Dig Dis Sci (2008) 53:2215–2221
DOI 10.1007/s10620-007-0113-x

ORIGINAL PAPER

Serum Ghrelin Levels in Inflammatory Bowel Disease with Relation to Disease Activity and Nutritional Status

Yuksel Ates · Bulent Degertekin · Ahmet Erdil · Halil Yaman · Kemal Dagalp

Received: 31 December 2006 / Accepted: 5 November 2007 / Published online: 13 December 2007

Abstract Ghrelin possesses various biological activities—it stimulates growth hormone (GH) release, plays a major role in energy metabolism, and is one of the hormones that affects body composition. It also plays a role in modulating immune response and inflammatory processes. In this study we aimed to determine whether serum ghrelin levels had correlation with markers associated with disease activation. We also investigated any probable relationship between serum ghrelin level and nutritional status. Serum levels of ghrelin and its relationship with disease activity and nutritional status were evaluated in 34 patients with ulcerative colitis (UC), 25 patients with Crohn's disease (CD), and 30 healthy controls. Serum ghrelin levels, serum IGF-1 and GH levels, and markers of disease activity (sedimentation, C-reactive protein, and fibrinogen) were measured in all subjects. Body composition and nutritional status was assessed by both direct (by anthropometry) and indirect (by bioimpedance) methods. Serum ghrelin levels were significantly higher in patients with active UC and CD than in those in remission (108 ± 11 pg/ml vs. 71 ± 13 pg/ml for UC patients, $P < 0.001$; 110 ± 10 pg/ml vs. 75 ± 15 pg/ml for CD patients, $P < 0.001$). Circulating ghrelin levels in UC and CD patients were positively correlated with sedimentation fibrinogen and CRP and was negatively correlated with IGF-1, BMI, TSFT, MAC, fat mass (%), and fat free mass (%). This study demonstrates that patients with active IBD have higher serum ghrelin levels than patients in remission and high levels of circulating ghrelin correlate with the severity of disease and the activity markers. Ghrelin levels in inflammatory bowel disease (IBD) patients show an appositive correlation with IGF-1 and bioelectrical impedance analysis, body composition, and anthropometric assessments. Finally, we arrived at the conclusion that ghrelin level may be important in determination of the activity in IBD patients and evaluation of nutritional status.

Keywords Ghrelin · Inflammatory bowel disease · Ulcerative colitis · Crohn's disease · IGF-1 · Nutritional status

Y. Ates · A. Erdil · K. Dagalp
Department of Gastroenterology,
Gulhane Military Medical Academy, Ankara, Turkey

B. Degertekin (✉)
Faculty of Medicine, Department of Gastroenterology,
Ufuk University, Ankara 06500, Turkey
e-mail: bulentd@med.umich.edu

H. Yaman
Department of Biochemistry,
Gulhane Military Medical Academy, Ankara, Turkey

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are characterized with chronic inflammation of the gastrointestinal tract [1, 2]. Weight loss, malnutrition, and developmental retardation are also frequently observed in inflammatory bowel disease (IBD), especially in CD [3, 4]. It has been reported that this malnutrition and developmental retardation in IBD is caused by several factors such as the irregularities in the GH–IGF-1 axis, inadequate calorie intake, increased catabolic activity, and absorption failure due to chronic inflammation [5–7].

Ghrelin is a 28-amino-acid peptide hormone that is mainly produced by the X/A-like cells located in the oxyntic mucosa of the stomach [8]. Ghrelin possesses various biological activities, including stimulation of growth hormone (GH) release [4]. It also plays a major role

in energy metabolism and is one of the hormones that affect body composition by stimulating food intake and enhancing the use of carbohydrates and reducing fat utilization [9, 10]. Plasma ghrelin levels are elevated by fasting and reduced by re-feeding, and its levels are negatively correlated with body mass index (BMI)—decreasing in obese subjects and increasing in those with anorexia nervosa [11–15]. Other than these effects it could also play a role in modulating immune response and inflammatory processes [16]. High circulating ghrelin levels have been found in rats with septic shock, Celiac Disease with active inflammation, and in inflammatory bowel disease in patients with active disease [17–21].

There are some reports in the literature stating the close relationship between the serum ghrelin level and severity of mucosal inflammation in the gastrointestinal tract [19, 22–24]. Lanzini et al. determined a positive correlation between ghrelin level and the inflammatory activity of intestinal mucosa in newly diagnosed Celiac disease patients. In this report they also found that ghrelin levels decreased after a gluten free diet [18]. In a recent paper, Perrachi et al. reported high serum ghrelin levels in patients with inflammatory bowel disease. They found positive correlation between serum ghrelin level and disease activity, TNF-alpha, and serum C-reactive protein (CRP) levels. They did not report any change of ghrelin level in patients with inactive IBD [20].

The GH–IGF-I axis is thought to play an important role in the regulation of body composition throughout life. Changes in body fat stores also affect the activity of the GH–IGF-I axis, and it is known that IGF-1 is a strong indicator of the peripheral effects of GH [25]. It has been reported in literature that such circulating inflammatory cytokines such as TNF-alpha and IL-6 reduce the expression of IGF-1 [26, 27]. It is also known that IGF-1 level is low in patients with IBD [28]. Eivindson et al. reported statistically low IGF-1 levels in active IBD cases with high sedimentation and CRP levels, and this low level of IGF-1 was negatively correlated with the nutritional status of the patients [29]. There are many studies in literature stating a negative correlation between ghrelin level and IGF-1 [30–33]. In a recent report, Poykko et al. reported an inverse proportion between ghrelin levels and IGF-1. They also stated that this relation between IGF-1 and ghrelin is modified by obesity and body mass index. This case is thought to be attributable to ghrelin and the IGF-1/GH axis [30].

IBD is a disease often characterized by catabolism, growth and developmental retardation. It is known that these patients suffer from lack of appetite and reduced food intake on active days in particular. We assumed that such a hormone as ghrelin, which has proven to be influential in energy homeostasis, regulation of appetite, determination of the nutritional level and fat rate of the body, as well as play an important role in the functioning of the GH/IGF-1 axis and in modulating immune responses and inflammatory processes, should have a role in the nutritional status and disease activation.

In our study we aimed to determine whether there is a change in serum ghrelin levels in IBD patients and find out the relationship between ghrelin levels and disease activity and learn whether this change, if any, showed a correlation between IGF-1, GH, and activation markers (sedimentation, fibrinogen, CRP). We also investigated any probable relationship between bioelectrical impedance analysis (BIA), which shows nutritional status of the body in IBD patients, body composition and anthropometric assessments, and serum ghrelin level.

This study is the first to investigate whether ghrelin plays a role in disease activation and nutritional status by analyzing body composition—using both direct (anthropometry) and indirect (bioimpedance) methods—in patients with IBD.

Methods

Patients

In this randomized prospective study, 59 IBD patients from the outpatient clinic of Gulhane Military Medical Hospital were consecutively included. For comparison, 30 healthy volunteers, matched for age, sex, and body mass index (BMI = kg/m^2), were also examined. All of the patients received anti-inflammatory therapy. Diagnosis of CD and UC was based on clinical, endoscopic, radiologic, and histologic criteria. See Table 1 for clinical characteristics and disease distributions. We employed the most frequently used indices to characterize disease activity: Crohn's disease activity index (CDAI) for CD and Rachmilewitz clinical and endoscopic activity index for UC [34, 35]. Values less than 150 for CD and less than 4 for UC were considered as remission. Those who had already had an operation, any chronic systemic disease, or who were receiving steroid or immunosuppressive therapy were not included in the study. The Regional Committee of Ethics approved of the study and all the participants signed an informed consent.

Nutritional assessment

Body composition was assessed both directly (by anthropometry) and indirectly (by bioimpedance). Patient's details (age, gender, etc.) and anthropometric measurements (height, weight, BMI, triceps skin-fold thickness [TSTF], mid-upper arm circumference [MAC]) were recorded. Additionally, the subjective global assessment

Table 1 Demographic and the clinical characteristics of the study population

		Ulcerative colitis	Crohn's disease	Healthy controls	*P* value
Number of patients (*n*)	Total	34	25	30	0.59
	Remission	18	15	–	
	Active	16	10	–	
Age (mean ± SD)	Total	38.3 ± 12.6	39.6 ± 12.4	36.1 ± 12.8	0.83
	Remission	39.5 ± 13.9	40.9 ± 11.9		
	Active	37.2 ± 11.7	37.8 ± 13.8		
Male/female (*n*)		20/14	14/11	18/12	0.85
BMI (kg/m^2)	Total	23.6 ± 3.9	23.3 ± 4.5	25.8 ± 3.2	0.66
	Remission	24.5 ± 3.0	24.4 ± 3.7	–	
	Active	22.1 ± 2.4	21.2 ± 2.5	–	
Duration of disease (months)	Total	78.4 ± 75.2	76.5 ± 75.2	–	0.82
	Remission	80.6 ± 75.2	79.9 ± 75.2	–	
	Active	71.4 ± 75.2	70.2 ± 75.2	–	
Localization of disease (*n*)	Proctocolitis	9	–	–	
	Left-sided colitis	10	–	–	
	Pancolitis	15	–	–	
	Ileal alone	–	12	–	
	Ileocolonic	–	8	–	
	Colonic alone	–	5	–	

(SGA) and body composition by bioelectrical impedance (BIA) were measured. Patients were categorized by BMI measurement as underweight (<20), normal (20–24.9), overweight (25–29.9), or obese (>30) .

Biochemical assessment

At 08:00 am, after overnight fasting longer than 12 h, whole blood was directly drawn into a centrifuge tube that contained 500 U of Aprotinin and 1.25 mg of EDTA–2Na per 1 ml of whole blood. The blood samples were immediately centrifuged at 1,500×g for 15 min at 4°C. Plasma samples were then acidified with 100 µl of 1 mol/l HCl per ml of collected plasma and stored at −80°C until assay. The Active Ghrelin ELISA kit (LINCO Research, Missouri, USA) recognizes the octanoyl modified portion of Ghrelin. Plasma levels of octanoyl ghrelin were measured using the octanoyl-ghrelin ELISA kit (LINCO Research, Missouri, USA), which is an enzymatically amplified "two-step" sandwich-type immunoassay. The method of the study followed the IGF-1 kit IRMA (Diagnostic Systems Laboratories Inc., Texas, USA).

Statistical analysis

The results are given as average ± standard deviation and as medium (min–max). Independent Student's *t*-test and the Mann–Whitney *U*- test were used to evaluate the statistical significance between the groups. Correlation between the variables was made with Spearman's correlation analysis and $P < 0.05$ was regarded as the key value for statistical significance. The statistical analysis was carried out with SPSS 10.0 for Windows.

Results

Demographic distribution

A total of 34 UC, 25 CD, and 30 healthy controls were included in the study. Of the patients in the UC and CD groups, 52.9% ($n = 18$) and 47.1% ($n = 15$) were in remission, respectively, whereas 64% ($n = 16$) and 36% ($n = 10$) were within the active disease period. There was no statistically significant difference between the CD, UC, and healthy control groups as regards to age, gender, and BMI ($P > 0.05$) (Table 1).

Of the UC patients, 26.4% ($n = 9$) were proctocolitis, 29.4% ($n = 10$) were left type, and 44.2% ($n = 15$) were pancolitis. Of the CD patients, 20% ($n = 5$) had disease localization at the colonic region, 48% ($n = 12$) were ileal alone, and 32% ($n = 8$) were ileocolonic type. The average disease periods of the UC and CD patients were 71.4 and 70.2 months, respectively, in the active disease group. This period was 80.6 and 79.9 months for the group included in

remission, respectively. There was no statistical difference between the groups as regards the disease period ($P > 0.05$) (Table 1).

Clinical nutritional parameters

In the healthy controls group, fat mass (%), fat mass (kg), fat free mass (%), and fat free mass (kg) were found as 27.45 ± 6.3%, 18.90 ± 6.2 kg, 72.50 ± 12.1%, and 49.60 ± 3.9 kg, respectively. In the UC group these parameters were 23.15 ± 5.5%, 14.90 ± 5.9 kg, 76.83 ± 10.6%, and 49.60 ± 4.1 kg, respectively, and for the CD group these parameters were found to be 23.02 ± 4.6%, 14.44 ± 4.4 kg, 76.80 ± 7.9%, and 48.35 ± 3.7 kg, respectively.

When the anthropometric tests were taken into consideration, in the healthy controls group body weight, BMI, TSFT, and MAC values were calculated as 68.80 ± 9.2 kg, 25.80 ± 3.2 kg/m^2, 1.71 ± 0.5 mm, and 26.50 ± 4.6 cm, respectively. In the UC group these parameters were 64.50 ± 6.9 kg, 23.60 ± 3.9 kg/m^2, 1.05 ± 0.6 mm, and 23.20 ± 3.3 cm, respectively, and for the CD group these parameters were found to be 62.80 ± 5.0 kg, 23.30 ± 4.5 kg/m^2, 1.02 ± 0.3 mm, and 22.10 ± 2.8 cm, respectively.

Considering the bioelectrical impedance analysis (BIA), body composition, and anthropometric assessment levels between the groups, the measured levels of the patients in the UC and CD groups were found to be significantly lower than the ones in the healthy group ($P < 0.05$) (Table 2).

Table 2 Results of bioelectrical impedance analysis (BIA), body composition, and anthropometric assessments in healthy controls and IBD patients

	Healthy controls, $n = 30$	UC total, $n = 34$	CD total, $n = 25$
BIA and body composition			
Fat mass (%)	27.45 ± 6.3	23.15 ± 5.5	23.02 ± 4.6
Fat mass (kg)	18.90 ± 6.2	14.90 ± 5.9	14.44 ± 4.4
Fat free mass (%)	72.50 ± 12.1	76.83 ± 10.6	76.80 ± 7.9
Fat free mass (kg)	49.60 ± 3.9	49.60 ± 4.1	48.35 ± 3.7
Body liquid (l)	26 ± 3.1	23 ± 4.8	23 ± 4.2
Anthropometric tests			
Body weight (kg)	68.80 ± 9.2	64.50 ± 6.9	62.80 ± 5.0
BMI (kg/m^2)	25.80 ± 3.2	23.60 ± 3.9	23.30 ± 4.5
TSFT (mm)	1.71 ± 0.5	1.05 ± 0.6	1.02 ± 0.3
MAC (cm)	26.50 ± 4.6	23.20 ± 3.3	22.10 ± 2.8

$P < 0.05$ for healthy controls vs. UC and healthy controls vs. CD when BIA, body composition, and anthropometric tests are considered

Laboratory findings

Ghrelin level was found to be 84 ± 14 pg/ml in healthy controls, 90 ± 22 pg/ml in UC patients, and 92 ± 26 pg/ml in CD patients. There was no statistical difference between the groups ($P > 0.05$) (Table 3). Ghrelin levels in active UC and CD patients were 108 ± 11 pg/ml and 110 ± 10 pg/ml, respectively, while in the patients in remission the levels were 71 ± 13 pg/ml and 75 ± 15 pg/ml, respectively. It was determined that Ghrelin levels of UC and CD patients were statistically significantly higher than those of the cases in remission ($P < 0.001$) (Table 3).

When we evaluated serum GH levels between the groups, it was found that the measured values of the patients in UC and CD groups did not show any difference from the healthy control group ($P > 0.05$) (Table 3). As for the IGF-1 levels, they were found to be considerably lower in UC and CD patients than in the healthy control group ($P < 0.001$). IGF-1 levels in active UC and CD patients were 113 ± 15 and 110 ± 12 ng/ml, respectively, while they were 185 ± 24 and 183 ± 11 ng/ml in the patients in remission, respectively. It was found that IGF-1 levels of active UC and CD patients were statistically significantly lower than those of the patients in remission ($P = 0.011$) (Table 3).

Correlation between ghrelin and nutritional or inflammatory parameters

Spearman's correlation test was applied to investigate the relationship between ghrelin levels and the other parameters.

Circulating ghrelin levels in UC were negatively correlated with IGF-1 ($r = -0.45$, $P < 0.01$), BMI ($r = -0.47$, $P < 0.01$), TSFT ($r = -0.43$, $P < 0.05$), MAC ($r = -0.44$, $P < 0.01$), fat mass (%) ($r = -0.46$, $P < 0.01$), and fat free mass (%) ($r = -0.47$, $P < 0.01$). Circulating ghrelin levels in CD negatively correlated with IGF-1 ($r = -0.45$, $P < 0.05$), BMI ($r = -0.46$, $P < 0.05$), TSFT ($r = -0.43$, $P < 0.05$), MAC ($r = -0.44$, $P < 0.05$), fat mass (%) ($r = -0.58$, $P < 0.01$), and fat free mass (%) ($r = -0.50$, $P < 0.05$). It was found that the ghrelin levels of UC and CD patients showed a statistically significant negative correlation with IGF-1, body weight, BMI, TSFT, MAC, fat mass (%), fat mass (kg), fat free mass (%), and fat free mass (kg) and this correlation was more common and intense in the active IBD patients than in the cases in remission. There was no statistical correlation with ghrelin levels in patients with UC and CD patients in remission only in terms of BMI and body weight (Table 4).

Circulating ghrelin levels in UC were positively correlated with sedimentation ($r = 0.44$, $P < 0.01$), fibrinogen

Table 3 Descriptive data of the markers associated with disease activation in patients with UC, CD, and healthy controls

Parameter	Healthy controls, $n = 32$	UC total, $n = 34$	UC active, $n = 16$	UC remission, $n = 18$	CD total, $n = 25$	CD active, $n = 10$	CD remission, $n = 15$
Ghrelin (pg/ml)	84 ± 14	90 ± 22	108 ± 11	71 ± 13	92 ± 26	110 ± 10	75 ± 15
IGF-1 (ng/ml)	224 ± 86	166 ± 43	113 ± 15	185 ± 24	162 ± 39	110 ± 12	183 ± 11
GH (ng/ml)	1.95 ± 0.11	1.94 ± 0.51	1.84 ± 0.42	1.96 ± 0.45	1.88 ± 0.46	1.85 ± 0.38	1.90 ± 0.35
CRP mg/l	4 ± 2	10 ± 5	18 ± 9	5 ± 3	7 ± 4	15 ± 2	5 ± 2
Fibrinogen	225 ± 108	491 ± 164	784 ± 191	296 ± 106	589 ± 173	610 ± 196	284 ± 103
ESR (mm/h)	4 ± 1	14 ± 8	26 ± 3	6 ± 2	18 ± 9	28 ± 2	7 ± 3

When UC active vs UC remission and CD active vs CD remission are compared, $P < 0.001$ for ghrelin and fibrinogen, $P = 0.011$ for IGF-1, $P > 0.05$ for GH, $P = 0.044$ for CRP, and $P = 0.039$ for ESR

($r = 0.66$, $P < 0.001$), and CRP ($r = 0.48$, $P < 0.01$). Circulating ghrelin levels in CD were also positively correlated with sedimentation ($r = 0.45$, $P < 0.05$), fibrinogen ($r = 0.48$, $P < 0.05$), and CRP ($r = 0.48$, $P < 0.05$). When we attempted to determine whether there was a relationship between the ghrelin levels and inflammatory markers used for IBD, we found that ghrelin levels showed a statistically significant positive correlation with CRP, ESR, and fibrinogen levels and this correlation was more common and intense in the active IBD patients than in the cases in remission (Table 4).

Discussion

In our study we found the serum ghrelin levels to be similarly high in the healthy group, as well as the UC and CD patients. However, we determined that in both UC and CD patients, the ghrelin levels were statistically higher in those with active disease than in those in remission ($P < 0.001$). It was found that the higher ghrelin levels were accompanied by such activity markers as CRP, fibrinogen, and ESR and that there was a significant correlation between these markers and ghrelin level ($P < 0.01$).

In the literature, Lanzini et al. reported that in Celiac disease, there was a positive relationship between serum ghrelin levels and disease severity and inflammatory activity in the gastrointestinal mucosa [18]. In a recent report, Nishi et al. reported normal ghrelin levels in inactive CD patients [36]. Also, Perrachi et al. did not report any change of ghrelin levels in patients with inactive UC and CD, but Perrachi et al. did report high serum ghrelin levels in patients with UC and CD. They found positive correlation between serum ghrelin levels and disease activity, TNF-alpha, and serum CRP levels [20]. In

Table 4 The correlation results of ghrelin with disease activity markers and nutritional parameters

Correlation with ghrelin	UC total, $n = 34$	UC active, $n = 16$	UC remission, $n = 18$	CD total, $n = 25$	CD active, $n = 10$	CD remission, $n = 15$
IGF-1	−0.45**	−0.68**	−0.54*	−0.45*	−0.66*	−0.55*
CRP	0.48**	0.68**	0.53*	0.48*	0.66*	0.58*
Fibrinogen	0.66***	0.67**	0.61**	0.48*	0.70*	0.63*
ESR	0.44**	0.68**	0.65**	0.45*	0.65*	0.56*
Body weight (kg)	−0.47**	−0.67**	NS	−0.46*	−0.67*	NS
BMI (kg/m^2)	−0.47**	−0.66**	NS	−0.46*	−0.64*	NS
TSFT (mm)	−0.43*	−0.53*	−0.51*	−0.43*	−0.67*	−0.54*
MAC (cm)	−0.44**	−0.54*	−0.52*	−0.44*	−0.68*	−0.58*
Fat mass (%)	−0.46**	−0.69**	−0.58*	−0.58**	−0.65*	−0.58*
Fat mass (kg)	−0.45**	−0.69**	−0.56*	−0.45*	−0.64*	−0.59*
Fat free mass (%)	−0.47**	−0.50*	−0.58*	−0.50*	−0.69*	−0.60*
Fat free mass (kg)	−0.47**	−0.52*	−0.57*	−0.52**	−0.64*	−0.58*
Body liquid (l)	NS	NS	NS	NS	NS	NS

All of the values are given as Spearman's rho/significance

NS nonsignificant correlation

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

accordance with Perrachi et al., we found statistically high ghrelin levels in the patients with active disease compared with those in remission. We also found a positive correlation between disease severity and ghrelin levels. These results make it possible to ascertain that ghrelin is a marker that rises with disease activation and increases in relation to the mucosal inflammation observed in the active period of the disease.

Street et al. reported that IGF-1 levels showed an inverse correlation with some cytokines, such as IL-6, which are indicators of mucosal inflammation and activity markers in IBD patients [37]. Similarly, we found that IGF-1 levels showed an inverse correlation with activity markers in IBD patients. This result is in accordance with the findings by Eivindson et al. and Poykko et al. [29, 30].

It is known that there is an inverse relation between ghrelin level and nutritional status [14, 27, 38]. Kotidis et al. reported decreases in serum ghrelin levels after weight loss in obese patients [39]. In a previous report, Greenman et al. reported that ghrelin levels showed an inverse correlation with the BMI and anthropometric tests in determining nutritional status [40]. Our results are concordant with these results. We have found in our study that there is a statistically significant negative correlation between ghrelin levels and patient's nutritional status. We also found a negative correlation between ghrelin levels and IGF-1. IGF-1 levels showed a statistically positive correlation with nutritional status and a negative correlation with ghrelin levels. In the light of these results, we believe that ghrelin and IGF-1 could be one of the factors that play a role in malnutrition in these patients and IGF-1 and ghrelin levels are important in determining the nutritional status in IBD.

This study demonstrates that patients with active IBD have higher serum ghrelin levels than in patients in remission and high levels of circulating ghrelin correlate with the severity of disease and the activity markers (CRP, sedimentation, and fibrinogen). However, ghrelin levels in IBD patients shows an appositive correlation with IGF-1 and bioelectrical impedance analysis (BIA), body composition, and anthropometric assessments, which show the nutritional status of the body.

Finally, we concluded that ghrelin level may be important in determination of the activity in IBD patients and evaluation of nutritional status. This study is the first to investigate whether ghrelin level plays a role in disease activity and nutritional status in IBD patients.

References

1. Forbes A (2002) Review article: Crohn's disease; the role of nutritional therapy. Aliment Pharmacol Ther 16(Suppl 4):48–52
2. Goh J, O'Morain CA (2003) Review article: nutrition and adult inflammatory bowel disease. Aliment Pharmacol Ther 17:307–320
3. Tenore A, Berman WF, Parks JS, Bongiovanni AM (1977) Basal and stimulated serum growth hormone concentrations in inflammatory bowel disease. J Clin Endocrinol Metab 44:622–628
4. Ballinger AB, Camacho-Hübner C, Croft NM (2001) Growth failure and intestinal inflammation. QJM 94:121–125
5. Chong SK, Bartram C, Campbell CA, Williams CB, Blackshaw AJ, Walker-Smith JA (1982) Chronic inflammatory bowel disease in childhood. Br Med J 284:101–103
6. Juul A (2003) Serum levels of insulin-like growth factor I and its binding proteins in health and disease. Growth Horm IGF Res 13:113–170
7. Bannerjee K, Camacho-Hübner C, Babinska K, Dryhurst KM, Edwards R, Savage MO, Sanderson IR (2004) Anti-inflammatory and growth-stimulating effects precede nutritional restitution during enteral feeding in Crohn disease. J Pediatr Gastroenterol Nutr 38:270–275
8. Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T, Matsukura S, Kangawa K, Nakazato M (2000) Ghrelin, a novel growth hormone releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology 141:4255–4261
9. Murray CD, Kamm MA, Bloom SR, Emmanuel AV (2003) Ghrelin for the gastroenterologist: history and potential. Gastroenterology 125:1492–1502
10. Gale SM, Castracane VD, Mantzoros CS (2004) Energy homeostasis, obesity and eating disorders: recent advances in endocrinology. J Nutr 134:295–298
11. Ukkola O, Pöykkö S (2002) Ghrelin, growth and obesity. Ann Med 34:102–108
12. Nakagawa E, Nagaya N, Okumura H (2002) Hyperglycaemia suppresses the secretion of ghrelin, a novel growth hormone-releasing peptide: responses to the intravenous and oral administration of glucose. Clin Sci 103:325–328
13. Soriano-Guillen L, Barrios V, Campos-Barros A, Argente J (2004) Ghrelin levels in obesity and anorexia nervosa: effect of weight reduction or recuperation. J Pediatr 144:36–42
14. Nagaya N, Uematsu M, Kojima M, Date Y, Nakazato M, Okumura H, Hosoda H, Shimizu W, Yamagishi M, Oya H, Koh H, Yutani C, Kangawa K (2001) Elevated circulating level of ghrelin in cachexia associated with chronic heart failure: relationships between ghrelin and anabolic/catabolic factors. Circulation 104:2034–2038
15. Otto B, Cuntz U, Fruehauf E, Wawarta R, Folwaczny C, Riepl RL (2001) Weight gain decreases elevated plasma ghrelin concentrations of patients with anorexia nervosa. Eur J Endocrinol 145:669–673
16. Korbonits M, Goldstone AP, Gueorguiev M (2004) Ghrelin—a hormone with multiple functions. Front Neuroendocrinol 25:27–68
17. Chang L, Du JB, Gao LR, Pang YZ, Tang CS (2003) Effect of ghrelin on septic shock in rats. Acta Pharmacol Sin 24:45–49
18. Lanzini A, Magni P, Petroni ML, Motta M, Lanzarotto F, Villanacci V, Amato M, Mora A, Bertolazzi S, Benini F, Ricci C (2006) Circulating ghrelin level is increased in coeliac disease as in functional dyspepsia and reverts to normal during gluten-free diet. Aliment Pharmacol Ther 23(7):907–913
19. Peracchi M, Conte D, Terrani C (2003) Circulating ghrelin levels in celiac patients. Am J Gastroenterol 98:2474–2478
20. Peracchi M, Bardella MT, Caprioli F, Massironi S, Conte D, Valenti L, Ronchi C, Beck-Peccoz P, Arosio M, Piodi L (2006) Circulating ghrelin levels in patients with inflammatory bowel disease. Gut 55:432–433

21. Otero M, Nogueiras R, Lago F (2004) Chronic inflammation modulates ghrelin levels in humans and rats. Rheumatology 43:306–310
22. Nwokolo CU, Freshwater DA, O'Hare P, Randeva HS (2003) Plasma ghrelin following cure of *Helicobacter pylori*. Gut 52:637–640
23. Capristo E, Farnetti S, Mingrone G, Certo M, Greco AV, Addolorato G, Gasbarrini G (2005) Reduced plasma ghrelin concentration in celiac disease after gluten-free diet treatment. Scand J Gastroenterol 40(4):430–436
24. Suzuki H, Masaoka T, Hosoda H, Ota T, Minegishi Y, Nomura S (2004) Helicobacter pylori infection modifies gastric and plasma ghrelin dynamics in Mongolian gerbils. Gut 53:187–194
25. Yakar S, Kim H, Zhao H, Toyoshima Y, Pennisi P, Gavrilova O, LeRoith D (2005) The growth hormone-insulin like growth factor axis revisited: lessons from IGF-1 and IGF-1 receptor gene targeting. Pediatr Nephrol 20:251–254
26. Murch SH, Lamkin VA, Savage MO, Walker-Smith JA, MacDonald TT (1991) Serum concentrations of tumor necrosis factor alpha in childhood chronic inflammatory bowel disease. Gut 32:913–917
27. Karmiris K, Koutroubakis IE, Xidakis C, Polychronaki M, Voudouri T, Kouroumalis EA (2006) Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. Inflamm Bowel Dis 12:100–105
28. Katsanos KH, Tsatsoulis A, Christodoulou D, Challa A, Katsaraki A, Tsianos EV (2001) Reduced serum insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 levels in adults with inflammatory bowel disease. Growth Horm IGF Res 11(6):364–367
29. Eivindson M, Nielsen JN, Gronbak H, Flyvbjerg A, Hey H (2005) The insulin-like growth factor system and markers of inflammation in adult patients with inflammatory bowel disease. Horm Res 64:9–15
30. Poykko SM, Ukkola O, Kauma H, Kellokoski E, Horkko S, Kesaniemi YA (2005) The negative association between plasma ghrelin and IGF-I is modified by obesity, insulin resistance and type 2 diabetes. Diabetologia 48(2):309–316
31. Chanoine JP, Yeung LP, Wong AC, Birmingham CL (2002) Immunoreactive ghrelin in human cord blood: relation to anthropometry, leptin, and growth hormone. J Pediatr Gastroenterol Nutr 35:282–286
32. Lazarczyk MA, Lazarczyk M, Grzela T (2003) Ghrelin: a recently discovered gut-brain peptide. Int J Mol Med 12:279–287
33. Yis U, Ozturk Y, Buyukgebiz B (2005) Ghrelin; a new hormone for the regulation of energy metabolism. Cocuk Sagligi ve Hastaliklari Dergisi 48:196–201
34. Seo M, Okada M, Yao T, Ueki M, Arima S, Okumura M (1992) An index of disease activity in patients with ulcerative colitis. Am J Gastroenterol 87:971–976
35. Best WR, Becktel JM, Singleton JW et al (1976) Development of a Crohn's disease activity index: national cooperative Crohn's disease study. Gastroenterology 70:439–444
36. Nishi Y, Isomoto H, Ueno H, Ohnita K, Wen CY, Takeshima F, Mishima R, Nakazato M, Kohno S (2005) Plasma leptin and ghrelin concentrations in patients with Crohn's disease. World J Gastroenterol 11(46):7314–7317
37. Street ME, De'Angelis G, Camacho-Hübner C, Giovannelli G, Ziveri MA, Bacchini PL, Bernasconi S (2004) Relationships between serum IGF-1, IGFBP-2, interleukin-1 and interleukin-6 in inflammatory bowel disease. Horm Res 61:159–164
38. Cummings DE, Weigle DS, Frayo RS et al (2002) Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med 346:1623–1630
39. Kotidis EV, Koliakos GG, Baltzopoulos VG, Ioannidis KN, Yovos JG, Papavramidis ST (2006) Serum ghrelin, leptin and adiponectin levels before and after weight loss: comparison of three methods of treatment—a prospective study. Obes Surg 16:1425–1432
40. Greenman Y, Golani N, Gilad S, Yaron M, Limor R, Stern N (2004) Ghrelin secretion is modulated in a nutrient—and gender-specific manner. Clin Endocrinol 60:382–388