinical and prognostic value of FR for fecal incontinence deserves further investigation in IBD.

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AP conceived the study, participated in its design, performed the acquisition, analysis, interpretation of data and statistical analysis, and prepared the manuscript. KK performed the acquisition, analysis, interpretation of data and statistical analysis, and prepared the manuscript. AT verified the statistical analyses and critically reviewed the manuscript. DK participated in data acquisition and analysis. ET contributed to study design, supervised the study and critically reviewed the manuscript. All authors read and approved the final manuscript.

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