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BRIEF REPORT

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Intestinal barrier integrity in anorexia nervosa (a pilot study)

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Abstract

Objective: There is no conclusive evidence for involvement of intestinal barrier alteration in the etiology of anorexia nervosa (AN). The aims of this pilot study were to identify serum markers of intestinal barrier integrity in patients with AN and to determine the relationships between those markers and body mass index (BMI), eating disorder symptoms, gastrointestinal complaints, and liver synthesis function (international normalized ratio [INR]).

Method: Twenty-five outpatients with AN prior to starting treatment and 28 healthy controls (HC) were assessed. BMI and serum markers of intestinal barrier integrity were measured, including zonulin family peptides (ZFP), lipopolysaccharide-binding protein (LBP), and intestinal fatty-acid-binding protein (i-FABP). Eating disorder symptoms and gastrointestinal complaints were evaluated via questionnaires.

Results: The serum ZFP concentration was significantly lower in patients with AN than in HC (44.2 [7.4] vs. 49.2 [5.6] ng/ml, mean [standard deviation], $p = .008$). LBP and i-FABP did not differ between the two groups. In patients with AN, serum ZFP was significantly predicted by BMI ($\beta = 0.479$, $p = .009$), age ($\beta = 0.411$, $p = .020$), and INR ($\beta = -0.388$, $p = .028$). No such associations were found for either gastrointestinal complaints or eating disorder symptoms.

Discussion: Abnormal levels of serum ZFP were observed in patients with AN. Further studies with other assessment methods are warranted to examine intestinal barrier function in AN.

Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT02745067.

KEYWORDS

anorexia nervosa, biomarkers, fatty-acid-binding proteins, feeding and eating disorders, irritable bowel syndrome, permeability, small intestine

1 | INTRODUCTION

A unifying theory for the etiology and pathophysiology of anorexia nervosa (AN) has yet to be established, and therefore no biological treatments directed against possible causal factors have been identified. Increased intestinal permeability is one factor that may be involved, thus constituting a possible treatment target (Breton, Dèchelotte, & Ribet, 2019; Seitz et al., 2019). The intestinal barrier has several functions in healthy individuals, including protection of the internal environment from harmful substances while allowing

TABLE 1 Clinical characteristics and serum concentrations of intestinal barrier integrity markers for patients with anorexia nervosa (AN) and healthy controls

	Patients with AN ($n = 25$)			Healthy controls ($n = 28$)			Distribution of scores		Student's t test for independent samples		Effect size
	Mean	SD	Min–Max	Mean	SD	Min–Max	Skewness	Kurtosis	p	95% CI	Cohen's d
Age (years)	21.0	5.5	16–38	20.8	5.1	16–38	1.7	2.8	.903	−2.7, 3.1	0.03
Self-reported duration of illness (years)	2.65	3.24	0–10								
BMI (kg/m^2)	16.3	1.9	12.5–19.5	23.2	2.4	19.5–28.7	0.2	−0.8	**<.001**	−8.1, −5.7	1.69
EDE-Q global score (0–6)	3.9	1.3	0.8–5.7	0.5	0.4	0–1.5	0.6	−1.3	**<.001**	2.8, 3.9	1.74
CIA total score (0–48)	34.0	10.5	13–48	1.8	2.0	0–7	0.50	−1.49	**<.001**	27.6, 36.4	1.81
IBS-SSS total score (0–500)[a]	221.5	123.9	50–425	90.9	107.6	0–426	0.91	−0.38	**<.001**	63.1, 198.2	1.00
ZFP (ng/ml)	44.2	7.4	32.2–62.7	49.2	5.6	42.4–61.9	0.35	−0.10	**.008**	−8.6, −1.4	0.72
LBP (ng/ml)	3,628	1,360	859–6,663	4,022	1,457	864–7,435	0.26	−0.06	.315	−1,174, 385	0.028
i-FABP (ng/ml)[b]	1.9	0.8	0–3.9	1.9	1.4	−0.9 to 4	0.74	0.45	.988	−0.6, 0.6	0.004

Noe: Bold values denote statistical significance at the $p < 0.05$ level.

Abbreviations: BMI, body mass index; CI, confidence interval; CIA, Clinical Impairment Assessment; EDE-Q, Eating Disorder Examination Questionnaire; IBS-SSS, Irritable Bowel Syndrome Severity Scoring System; i-FABP, intestinal fatty-acid-binding protein; LBP, lipopolysaccharide-binding protein; SD, standard deviation; ZFP, zonulin family peptides.

[a]Five patients with AN did not answer the questionnaire.

[b]Statistical analysis performed on logarithmically transformed data.

uptake of nutrients and water (Schoultz & Keita, 2020). An impaired intestinal barrier contributes to increased translocation of bacterial products from the intestinal lumen into the systemic circulation. Bacterial products of interest in AN include immune-activating substances stimulating the production of autoantibodies that target neuropeptides, such as the appetite-suppressing α-melanocyte-stimulating hormone (Breton et al., 2019; Fetissov & Hökfelt, 2019). Many patients with AN experience symptoms of several functional gastrointestinal disorders, such as irritable bowel syndrome (IBS) (Hetterich, Mack, Giel, Zipfel, & Stengel, 2019; Kessler et al., 2020), which may be associated with an impaired intestinal barrier (Hanning et al., 2021). Unfortunately, the complex regulation of intestinal permeability is only partly understood (Fasano, 2020) and is challenging to assess in vivo with noninvasive methods (Schoultz & Keita, 2020). Therefore, noninvasive methods of assessing intestinal barrier integrity have been sought.

Zonulin is a protein that binds to surface receptors of the intestinal epithelia, triggering a cascade of biochemical reactions that induce disassembly of tight junctions and thus increased intestinal permeability (Fasano, 2020). Zonulin is an established marker of intestinal permeability; however, it has recently been suggested that currently available enzyme-linked immunosorbent assay (ELISA) methods detect zonulin family peptides (ZFP) (Fasano, 2020), including properdin (Scheffler et al., 2018). Another noninvasive method of assessing intestinal permeability is measurement of the lactulose–mannitol ratio (L:M) in urine after sugar ingestion; an increased ratio indicates reduced small-intestine integrity (Schoultz & Keita, 2020).

Several circulating biomarkers can be used to assess intestinal barrier integrity and function, such as lipopolysaccharide-binding protein (LBP) (Schoultz & Keita, 2020). Increased circulating levels of LBP result from increased translocation of bacterial lipopolysaccharides that have split from intestinal Gram-negative bacteria and leaked into the circulation, where they bind to LBP (Schoultz & Keita, 2020). Another biomarker of interest is intestinal fatty-acid-binding protein (i-FABP), which is present within intestinal enterocytes. Increased circulating levels of i-FABP indicate a damaged intestinal epithelium (Schoultz & Keita, 2020).

While impaired intestinal barrier function is included in recent models of the pathophysiology of AN, it has been assessed in patients with AN in only two studies. Monteleone et al. (2004) found that intestinal permeability (assessed via the L:M test) was lower in patients with AN than in healthy controls (HC), and Mörkl et al. (2018) found no correlation between serum zonulin concentration and body mass index (BMI).

The aims of the current study were twofold: (a) to compare serum levels of markers of intestinal barrier function and integrity (ZFP, LBP, and i-FABP) in patients with AN and HC, and (b) to identify possible associations between these serum markers and BMI, eating disorder symptoms, gastrointestinal complaints, and liver synthesis function in patients with AN.

2 | METHOD

This pilot study, which was part of an ongoing treatment trial that is described elsewhere (Danielsen, Rekkedal, Frostad, & Kessler, 2016),

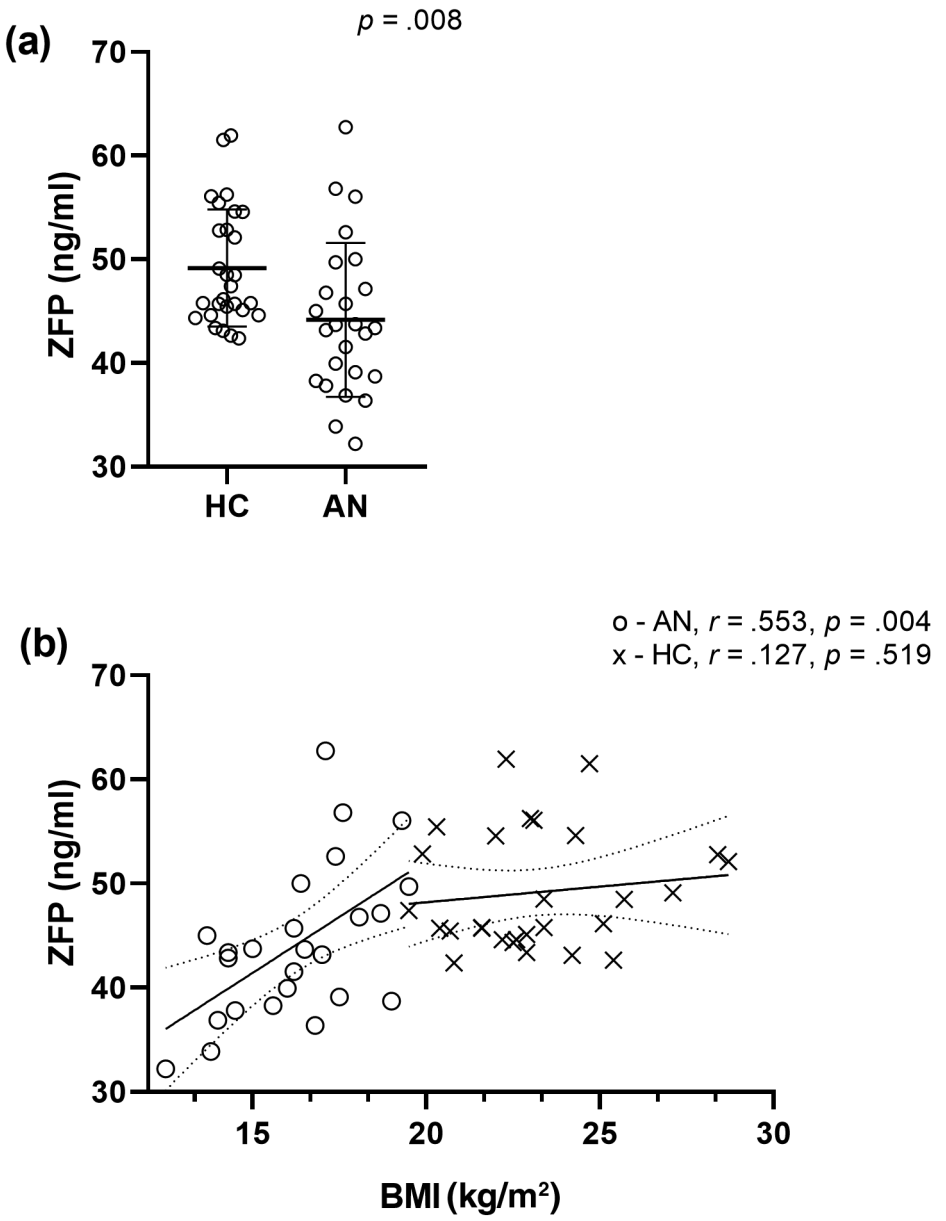

FIGURE 1 A biomarker of intestinal barrier function. (a) Concentration of serum zonulin family peptides (ZFP) in patients with anorexia nervosa (AN) and healthy controls (HC). (b) Correlation of serum ZFP with body mass index (BMI) in patients with AN and HC, presented with the linear regression and 95% confidence intervals

had a cross-sectional design, assessing patients prior to starting treatment. The diagnosis of AN (including atypical AN with BMI >18.5 kg/m^2) was established by the treating psychologist according to the Diagnostic and Statistical Manual of Mental Disorders (fifth edition; DSM-5) criteria. The study was approved by the Regional Committee for Medical and Health Research Ethics, Western Norway (REK Vest 2015/2328).

2.1 | Participants

All patients aged >16 years who agreed to receive cognitive behavioral therapy for AN at our outpatient unit between December 2016 and August 2019 were asked to participate in the study ($n = 33$). Twenty-five patients with AN were eligible for inclusion in the statistical analysis (five patients did not provide blood samples, and a further three were excluded due to a history of gastric surgery, diagnosis of celiac disease, and BMI >21.5 kg/m^2). The participants in the current study are to a large extent overlapping with the participants in a previous publication on gastrointestinal complaints in patients with AN (Kessler et al., 2020). Twenty-eight age-matched HC were recruited. Exclusion criteria included regular use of nonsteroidal anti-inflammatory drugs and use of immunosuppressive therapy (medications known to influence intestinal permeability) or anticoagulants (medications known to influence the international normalized ratio [INR]). All participants gave written informed consent before study participation.

2.2 | Questionnaires

Eating disorder symptoms and the severity of psychosocial impairment associated with eating disorders were evaluated using the Eating

Disorder Examination Questionnaire (Fairburn & Beglin, 2008) and the Clinical Impairment Assessment (Bohn et al., 2008), respectively. Gastrointestinal complaints were evaluated using the Irritable Bowel Syndrome Severity Scoring System (IBS-SSS), a validated questionnaire for monitoring the severity of IBS symptoms (Francis, Morris, & Whorwell, 1997).

2.3 | Analysis of serum intestinal barrier integrity markers

Serum concentrations of the intestinal barrier integrity markers ZFP, LBP, and i-FABP were analyzed in duplicate using the following commercially available ELISA kits: IDK® Zonulin (Ref# K5601; Immundiagnostik, Bensheim, Germany), Human LBP (Cat# EKH3120, Nordic BioSite, Taby, Sweden), and Human (intestinal) FABP2 (Cat# EHFABP2, Invitrogen, Thermo Fisher Scientific, Waltham, MA). Blood samples were drawn between 9:00 a.m. and 1:00 p.m.

2.4 | Marker of liver synthesis function

INR was analyzed using standard methods at the Laboratory Clinic, Haukeland University Hospital.

2.5 | Statistical analyses

Data were analyzed using SPSS (version 26.0.0.1). The normality of variable distributions was evaluated by assessing skewness and kurtosis. After logarithmic transformation of i-FABP, all data were regarded as normally distributed. Student's *t* test for independent samples was used to compare group means. In patients with AN, associations between variables were assessed using bivariate correlation analyses (Pearson correlation coefficient, *r*), and variables for which the relationship was moderate ($r = .3–.49$) or strong ($r = .5–1$) were entered in a standard multiple regression analysis.

3 | RESULTS

3.1 | Demographic and clinical characteristics and serum markers of intestinal barrier integrity

All participants were female. The clinical characteristics and serum concentrations of ZFP, LBP, and i-FABP for patients with AN and HC are presented in Table 1. Patients with AN had significantly lower serum concentrations of ZFP compared with HC (44.2 [7.4] vs. 49.2 [5.6] ng/ml, mean [SD]), $p = .008$; Figure 1a). Serum LBP and i-FABP did not differ significantly between the two groups. The mean INR in patients with AN was 1.1 (range 0.9–1.3, $n = 19$; INR in HC was not analyzed).

3.2 | Associations between intestinal barrier integrity markers and BMI, eating disorder symptoms, gastrointestinal complaints, and liver synthesis

In patients with AN, serum concentration of ZFP was strongly and positively correlated with BMI ($r = .553$, $p = .004$; Figure 1b) and moderately and positively correlated with age ($r = .448$, $p = .025$; Figure S1b), whereby higher BMI and age were associated with higher serum ZFP. Serum concentrations of ZFP were also moderately and negatively correlated with INR ($r = -.450$, $p = .053$; Figure S1c), with lower INR being associated with higher serum ZFP. No correlation was found between serum ZFP and either gastrointestinal complaints (IBS-SSS) or eating disorder symptoms. Multiple regression analysis revealed that the three independent variables together explained 62.4% of the total variance in ZFP ($p = .002$). In this model, variance in ZFP was significantly predicted by BMI ($\beta = 0.479$, $p = .009$), age ($\beta = 0.411$, $p = .020$), and INR ($\beta = -0.388$, $p = .028$). No significant correlations were found between serum concentrations of either LBP or i-FABP and BMI, age, eating disorder symptoms, gastrointestinal complaints, and liver synthesis. No intercorrelation was observed between the three markers of intestinal barrier function (ZFP, LBP, and i-FABP).

4 | DISCUSSION

The primary aim of this study was to compare circulating markers of intestinal barrier function in patients with AN and HC. Serum levels of ZFP were lower in patients with AN than in HC, whereas LBP and i-FABP did not differ between the two groups. Furthermore, in patients with AN, lower serum ZFP was significantly predicted by lower BMI, lower age, and higher INR (high INR indicates reduced vitamin K dependent prothrombin synthesis in the liver), while no such associations were found for either gastrointestinal complaints or eating disorder symptoms.

Lower serum concentrations of zonulin may indicate reduced intestinal permeability (Fasano, 2020). However, the present findings should be interpreted with caution, as the ELISA kit used in this study may also quantify other peptides of the zonulin family (Dschietzig, 2019). That said, reduced intestinal permeability is consistent with findings reported in patients with AN using the L:M test (Monteleone et al., 2004). Mörkl et al. (2018) found no significant correlation between serum zonulin concentration and BMI in a sample of participants with AN and controls of normal weight or with overweight or obesity. However, when the median zonulin concentration was used to divide participants into high- and low-zonulin groups, the majority (65%) of the patients with AN was in the low-zonulin group.

BMI, age, and INR contributed uniquely and significantly to the variance in ZFP in patients with AN. A positive correlation between BMI and serum zonulin has also been reported in a population-based cohort study ($n = 235$) (Ohlsson, Orho-Melander, & Nilsson, 2017). In line with our findings, that study further demonstrated no association between the zonulin concentration and gastrointestinal symptoms

(Ohlsson et al., 2017). Intestinal permeability, as measured by the serum zonulin concentration (Aasbrenn, Lydersen, & Farup, 2020) and the L:M test (Damms-Machado et al., 2017), appears to decrease after weight reduction in individuals with obesity, suggesting that intestinal permeability is proportional to energy intake (Mörkl et al., 2018; Zak-Gołąb et al., 2013). The positive correlation between ZFP and age is in line with the findings of a study analyzing serum zonulin in participants with obesity and normal weight without concomitant diseases (Zak-Gołąb et al., 2013). Furthermore, we found a negative correlation between ZFP and liver synthesis function (INR). However, it is noteworthy that the vast majority of patients with AN with available samples in this study had normal INR values (0.8–1.2).

To the best of our knowledge, this is the first study to assess LBP in patients with AN. The hypothesis of increased translocation of LPS from the gastrointestinal tract to the circulatory system in AN was not supported by our findings, since there were no significant differences in LBP between patients with AN and HC. Additionally, serum levels of i-FABP did not support a hypothesis of intestinal epithelial damage.

To date, there is no support from human studies (including the present study) of increased intestinal permeability in patients with AN. However, animal studies have found increased colonic permeability in mice with activity-based anorexia (Jésus et al., 2014). These findings may be due to the use of an activity-based rather than malnutrition-based model of AN in the animal studies, or to assessment methods, which focused on colonic permeability. In the present study, permeability was assessed mainly in the small intestine, since it has been reported that zonulin is not active in the colon (Vanuytsel, Vermeire, & Cleynen, 2013); thus, our findings may only represent permeability in the small intestine. Whether colonic intestinal permeability is altered in patients with AN remains unknown. Likewise, there are indications that i-FABP is mainly expressed in the small intestine (Pelsers et al., 2003), while a potential increase of LBP could be due to translocation of the endotoxin LPS from the whole GI-tract (Schoultz & Keita, 2020).

Limitations of the present study include the small sample size and the method used to measure serum zonulin. Moreover, we have no data on diet.

In conclusion, reduced serum concentrations of ZFP were observed in patients with AN, and this was associated with BMI, age, and INR, but not with gastrointestinal complaints or eating disorder symptoms. Since ZFP is thought to mediate permeability primarily in the small intestine, the possibility of alterations of intestinal permeability in the colon cannot be excluded. Although intestinal permeability is challenging to assess in vivo (Schoultz & Keita, 2020), further studies with other assessment methods are warranted, and should ideally include colonic intestinal barrier function.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable written request.

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SUPPORTING INFORMATION

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