

BOWEL DISEASE WITH BONE LOSS

PhD thesis

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1. INTRODUCTION

Decreased bone mineral density (BMD) is a frequent finding in gastrointestinal diseases. Diseases of the gut that contribute to malabsorption syndrome, that require glucocorticoid treatment, that are accompanied by elevated levels of inflammatory cytokines or cause hypogonadism can lead to altered bone metabolism. As the density of the bone has a very strong correlation to fracture risk – and bone fractures have major social and economical consequences – prevention, diagnosis and therapy of osteoporosis associated with gastrointestinal diseases is a remarkable problem.

Intestinal diseases commonly associated with bone loss, coeliac disease (gluten-sensitive enteropathy - CeD) and inflammatory bowel diseases (inflammatory bowel disease - IBD) associated bone loss have been widely studied. However, less data are available in hardly definable specific bowel disease (microscopic colitis (MC) and dermatitis herpetiformis (DH) associated with asymptomatic CeD).

Microscopic colitis (MC) is defined by chronic, watery diarrhoea, abdominal pain and weight loss. However, macroscopically normal colonic mucosa is evident on radiological and endoscopic examination, microscopic examination is required for the detection of diagnostic histopathological features. MC normally occurs in middle-aged patients, with a peak incidence in individuals aged approximately 65 years. The significance of these morphologically distinct diseases is underestimated in daily clinical practice. Two types of MC were initially described more than 30 years ago. Collagenous colitis (CC) is defined by a sub-epithelial collagen layer wider than 10 μm . Diagnostic criteria of lymphocytic colitis (LC) is more than 20 intraepithelial lymphocytes (IEL)/100 epithelial cells of the colonic mucosa. Microscopic colitis is thought to be a multifactorial disease but the exact cause is unknown. A relationship between MC and members of the classic inflammatory bowel disease (IBD) group is based on epidemiological, pathological and clinical associations. Several case reports demonstrate that MC can progress to IBD. Olesen et al. demonstrated that 12% of patients with LC reported a family history of other autoimmune bowel disorders. There are currently no studies concerned with possible alterations in bone metabolism in MC patients.

Dermatitis herpetiformis (DH), or Duhring's disease is a chronic blistering skin condition. Dermatitis herpetiformis is linked to gluten sensitivity and has a clear relationship to coeliac disease, but enteropathy is usually less severe than that found in patients with

coeliac disease (CeD). Tissue transglutaminase is the major autoantigen of CeD, which is an ubiquitous molecule in many tissues (8, 9). In patients with DH, epidermal transglutaminase appears to be the dominant autoantigen which will be the initial to create granular IgA complexes and deposits in the dermal papillae of the skin.

As it is well known, Fracture is the end point of bone loss, therefore it would be useful to develop methods which can calculate the risk of fracture with clinical or other appropriate methods. This method is not currently available related to the digestive diseases.

The American College of Gastroenterology and the British Society of Gastroenterology recommendations for IBD associated osteoporosis are almost 10 years old. The most widely accepted clinical tool for determining fracture risk is the Fracture Risk Assessment Tool (FRAX) created by Kanis et al. It's data are validated in 30 countries, including Hungary. FRAX can determine individual risk of fracture for the next 10 years using clinical parameters (age, sex, height, weight, smoking habits, alcohol consumption, previous fracture, maternal fracture history, steroid use, secondary osteoporosis and rheumatoid arthritis). The BMD measurement is not obligatory while calculating the risk of fracture with this method. Value of fracture risk score calculated without BMD (clinical FRAX – c-FRAX) may alter the score considering BMD (bmd-FRAX). FRAX score could be calculated regarding all major sites of osteoporotic fractures (wrist, upper arm, hip and clinical spine fracture) and could thus be computed for the risk of hip fracture. Current guidelines do not indicate performing BMD measurements in all IBD patients, however BMD enhanced FRAX could alter the risk stratification compared to c-FRAX.

Vitamin D deficiencies is a classical factor which may affect bone metabolism and an important factor for normal immune function as well. There are no local data was available severity of Vitamin D deficiency in Hungarian IBD patients.

2. AIMS

Our aim was to estimate non-classical diarrheal diseases related bone loss. Estimate fracture risk in Hungarian IBD patients with FRAX system and evaluate vitamin D level.

3. METHODS

3.1. Patients

Patients were enrolled from the outpatient clinic of 2nd Department of Medicine, Semmelweis University in A and B study, in C we enrolled IBD patients from three Hungarian IBD centres. The diagnosis of IBD was based on the Lennard-Jones criteria, while

patients were classified by the Montreal classification. Lymphocytic colitis was defined as more than 10 IELs/100 epithelial cells situated in the mucosa, and the diagnostic criterion for CC was a subepithelial collagen layer wider than 10 μm . Enrolment criteria included asymptomatic patients who had not taken medication for six weeks prior to commencement of the study. Those patients, who had been subjected to treatment with budesonide for longer than eight weeks, or within six weeks prior to enrolment in the study, were excluded from participating. Controls were selected age and gender match workers from our department. The study protocol was approved by the local Ethic Committee and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki. Small bowel biopsies in the DH and CeD group were stained with hematoxylin-eosin. A grading system, broadly based on Marsh-Oberhuber classification of small intestinal enteropathy was used to assess the histological abnormality: grade 0 - normal mucosa; grade 1 - increased intraepithelial lymphocyte count; grade 2 - cryptal hyperplasia and increased intraepithelial lymphocyte count; and grade 3a-3c - mild/moderate/severe villous atrophy with increased intraepithelial lymphocyte (18).

3.2. *Densitometry*

Bone mineral density measurements were performed by dual-energy X-ray absorptiometry of lumbar spine, left femoral neck and non-dominant radius using Hologic QDR 4500C instrument. Z-scores were calculated according to the manufacturer's reference curves (as the number of standard deviations from age- and sex-matched healthy controls). World Health Organization criteria for low BMD were applied for this analysis. Osteopenia was defined as a BMD t-score below -1 and -2.5, osteoporosis was defined as a BMD t-score were under -2.5. Quality control was maintained by daily scanning of an anthropometric spine phantom.

3.3. *Labortory tests*

Serum calcium (normal: 2.25-2.61 mmol/l), parathyroid hormone (normal: 10-65 pg/ml) and thyroid stimulating hormone (normal: 0.3-3.3 mU/L) levels were determined before the study commenced to exclude the presence of other types of metabolic bone diseases.

In study 'A' fasting blood samples were taken for evaluating bone formation - Osteocalcin (OC) and bone resorption - beta-crosslaps (bCL). Serum OC and bCL levels were measured by electrochemiluminescence immunoassay (Elecsys N-MID Osteocalcin and Elecsys b-CrossLaps, Roche). The normal serum concetration was 0-320 pg/ml for bCL and 200-480 pg/ml for OC.

In study 'B' anti-endomysium antibody was assessed by indirect immunfluorescence on monkey esophagus section using fluorescein isothiocyanate antihuman IgA as secondary

antibody.

In study 'C' serum vitamin D levels were measured by electrochemiluminescence immunoassay (Elecsys Vitamin D, Roche). Vitamin D deficiency was defined as <15 ng/mL, insufficiency 15-30 ng/mL and normal >30 ng/mL.

3.4. Other

In study 'C' we used questionnaires to assess patients' medical history and other relevant information about bone metabolism. The degree of possible malabsorption was calculated with the aid of the Malnutrition Universal Screening Tool.

FRAX-scores were calculated with and without BMD using the Hungarian algorithm of the online tool (<http://www.shef.ac.uk/FRAX/>).

3.5. Statistical analysis

Calculations were performed with SPSS statistics 15.0 software. Paired and independent sample Student's t-tests, Pearson correlations were applied. Results were presented as mean \pm standard deviation. Results were considered significant when $p < 0.05$.

4. RESULTS

4.1. Study A results

Fourteen MC patients (12 women and two men with a mean age of 49.79 ± 13.06 years) were included into the study. Ten of them were diagnosed with LC and four with CC. Twenty-eight healthy persons (HC) and 28 CD patients matched for age, gender and postmenopausal state were enrolled as controls.

Low bone mass was detected in 57%, 46% and 10.7% of MC patients, CD patients and the HC group, respectively. Incidence of low bone mass was significantly lower in MC and CD patients than in the HC group ($p < 0.01$). One of 14 patients with MC had osteoporosis (t-score < -2.5), while seven had osteopenia (t-score < -1.0). Five CD patients had osteoporosis and 12 had osteopenia, according to the WHO criteria; three patients from the HC group had osteopenia. BMD was lower at the femoral neck in MC and CD patients than in healthy controls (HC).

There was no significant difference between femoral neck BMD levels from MC and CD patients. Bone density of lumbar spine in MC patients was lower than in the HC group, but higher than among CD patients. BMD measured at the non-dominant radius was lower in MC patients than in the HC group and CD patients. Femoral and radius t-score values were lower in MC patients than in controls (Table 1.)

Table 1. Major objective bone density parameters in microscopic colitis, Crohn's disease and healthy controls.

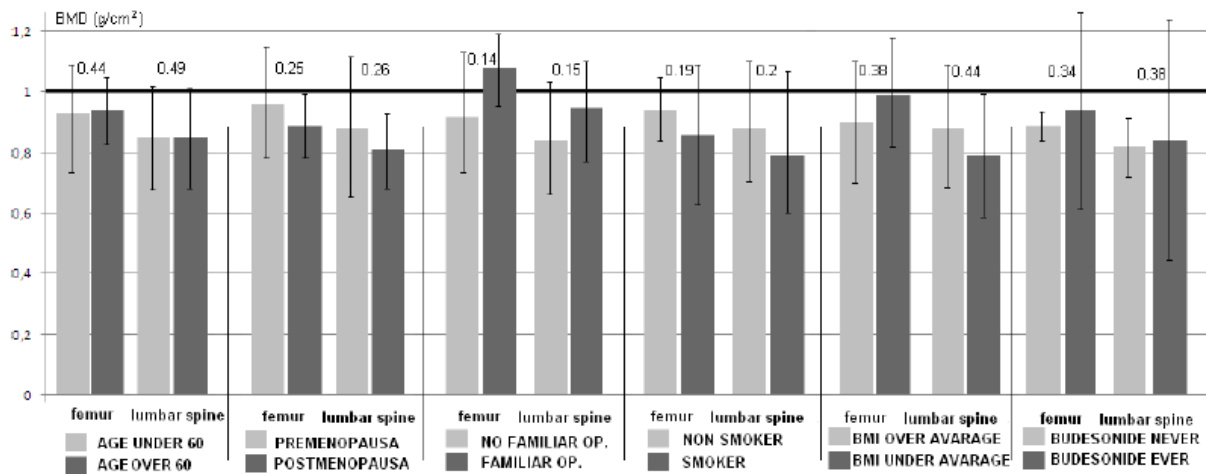
	HC	MC	significance (MC vs. CD)	CD
Femoral BMD (g/cm²)	1.056 \pm 0.126	0.852 \pm 0.165**	ns.	0.807 \pm 0.136**
Lumbar BMD (g/cm²)	0.949 \pm 0.112	0.928 \pm 0.156	$p < 0.05$	0.847 \pm 0.112
Radius BMD (g/cm²)	0.667 \pm 0.072	0.565 \pm 0.093*	ns.	0.672 \pm 0.056*

Bone metabolism was evaluated by detecting the bone resorption and formation markers, bCL and OC. The mean bCL concentration was higher in MC patients and CD patients than in the HC group (HC: 264.75 ± 138.65 pg/ml vs. MC: 417.714 ± 250.37 pg/ml vs. CD: 466.071 ± 249.96 pg/ml). There was a negative correlation between the bCL concentration and the femoral and radius t-score values in MC patients (-0.8 and -0.77 , respectively, $p < 0.05$) and CD patients (-0.83 and -0.79 , respectively, $p < 0.05$). Significantly higher serum

concentrations of the bone formation marker OC were measured in MC and CD patients than in the HC group. However, the mean concentration of OC was within the normal range in each group.

There was no significant difference in the BMD of MC patients with or without associated risk factors (Figure 1.).

Figure 1. Bone mass does not differ in microscopic colitis patients, with or without known risk factors for osteoporosis.



4.2. Study B results

34 coeliac patients and 53 with dermatitis herpetiformis were selected from the outpatient clinic of our department. Their data were compared to 42 healthy controls in this cross sectional study. The mean age was 38.0 ± 12.1 in coeliac disease, 32.18 ± 14.95 in dermatitis herpetiformis patients and 35.33 ± 10.41 in healthy controls. 8.8% CD, 7.4% DH patient and 7.1% HC were postmenopausal women.

We observed lower BMD at lumbar spine in patients groups (DH and CD) compared to HC (0.993 ± 0.136 g/cm² and 0.880 ± 0.155 g/cm² vs. 1.0565 ± 0.126 g/cm²; $p < 0.01$). Lumbar BMD was significantly lower in CD compared to DH patients. Femoral and radius BMD did not differ in DH and HC subjects, however lower BMD was observed at both sites in CD patients (0.733 ± 0.151 g/cm² vs. 0.841 ± 0.119 g/cm², $p < 0.01$; and 0.618 ± 0.067 g/cm² vs. 0.667 ± 0.072 g/cm², $p < 0.05$) compared to HC subjects.

Low bone mass was observed at the lumbar spine ($n=26$, 49%) and radius ($n=31$, 58%) in DH patients, however, ratio of the low bone density was low at the femoral neck ($n=11$, 21%) in this group. Sixty two percent ($n=21$) of CD patients had low bone mass at the lumbar spine and 71% ($n=24$) at non-dominant radius, respectively. Also, the proportion of low bone mass at the femoral neck was lower ($n=17$, 50%) in CD patients. The minority of

subjects (n=2, 5%) had low bone mass in the HC group, independently from the site of the measurement.

Higher ratio of patients had severe villous atrophy in the CD group compared to DH patients according to Marsh-Oberhuber grading system (CD: 3%-grade 0, 9%-grade 1-2, 26%-grade 3a, 15%-grade 3b, 47%-grade 3c; DH: 8%-grade 0, 24%-grade 1-2, 38%-grade 3a, 13%-grade 3b, 17%-grade 3c).

There was a tendency but no significant difference in bone mineral density in DH patients with normal villous structure (Marsh-Oberhuber grade 0-2.) compared to patients with villous atrophy (grade 3a-c) (lumbar: 0.985 ± 0.092 vs. 0.997 ± 0.145 g/cm², NS; femoral neck: 0.912 ± 0.034 vs. 0.890 ± 0.123 g/cm², NS; radius: 0.757 ± 0.062 vs. 0.686 ± 0.079 g/cm²; NS). 62% of DH patients were EMA positive, bone density not differed significantly in DH patients with or without EMA positivity (EMA+ and EMA- BMD: L1-4: 0.795 ± 0.344 g/cm² vs. 0.885 ± 0.320 g/cm², NS; FN: 0.553 ± 0.395 vs. 0.698 ± 0.229 g/cm², NS; and R: 0.551 ± 0.272 vs. 0.608 ± 0.204 g/cm²).

There was no correlation neither between BMD and EMA status, nor the Marsh grade of enteropathy.

Serum Ca concentrations were adjusted to serum albumin in all groups of subjects. Adjusted Ca value was not significantly different between the DH vs. CD groups (10.33 ± 0.48 vs. 9.89 ± 0.71 mg/dL; NS). There was higher albumin concentration in DH vs. CD patients (4.58 ± 0.33 vs. 4.46 ± 0.52 g/dL; $p<0.05$, respectively), however serum calcium levels differed significantly. Higher phosphorous concentration was observed in DH vs. CD patients (1.16 ± 0.16 vs. 1.14 ± 0.12 mg/dL, $p<0.01$).

Thirty three percent of DH patients did not follow the GFD. Bone mineral density parameters of non-adherent DH patients did not differ from those who followed GFD (lumbar: 0.995 ± 0.152 vs. 1.025 ± 0.111 g/cm², NS; femoral neck: 0.833 ± 0.186 vs. 0.888 ± 0.155 g/cm², NS; and radius: 0.679 ± 0.146 vs. 0.670 ± 0.088 g/cm², NS; respectively).

Mean parathyroid hormone concentrations were in the normal ratio in all groups of subjects.

4.3. Study C results

We enrolled 187 Crohn's disease (CD) and 66 ulcerative colitis (UC) patients into our study. The men/women ratio was 124/129. Mean age was 35.9 ± 11.7 years, 74.7% (n=189) of the patients were younger than 40 years; while 25.3% (n=64) of them were older. Fifteen patients (5.9%) were postmenopausal women. Mean body mass index (BMI) was 23.0 ± 4.7 kg/m².

Bone loss was more prominent at L1-L4 compared to FN based on T-score results (-0.601 ± 1.186 vs. -0.867 ± 1.321 , $p < 0.05$). Osteopenia and osteoporosis were observed in 35% ($n=89$) and 13% ($n=33$) of patients at L1-L4, and 34% ($n=86$) and 4% ($n=11$) at the FN, respectively.

4.3.1. *Fracture risk in inflammatory bowel diseases*

The major osteoporotic c-FRAX score was higher than bmd-FRAX ($3.0 \pm 3.3\%$ vs. $2.3 \pm 2.5\%$, $p < 0.05$). We found the same tendency regarding hip fracture risks scores (c-FRAX: $0.8 \pm 1.4\%$ vs. bmd-FRAX: $0.5 \pm 1.2\%$, NS).

Fracture risks did not differ in CD vs. UC patients neither for major fracture risk (c-FRAX: $3.0 \pm 3.4\%$ vs. $3.0 \pm 3.1\%$, NS; bmd-FRAX: $2.3 \pm 2.6\%$ vs. $2.3 \pm 2.3\%$, NS), nor for hip fracture risk (c-FRAX: $0.8 \pm 1.5\%$ vs. $0.7 \pm 1.3\%$, NS; bmd-FRAX: $0.6 \pm 0.4\%$ vs. $0.4 \pm 0.7\%$, NS).

As both types of IBD have known clinical factors showing unfavourable prognosis, we evaluated our data regarding age, behaviour and extent of disease in subgroup analyses.

By dividing the patients by age (older or younger than 40 years) we observed that c-FRAX and bmd-FRAX scores were similar in UC patients, while CD patients younger than 40 years had significantly higher c-FRAX scores (Table 2.).

Table 2. Major osteoporotic and hip fracture risk by age and disease type.

	Age of patients	older than 40 years n=46 (51.1±8.3 years)		younger than 40 years n=141 (29.8±5.9 years)	
	Fracture risk	Major osteoporotic	Hip fracture	Major osteoporotic	Hip fracture
CD	bmd-FRAX (%)	4.53±4.05	1.40±2.36	1.47±0.81	0.28±0.56
	c-FRAX (%)	5.13±4.10	1.28±1.56	1.98±1.14	0.49±0.82
	Significance of difference	NS	NS	<0.01	<0.05
UC	bmd-FRAX (%)	4.21±2.74	0.77±0.97	1.13±0.64	0.13±0.34
	c-FRAX (%)	5.29±3.87	1.32±1.87	1.56±1.05	0.26±0.46
	Significance of difference	NS	NS	NS	NS

Patients with penetrating CD also had lower bmd-FRAX than c-FRAX-scores compared to patients with non-penetrating type of CD (Table 3.).

Table 3. c-FRAX and bmd-FRAX scores by behaviour of CD

	Non-stricturing/ Non-penetrating (n=99)		Stricturing (n=16)		Penetrating (n=72)	
	Major osteoporotic	Hip fracture	Major osteoporotic	Hip fracture	Major osteoporotic	Hip fracture
Fracture risk						
c-FRAX (%)	2.63±3.55	0.74±1.76	2.66±1.72	0.74±0.61	2.86±2.73	0.84±1.46
bmd-FRAX (%)	1.97±2.07	0.44±1.01	1.94±1.06	0.52±0.45	1.84±1.77	0.23±0.49
Significance	NS	NS	NS	NS	<0.05	<0.05

There was neither significant difference between bmd-FRAX and c-FRAX scores among patients according to Montreal Classification (CD), and extent (UC).

Seventy-seven patients (26 %) had previously experienced a bone fracture. Fractures were more frequent among CD patients compared to UC patients (n=60, 32% vs. n=17%). There was no hip fracture in this cohort, but 34% of the fractures (n=23) could be regarded as a major osteoporotic fracture (wrist and forearm fractures).

Sixty four percent (n=156) of the patients had more than three months corticosteroid therapy during their disease course, and 18% (n=46) of them received corticosteroids continuously for more than one year. Patients received 10766±17232mg prednisone equivalent systemic dose of steroid during their lifetime. The cumulative steroid dose was neither associated with the c-FRAX (CD: r=0.07, UC: r=0.01), nor bmd-FRAX (CD: r=-0.23, UC: r=0.19) scores.

We observed no correlation between the FRAX scores and calcium intake, risk of malnutrition, and duration of the disease.

4.3.2. Vitamin D level in Hungarian patients with inflammatory bowel diseases.

We measured 169 IBD patients from C study (128 CD és 41 UC). The median vitamin D

level was 22.74 ± 10.61 ng/ml. Fifty two percent of IBD patients had vitamin D insufficiency (CD: 53%, UC: 48%), 28% of them (CD: 25%, UC: 33%) had severe vitamin D deficiency. Only 20% of the IBD patients (CD: 22%, UC: 19%) had adequate vitamin D level (> 30 ng/ml).

Vitamin D levels did not differ regarding the type of the IBD (23.65 ± 11.19 ng/ml vs. 19.89 ± 7.66 in CD vs. UC; NS). There were no significant difference in vitamin D levels considering disease extent (CD-L1: 23.94 ± 7.99 ng/ml, CD-L2: 23.79 ± 8.62 ng/ml, CD-L3: 22.23 ± 12.67 ng/ml; NS and UC-E1: 19.27 ± 6.68 ng/ml, UC-E2: 19.60 ± 6.54 ng/ml, UC-E3: 18.93 ± 8.49 ng/ml; NS).

Vitamin D concentration did not correlated neither to clinical activity indexes (partial Mayo score: $r = -0.143$; Crohn's disease activity index: $r = -0.253$) nor inflammatory parameters (C-reactive protein: $r = 0.008$; erythrocyte sedimentation rate: $r = 0.012$).

During the summer months vitamin D level was significantly higher than in winter month.

There was no difference in vitamin D levels between patients with osteoporosis, osteopenia and normal BMD (19.47 ± 8.95 vs. 24.10 ± 10.61 vs. 22.84 ± 10.65 , NS). There were no correlation between BMD and level of vitamin D (lumbar spine: $r = -0.08$, femoral neck: $r = -0.04$).

5. CONCLUSION

Present study demonstrates that bone loss can be an important problem in MC. A similarly decreased BMD was observed in patients with MC and CD. Low bone mass was detected in the femur and radius, and these bones contain more cortical than trabecular bone. Uncoupled bone remodelling was demonstrated in MC, with bone resorption demonstrated to exceed compensatory bone formation. The current findings are similar to the changes observed in bone homeostasis in CD.

We observed higher ratio of low bone mass in DH patients compared to healthy subjects, however it was observed to be lower than in CeD. There is no data regarding the cause of low bone mass in DH in the literature.

Bone mineral content was significantly lower in DH patients compared to healthy controls, however the grade of the bone loss was less than that of CD patients. Bone loss was more prominent in bones containing more trabecular than cortical bone. This phenomenon

may show similar pathogenetic background of DH and CD associated osteopenia. However, a lack of a relationship between the grade of villous atrophy and bone loss suppose some different pathogenetic mechanisms.

In CD, the cause of lowered bone mass is multifactorial. The most plausible causes are enteropathy and concomitant malabsorption. We observed a tendency between the grade of villous atrophy and the BMD in DH patients, however, the correlation was not significant.

Inflammatory bowel disease patients have some additional risk factors for bone loss compared to the general population. In our study c-FRAX calculated from the clinical parameters was significantly higher than bmd-FRAX. This difference was more significant in CD patients younger than 40 years. Both major osteoporotic and hip fracture FRAX scores were higher in younger patients.

We observed higher c-FRAX than bmd-FRAX values in penetrating type CD compared to stricturing and non-stricturing/non-penetrating ones.

However c-FRAX predict fractures accurately in IBD patients the above mentioned limitations we do not suggest to change the clinical practice of whether to perform DEXA or not in IBD patients at the time of the diagnosis. DEXA is offered to all patients who are expected to be treated based on their IBD specific or general risk factors for bone loss.

Further prospective validation is needed to decide whether these DEXA examinations are needed or not, and whether considering c-FRAX is an overestimation of the fracture risk.

Vitamin D deficiency is common in Hungarian patients with IBD. Vitamin D levels did not differ regarding the type of the IBD (UC and CD). In contrast with results of previously performed studies, our results show that Vitamin D concentration is independent from disease extent or severity in IBD patients.

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Hungarian

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