**Review article**

**Ghrelin and eating disorders**

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**Abstract**

**Background:** Ghrelin is a potent hormone with central and peripheral action. This hormone plays an important role in the regulation of appetite, food intake, and energy balance. Studies have suggested that ghrelin is involved with eating disorders (ED), particularly binging and purging. Genetic variants have also been studied to explain changes in eating behavior. **Methods:** We conducted a literature review; we searched PubMed, Scientific Electronic Library Online (SciELO), and LILACS databases using the keywords “eating disorder”, “ghrelin”, “polymorphism”, “anorexia nervosa”, “bulimia nervosa”, “binge eating disorder”, and their combinations. We found 319 articles. Thirty-nine articles met the inclusion criteria. **Results:** High levels of ghrelin were found in patients with anorexia nervosa (AN), especially in the purging subtype (AN-P). There was also a positive correlation between fasting ghrelin level and frequency of episodes of binging/purging in bulimia nervosa (BN) and the frequency of binging in periodic binge eating disorder (BED). Some polymorphisms were associated with AN and BN. **Conclusion:** Changes in ghrelin levels and its polymorphism may be involved in the pathogenesis of EDs; however, further studies should be conducted to clarify the associations.

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**Keywords:** Eating disorders, ghrelin, ghrelin receptors, single nucleotide polymorphism, genetics.

**Introduction**

Eating disorders (ED) are characterized by severe changes in eating behavior³⁻⁵. Anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED) are EDs known for their high morbidity and mortality affecting mostly adolescents and young adult females and can lead to major biological, psychological and social complications⁶⁻⁸. AN is characterized by intense fear of weight gain, severe food restriction, low body weight and a distorted perception of the body image. BN is characterized by episodes of binge eating (uncontrolled consumption of a large amount of food in a short period of time) followed by inappropriate compensatory behaviors aimed at preventing weight gain (such as: self-induced vomiting, abuse of laxatives, diuretics, amphetamines and/or excessive physical activity), these episodes must occur at least once per week for three months. Finally, BED is characterized by episodes of binge eating as described previously but without the use of compensatory methods, as frequently quoted in BN⁹⁻¹⁰.

Studies indicate a prevalence of ED ranging from 0.4% to 1.6%, with the highest frequency found in young women (between 18 and 32 years old)¹¹⁻¹³. In Brazil, there is still a scarce number of epidemiological studies involving ED, even if the number of these studies has increased in recent years⁸.

The etiology of an ED is complex and although widely studied, is still poorly understood. It is believed that the disease is multifactorial with a complex interaction of several factors: biological, psychological, sociocultural and family-related which are responsible for initiating and maintaining ED¹⁴⁻¹⁵. There is substantial evidence that genetic factors have up to an 80% stake in the etiology of AN¹⁶, however, little is known about the molecular mechanism of these cases¹⁷.

Most genetic studies on ED are focused on the investigation of candidate genes. Several genes that play an important role in appetite regulation and satiety are considered candidates and may be related to the development of ED¹⁸⁻¹⁹, but the results of these studies are still inconsistent¹⁹⁻²⁰.

One of the major hormones involved in the regulation of food intake is ghrelin. Although there are many neuropeptides that stimulate food intake, ghrelin is the most established orexigenic peptide known until now²¹.

**Methods**

We conducted a literature review to human studies in PubMed, Scientific Electronic Library Online (SciELO) and Lilacs databases, published between January 2000 and December 2014. The main keywords were used: “eating disorder” and “ghrelin”, and filtered the results to the terms: “anorexia nervosa”, “bulimia nervosa”, “binge eating disorder”, “polymorphism” and their combinations. The inclusion criteria were: 1) articles in English, Portuguese and Spanish; 2) articles that fully approached the topic ghrelin, eating disorders and their possible biological/genetic changes; 3) only studies in patients with diagnoses AN, BN and BED.

Three hundred and nineteen articles were found and only 39 contemplated these criteria (5 review articles, meta-analysis 1 and 33 experimental articles). Review articles and meta-analysis on the subject were consulted and cited in the discussion of this review, but for the presentation of data only original articles were used. We excluded studies in other languages and case reports as well, as articles that exclusively broached the topic obesity and ghrelin.

**Results**

The synthesis of these studies is presented in tables 1 and 2, sorted by month and year of publication. All data were taken from the original articles. To facilitate comparison we standardized the display of age and BMI and consider only one house after the comma without rounding.

**Ghrelin and the regulation of appetite**

The arcuate nucleus (ARC) of the hypothalamus and the brain stem are important regions involved in the regulation of appetite, body weight and energy balance²². The variety of hypothalamic appetite regulators are divided into two groups: The orexigenic types (appetite stimulators) which include the neuropeptide Y (NPY), the agouti-related peptide (AgRP), ghrelin, orexin and cannabinoids, while the anorectics (appetite suppressants) which include proopiomelanocortin (POMC), and cocaine and amphetamine regulated transcript (CART), thyrotropin releasing hormone (TRH), cortico-
Ghrelin releasing hormone (CRH), peptide YY (YY), cholecystokinin (CCK) and glucagon-like-peptide (GLP 1), among other.

Ghrelin is a peptide of 28 amino acids, synthesized mainly by the oxyntic glands of the stomach24. It is acylated in the third residue which is a serine, the introduction of fatty acid (n-octanoyl) is essential for its activity25.

It is one of the major signaling mechanisms for the start of the meal26. In humans, its concentration stays high during periods of fasting and periods that precede meals, falling soon after the start of food intake27,28.

It is also involved in stimulating the secretion of growth hormone (GH) via the endogenous ligand of the GH secretagogue receptor (GHS-R)29. There are two subtypes of receptors, GHS-R1a, which is active, and GHS-R1b, a smaller isoform, which apparently has no biological activity25. This receptor (GHS-R) is present in various tissues including the anterior hypophysis and the hypothalamus, and in other areas of the brain, such as the hippocampus and gray matter. Because of its location, it has been suggested that GHS-R can modulate biological rhythms, mood, memory, learning and appetite30.

Ghrelin is an orexigenic hormone that acts on the Central Nervous System (CNS) by activating the NPY/AgRP32 neurons in the ARC via the GHS-R receptor. Thus, it promotes the production and secretion of other orexigenic neuropeptides that suppress neuronal activity of the POMC/CART, while stimulating food intake33, this could lead to increased food intake27,28.

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Ghrelin in EDs

The role of ghrelin has been extensively investigated in the etiology of obesity and contrary to what was expected, plasma levels seem to have an inverse correlation with the body mass index (BMI)36-38. Studies have shown that ghrelin levels are lower in obese subjects as compared to control subjects39,40. One study noted that the decrease in ghrelin after the meal was lower in obese individuals compared to normal weight individuals40, and can thereby maintain the feeling of hunger. Studies with obese children also found low plasma ghrelin levels41-43 and when these children have reduced 50% of their BMI, ghrelin levels remained lower in comparison to control subjects41. The same finding was observed in obese adults who normalized their BMI44.

Studies conducted with AN patients found high levels of ghrelin in the plasma of these patients when compared with control of normal-weight individuals45-47 which may suggest that this change may be a supportive adaptive response to prolonged starvation48. Tolle et al. compared the levels of ghrelin plasma in 3 groups: healthy women considered thin (CT), who had a BMI similar to women with AN; patients with AN and women with normal weight (NW)49. It was demonstrated that ghrelin plasma concentrations in fasting patients with AN, was increased and remained high throughout the day (measured every 4 hours over a period of 24 hours) as compared to CT and NW. The study noted that these levels normalized after the patient gained the weight back, suggesting that in addition to body weight, levels of ghrelin may also be affected by the nutritional state51. Body fat instead of BMI has best explained changes in the levels of ghrelin52, some of the groups that did not contradict results between the correlation of BMI and ghrelin showed consistent results for body fat53. Studies have shown that ghrelin levels in patients with AN Restrictive (AN-R) have not been fully standardized, even after treatment55-56.

Differences in ghrelin levels between subtypes of AN have also been reported. Tanaka et al. in 2003 found higher plasma levels of ghrelin in patients with AN Purging (AN-P) than in AN-R46,47. In 2004, the group of Tanaka replicated their findings in a later study which included a third subgroup of AN, a subgroup that required emergency hospitalization; in this group the patients were unable to eat and had an extreme loss of weight. It showed that the emergency group had higher plasma levels of ghrelin than AN-P, and that AN-P still had levels greater than the AN-R levels. The three groups experienced a decrease in their plasma levels of ghrelin after treatment, but patients with AN-P still kept the plasma levels of ghrelin higher than the control group at the end of rehabilitation48. In 2005 Troisi et al., found higher levels of ghrelin during fasting in AN-R patients when compared to the AN-P patients51. However, the Troisi group compared data between patients with AN-P and BN, which probably had a higher BMI, which may explain the difference between the results of the two studies. There seems to be a relationship between ghrelin concentrations and patients with the compulsive/purging subtype for both AN (AN-P) and for BN52-53. However, this finding has still not reached a consensus, Monteleone et al. 200854 found no significant difference in the concentration of plasma ghrelin when fasting in groups with AN-R and AN-P. One explanation for these conflicting results is the method used to measure ghrelin and how it was performed, the preference for using plasma or serum can affect the levels obtained in different studies. The Monteleone study has confirmed this hypothesis; the study in 2008 obtained the result by screening for ghrelin plasma by way of the ELISA method (enzyme-linked immunosorbent assay). Whereas in 201048, in order to study patients with BN, they used the same test used by the group of Tanaka in 2003: the RIA (Radioimmunoassay) method and observed similar results, higher levels of ghrelin in these patients as compared to controls.

Tanaka et al. 200246 and Kojima et al. 200550 also observed elevated levels of fasting ghrelin in patients with BN. In addition, Tanaka in 2002 noted that ghrelin levels were negatively correlated with BMI and body fat percentage in both BN, as in the control group46. On the other hand, Nakazato et al. in 2004 found no significant difference between the levels of ghrelin plasma in patients with BN and the control group51. One possible explanation for this would be that Nakazato et al. 2004 measured ghrelin levels in the serum randomly.
between 11:00 am-12:00 pm (postprandially), unlike Tanaka et al. 2002 who measured when fasting. When Kojima in 2005 measured the pre-and postprandial ghrelin, it was noted that the decrease in postprandial ghrelin was significantly attenuated in women with BN compared to the control group\(^66,67\), generating a possible delay in the reduction of the hunger sensation in these patients.

Patients with BED tend to show a decrease in ghrelin when fasting\(^53,63,68\) and a lower postprandial decline compared to the obese control group\(^68\). This decrease in ghrelin does not seem to reduce the propensity to gain weight in BED patients. Low ghrelin levels were also found in obese patients and seem to be more related to a sub-regulation of the release of ghrelin in response to excess weight and a lower postprandial decline, possibly acting to maintain the hunger\(^21\).

A meta-analysis in 2009 found plasma concentrations in fasting and postprandial appetite hormones (gut hormones) in patients with AN, BN subtypes. It observed that in 8 studies analyzed, seven found elevated levels of plasma ghrelin in all diagnoses, with the exception of a single study\(^69\).

In conclusion, the studies suggest that the changes found in ghrelin may be more related to the behavior of the binging and purging\(^60\). However, for the time being, it is still not clear as per whether ghrelin fundamentally participates as an important factor in the etiology of the EDs\(^70\).

### Ghrelin and the genes

The human ghrelin gene (GHLR, Gene ID: 51738)\(^71\) which encodes ghrelin is located in the short arm of the chromosome 3 (3p25-26)\(^33\). Initially it was thought that it would have 4 exons (coding part of the gene), but subsequent studies have identified a number of additional exons in humans\(^72\). The precursor to ghrelin, the pre-proghrelin, is formed in the post-transcriptional process of GHLR, it consists of 518 pb encoded in a sequence of 117 amino acids, distributed over 23 amino acids of the signal peptide and 94 amino acids of pro-ghrelin, which include 28 amino acids of the mature ghrelin and over 66 additional amino acids\(^89\), which include 23 of obestatin (a hormone with the antagonistic characteristics of ghrelin, which suppresses appetite and stomach activity)\(^74\). Therefore, ghrelin and obestatin are encoded by the same precursor gene (Figure 2).

The gene of the receptor (GHS-R, Gene ID: 2693)\(^71\) was also located in the chromosome 3 (3q26-31)\(^31\). The gene consists of two exons separated by one intron (non-coding part of the gene) (Figure 3). The exon 1 encodes the I-V transmembrane regions and exon 2 encodes the regions VI and VII\(^75\). The GHS-R gene encodes two types of mRNA: GHS-R1a and GHS-R1b\(^73\). The GHS-R1a contains all 7 transmembrane regions and possess a high affinity with ghrelin, while the physiological role of GHS-R1b is not yet entirely clear\(^89\).

![Figure 2](image1.png)

**Figure 2.** The human ghrelin gene (GHLR), also called the pre-proghrelin gene and its products. The upper boxes represent the exons, while the numbers at the bottom represent the amino acids. Adapted from Liu et al. 2011\(^70\).

![Figure 3](image2.png)

**Figure 3.** The growth hormone secretagogue receptor gene (GHS-R) and single nucleotide polymorphisms (SNPs) that are most researched in this gene, accompanied by their identification numbers. Adapted from Liu et al. 2011\(^70\).
The gene of GOAT (MBOAT4; Gene ID: 619373) is located in the chromosome 8 (8p12) and is expressed mainly in the stomach, in the pancreas and in lower concentrations in the bones. This gene represents a new candidate gene in genetic research for investigating complex phenotypes (Figure 4).

In table 2 below, you can see some studies that investigated single nucleotide polymorphisms (SNPs) in the ghrelin gene, in individuals with a diagnosis of an ED. It is noticeable that the studies were still inconclusive when the GHRL gene is investigated, these studies show different positive and negative associations with different EDs diagnoses. However, when they analyzed the genes of the GHS-R and of the GOAT some studies have found a positive association between polymorphisms and the EDs. In this sense, only two studies have found a positive association between polymorphisms in the GHS-R and in the GOAT with BN and AN respectively, which is that of Miyasaka et al. 2006 and Muller et al. 2010.

**Figure 4.** The enzyme ghrelin O-acyltransferase gene (GOAT) and single nucleotide polymorphisms (SNPs) that are most researched in this chromosome, accompanied by their identification numbers. Adapted from Liu et al. 2011.

**Table 1.** Studies of ghrelin plasma in different ED diagnoses, ordered by month and year of publication

<table>
<thead>
<tr>
<th>Authors and year</th>
<th>Diagnoses studied</th>
<th>Hypotheses/ Objectives</th>
<th>Sample</th>
<th>Age years (mean ± SD)</th>
<th>BMI kg/ score (mean ± SD)</th>
<th>Measurement ghrelin</th>
<th>Collection of the blood sample</th>
<th>Main analyzes used statistics</th>
<th>Results</th>
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<tbody>
<tr>
<td>Ariyasu et al. 2001</td>
<td>AN and GP</td>
<td>To estimate the plasma ghrelin in humans, ghrelin -LI fasting and after the meals</td>
<td>N</td>
<td>33 GP 68,0 ± 4,0 23,3 ± 2,8</td>
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<td>RIA</td>
<td>Overnight fasting plasma</td>
<td>Student’s t-test, linear regression analysis</td>
<td>The concentration of ghrelin was higher in AN, found a negative correlation between ghrelin levels and BMI compared to female CO</td>
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<td>Otto et al. 2001</td>
<td>AN</td>
<td>Investigate the involvement of ghrelin in the pathogenesis of EDs, analyze circulating levels of ghrelin and its possible correlations with clinical parameters before and after weight gain</td>
<td>N</td>
<td>36 AN 25,0 ± 1,0 DNS</td>
<td>20,7 ± 0,3 (20,4 ± 0,4 female)</td>
<td>RIA</td>
<td>Overnight fasting plasma</td>
<td>DNS</td>
<td>The concentration of plasma ghrelin was higher in AN, after partial improvement, there was a decrease in circulating ghrelin (25%). Negative correlation with Delta BMI</td>
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<td>Shiiya et al. 2002</td>
<td>OB, AN and DM2</td>
<td>Research on ghrelin in metabolic balance, measurement of plasma ghrelin responses in plasma ghrelin in CO and DM2 and investigation of 24 hours of circulating ghrelin profile</td>
<td>N</td>
<td>17 AN 22,2 ± 2,3 14,2 ± 0,5</td>
<td></td>
<td>RIA</td>
<td>Fasting plasma and postprandial (0, 30, 10, 15, 30, 60 and 120 min)</td>
<td>ANOVA, post hoc Fisher’s test, linear regression analysis</td>
<td>The concentration of plasma ghrelin was high in the AN, and low in BN, it was negatively correlated with BMI</td>
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<tr>
<td>Tanaka et al. 2002</td>
<td>BN</td>
<td>Concentration of plasma ghrelin fasting will be increased in the BN or show some specificity regarding the pathology</td>
<td>N</td>
<td>15 BN 23,3 ± 5,3 20,0 ± 2,9</td>
<td></td>
<td>RIA</td>
<td>Overnight fasting plasma</td>
<td>Student’s t-test, linear regression analysis</td>
<td>The concentration of ghrelin was greater in BN. Ghrelin fasting was negatively correlated with BMI and % body fat</td>
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<tr>
<td>Authors and year</td>
<td>Diagnoses studied</td>
<td>Hypotheses/ Objectives</td>
<td>Sample</td>
<td>Age years (mean ± SD)</td>
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<td>Measurement ghrelin</td>
<td>Collection of the blood sample</td>
<td>Main analyzes used statistics</td>
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<tr>
<td>Tolle et al. 2003a&lt;sup&gt;51&lt;/sup&gt;</td>
<td>AN</td>
<td>Measuring plasma levels of ghrelin in the AN before and after renutrition in women CT and CO</td>
<td>N</td>
<td>9 AN</td>
<td>17.2 ± 0.9</td>
<td>14.6 ± 0.4</td>
<td>RIA</td>
<td>Fasting plasma and postprandial (hours: 800, 1200, 1600, 2000, 2400 and 400 h)</td>
<td>ANOVA, t-test</td>
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<td>7 CT</td>
<td>23.3 ± 3.1</td>
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<td>10 CO</td>
<td>23.2 ± 1.1</td>
<td>21.5 ± 0.7</td>
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<tr>
<td>Tanaka et al. 2003b&lt;sup&gt;51&lt;/sup&gt;</td>
<td>AN</td>
<td>The presence and frequency of purging behaviors can influence the levels of ghrelin</td>
<td>N</td>
<td>21 AN-R</td>
<td>21.8 ± 8.9</td>
<td>13.9 ± 1.9</td>
<td>RIA</td>
<td>Overnight fasting plasma</td>
<td>Linear regression analysis, ANOVA, post-hoc Fisher’s test</td>
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<td>19 AN-P</td>
<td>24.6 ± 5.5</td>
<td>14.4 ± 2.1</td>
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<td>18 BN-P</td>
<td>22.7 ± 5.0</td>
<td>20.0 ± 2.1</td>
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<td>13 BN-NP</td>
<td>22.7 ± 6.5</td>
<td>21.2 ± 3.9</td>
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<td>15 CO</td>
<td>22.1 ± 3.4</td>
<td>21.4 ± 11.0</td>
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<tr>
<td>Nedvidkova et al. 2003&lt;sup&gt;50&lt;/sup&gt;</td>
<td>AN</td>
<td>Study the response of plasma ghrelin, to food intake, meal volume and nutritional value</td>
<td>N</td>
<td>5 AN</td>
<td>24.3 ± 2.6</td>
<td>15.2 ± 1.5</td>
<td>RIA</td>
<td>Fasting plasma and postprandial (30, 60, 90, 120 min)</td>
<td>Unpaired t-test, Mann-Whitney rank Test, correlations Spearman’s, ANOVA, Dunnet’s test</td>
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<td>6 CO</td>
<td>22.9 ± 4.7</td>
<td>21.6 ± 1.2</td>
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<tr>
<td>Tanaka et al. 2003b&lt;sup&gt;51&lt;/sup&gt;</td>
<td>AN</td>
<td>Measure plasma concentrations of ghrelin between subtypes of AN</td>
<td>N</td>
<td>19 AN-R</td>
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<td>13.6 ± 1.5</td>
<td>RIA</td>
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<td>Linear regression analysis, ANOVA, post-hoc Scheffe’s test</td>
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<td>11 CO</td>
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<td>Monteleone et al. 2003&lt;sup&gt;51&lt;/sup&gt;</td>
<td>BN</td>
<td>Study of ghrelin and leptin responses meals in BN and CO</td>
<td>N</td>
<td>9 BN-P</td>
<td>24.2 ± 2.3</td>
<td>21.7 ± 3.4</td>
<td>RIA</td>
<td>Fasting plasma and postprandial (0, 45, 60, 90, 120 and 180 min)</td>
<td>ANOVA, 2-way ANOVA with repeated measures post-hoc Turkey’s, correlation Pearson’s</td>
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<td>12 CO</td>
<td>24.5 ± 2.6</td>
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<tr>
<td>Tanaka et al. 2003c&lt;sup&gt;51&lt;/sup&gt;</td>
<td>AN</td>
<td>The differences in eating behavior can influence the secretion of ghrelin and insulin in AN</td>
<td>N</td>
<td>11 AN-R</td>
<td>18.5 ± 1.4</td>
<td>13.3 ± 0.4</td>
<td>RIA</td>
<td>Fasting plasma and postprandial (0, 30, 60, 120 and 180 min)</td>
<td>ANOVA, post-hoc Scheffe’s test, Kruskal–Wallis chi-square statistic</td>
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<td>9 AN-P</td>
<td>20.9 ± 1.4</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Soriano-Guillen et al. 2004a</td>
<td>OBCH, AD and AN</td>
<td>To investigate the role of ghrelin in the EDS analysis of baseline ghrelin level in OBCH and AN and the weight loss effect</td>
<td>N</td>
<td>26 OBCH 8.0 ± 1.3 16 AN 17.0 ± 1.6</td>
<td>21 CH 6.3 ± 3.0 20 AD 17.2 ± 0.4</td>
<td>RIA</td>
<td>Overnight fasting plasma</td>
<td>Student’s t test, ANOVA with repeated measures, post-hoc Scheffe’s test, correlation analysis</td>
<td>Ghrelin levels were decreased in OBCH and not normalized after weight reduction. Also found increased levels in AN</td>
</tr>
<tr>
<td>Misra et al. 2004a</td>
<td>AN</td>
<td>Ghrelin values may be higher in AN than in healthy adolescents</td>
<td>N</td>
<td>19 AN-R 16.1 ± 1.1</td>
<td>20 CO 15.4 ± 1.8</td>
<td>RIA</td>
<td>Overnight fasting plasma</td>
<td>Student’s t-test, Wilcoxon’s test, chi-square statistic</td>
<td>Ghrelin levels were higher and decreased postprandially ghrelin was also high in AN-R</td>
</tr>
<tr>
<td>Nakazato et al. 2004a</td>
<td>BN</td>
<td>Determination of serum ghrelin levels and compare with the BDNF reported in a previous article</td>
<td>N</td>
<td>18 BN (BN-P e BN-NP) 21.6 ± 4.0</td>
<td>21 CO 21.4 ± 1.7</td>
<td>EIA</td>
<td>Postprandial (11:00-12:00 am)</td>
<td>Student’s t-test, Mann-Whitney, correlation Pearson’s</td>
<td>There was no significant correlation between the levels of ghrelin and BDNF</td>
</tr>
<tr>
<td>Tanaka et al. 2004a</td>
<td>AN</td>
<td>Measuring ghrelin and GH in AN during treatment to evaluate the effect of nutritional rehabilitation of these substances in</td>
<td>N</td>
<td>7 AN-E 18.1 ± 1.2 14 AN-R 18.4 ± 1.3 13 AN-P 25.0 ± 1.3</td>
<td>9 CO 21.5 ± 0.9</td>
<td>RIA</td>
<td>Fasting plasma</td>
<td>Linear regression analysis, ANOVA, post-hoc Scheffés, Kruskal-Wallis, chi-square statistic</td>
<td>The fasting ghrelin was found too high in AN-E group, and the high in AN-P and AN-R before treatment. It remained high in AN-R during the treatment and after the treatment it maintained high only in the AN-P group. The concentration of ghrelin was negatively correlated with BMI before and during treatment</td>
</tr>
<tr>
<td>Kojima et al. 2005a</td>
<td>BN</td>
<td>To investigate the changes in plasma ghrelin and PYY postprandial after the meal in the BN and CO</td>
<td>N</td>
<td>10 BN-P 24.7 ± 1.5</td>
<td>12 CO 24.6 ± 0.8</td>
<td>RIA</td>
<td>Overnight fasting plasma and postprandial (0, 30, 60, 120 and 180 min)</td>
<td>Student’s t-test, ANOVA with repeated measures, correlation Pearson’s</td>
<td>Concentration of plasma ghrelin was high in the BN and remained high after the meal</td>
</tr>
<tr>
<td>Monteleone et al. 2005a</td>
<td>BN, BED and OB</td>
<td>To investigate the changes of plasma ghrelin in EDs</td>
<td>N</td>
<td>13 BED NO 26.9 ± 8.0 34 BED OB 33.6 ± 9.1 56 BN-P 23.4 ± 4.3</td>
<td>28 OB 38.4 ± 14.1 51 CO 22.6 ± 3.1</td>
<td>RIA</td>
<td>Overnight fasting plasma</td>
<td>Kruskal-Wallis, Mann-Whitney, correlations Spearman’s</td>
<td>Plasma ghrelin reduced in BED and OB, but found no changes in BN. Ghrelin was negatively correlated with body weight, BMI and body fat in all sample</td>
</tr>
<tr>
<td>Monteleone et al. 2005a</td>
<td>BN</td>
<td>Investigate the total PYY and ghrelin responses after a high fat meal in BN and CO</td>
<td>N</td>
<td>9 BN-P 24.5 ± 2.6</td>
<td>10 CO 24.2 ± 3.9</td>
<td>RIA</td>
<td>Fasting plasma and postprandial (0, 45, 60, 90, 120 and 180 min)</td>
<td>ANOVA, 2-way ANOVA with repeated measures, post hoc Turkey, multiple regression analysis</td>
<td>There was no difference in the concentration of ghrelin fasting. The postprandial ghrelin remained higher in BN</td>
</tr>
</tbody>
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<tr>
<td>Stock et al. 2005&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AN and OB</td>
<td>PYY may be higher in AN and the response of PYY, ghrelin, GIP and satiety to mixed meals can be impaired in AN and obesity</td>
<td>N</td>
<td>10 AN</td>
<td>16.5 ± 0.4</td>
<td>16.3 ± 0.4</td>
<td>Fasting plasma and postprandial (15, 60, 90, 120, 180 and 240 min)</td>
<td>ANOVA, post-hoc Bonferroni, correlation, Wald test, correlation Pearson’s</td>
</tr>
<tr>
<td>Geliebter et al. 2005&lt;sup&gt;a&lt;/sup&gt;</td>
<td>BED and SBED</td>
<td>BED patients have higher levels of postprandial ghrelin, as a gastric emptying rate slower and less that the postprandial CCK than CO</td>
<td>N</td>
<td>11 BED</td>
<td>29.0 ± 8.4</td>
<td>36.6 ± 6.2</td>
<td>Overnight fasting plasma and postprandial (-15, 0, 5, 15, 30, 60, 120 min)</td>
<td>GLM, post-hoc Turkey’s</td>
</tr>
<tr>
<td>Otto et al. 2005&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AN</td>
<td>To investigate the suppression of postprandial ghrelin in AN during weight gain</td>
<td>N</td>
<td>20 AN</td>
<td>25.6 ± 1.0</td>
<td>15.1 ± 0.3</td>
<td>Overnight fasting plasma and postprandial (20 and 60 min)</td>
<td>ANOVA of repeated measurement, Wilcoxon test</td>
</tr>
<tr>
<td>Troisi et al. 2005&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AN, BN and BED</td>
<td>To investigate the relationship between plasma ghrelin, cortisol, thyroid hormones and dietary patterns of AN, BN and BED. Analyzing the groups To by the criterion of bingeing and purging</td>
<td>N</td>
<td>13 AN-R</td>
<td>26.6 ± 6.7</td>
<td>15.9 ± 2.3</td>
<td>Overnight fasting plasma</td>
<td>ANOVA, Student’s t-test, post-hoc Sheffe, Stepwise’s regression</td>
</tr>
<tr>
<td>Janas-Kozik et al. 2007&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AN</td>
<td>To investigate the involvement of the AN dysfunction during treatment of ghrelin</td>
<td>N</td>
<td>30 AN-R</td>
<td>18.0 ± 2.0</td>
<td>15.1 ± 1.4</td>
<td>Fasting plasma</td>
<td>Student’s t-test and Spearman’s correlation</td>
</tr>
<tr>
<td>Nakahara et al. 2007&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AN</td>
<td>Measure ghrelin, PYY3-36, glucose and insulin after a meal to evaluate the effect of nutritional status in AN during hospitalization</td>
<td>N</td>
<td>14 AN-R</td>
<td>24.6 ± 6.0</td>
<td>12.4 ± 1.7</td>
<td>Overnight fasting plasma and postprandial (0, 30, 60, 120 and 180 min)</td>
<td>ANOVA and post-hoc Sheffe, 2-way ANOVA with repeated measures</td>
</tr>
<tr>
<td>Monteleone et al. 2008&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AN and BN</td>
<td>Measure circulating levels of ghrelin/obestatin and evaluating its relationship with anthropometric and clinical measures in BN, AN and CO</td>
<td>N</td>
<td>21 AN (AN-R e AN-P)</td>
<td>23.4 ± 7.5</td>
<td>16.6 ± 1.6</td>
<td>Overnight fasting plasma</td>
<td>Shapiro Wilk normality test, ANOVA, Pearson’s correlation</td>
</tr>
</tbody>
</table>
### Table 2. Studies of candidate genes for polymorphisms in the ghrelin gene (GHRL), the ghrelin O-acyltransferase (GOAT) and the GH secretagogue receptor (GHS-R) in EDs diagnoses

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<tr>
<td>Monteleone et al. 2010&lt;sup&gt;44&lt;/sup&gt;</td>
<td>BN</td>
<td>To investigate the ghrelin response in &quot;misleading&quot; feedback on BN and CO</td>
<td>6 BN-P</td>
<td>N</td>
<td>6 BN-P</td>
<td>DNS</td>
<td>DNS</td>
<td>Fasting plasma and postprandially (0, 15, 30, 45, 90 and 120 min)</td>
<td>ANOVA, 2-way ANOVA with repeated measures and post-hoc Turkey’s, Pearson’s correlation</td>
</tr>
<tr>
<td>Terra et al. 2013&lt;sup&gt;33&lt;/sup&gt;</td>
<td>AN</td>
<td>Studying levels of circulating adipocytokines in AN and CO</td>
<td>28 AN-R</td>
<td>27.4 ± 1.4</td>
<td>16.8 ± 0.2</td>
<td>ELISA</td>
<td>Overnight fasting plasma</td>
<td>Student’s t-test, Pearson’s correlation, linear regression analysis</td>
<td>There was no difference in the concentration of ghrelin fasting. Negative correlation with BMI and the plasma ghrelin in AN-R after treatment.</td>
</tr>
</tbody>
</table>

AD: adolescents; AN: anorexia nervosa; AN-E: anorexia nervosa with emergent hospitalization; AN-P: anorexia nervosa purging type; AN-R: anorexia nervosa restrictive type; ANOVA: analysis of variance (one-way); BED: binge eating disorder; BN: bulimia nervosa; BN-P: bulimia nervosa purging type; BN-NP: bulimia nervosa nonpurging type; BDTD: brain-derived neurotrophic factor; BMI: body mass index; CCK: cholecystokinin; CH: Childs; CO: controls; CT: constitutionally thin subjects; DM: diabetes mellitus; DM2: type 2 diabetes mellitus; DNS: data had not shown; ED: eating disorder; EIA: enzyme immunoassay; EDNOS: eating disorder not otherwise specified; ELISA: enzyme-linked immunosorbent assay; GH: growth hormone; GHRL-Leu72Met, GHRL-Gln90Leu, GHRL-Arg51Gln, 3056 T>C, 1086 A>G, 529 A>G, 31 AN-P, 27 AN-R | GIP: gastric inhibitory polypeptide; GLM: generalized linear model; GP: gastrectomized patients; NO: non-obese patients; OB: obese patients without eating disorders; OBCH: obese children without eating disorders; PYY: peptide YY; RIA: radioimmunoassay; SD: BMI curves above Spanish standards; SBD: subthreshold binge eating disorder. |
Conclusion

In recent years, ghrelin has been an object of study in the EDs, but we haven’t had any clear conclusions about its role in these pathologies. Genetic research could bring a different perspective and provide a new direction for research.

The studies suggest that some polymorphisms in the ghrelin gene, mainly in the genes of GHS-R and the GOAT, may be involved in the pathogenesis of the EDs and possibly related to the behavior of binge eating and purging. However, this is a case of only two studies, further work should be conducted with larger samples addressing the need to compare the polymorphisms found between the three main types of eating disorders (AN, BN and BED) in order for greater clarity in the associations.

Acknowledgments

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References

29. Kindler et al. 2011™


