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Ghrelin and Eating Disorders

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Abstract

There is growing evidence supporting a multifactorial etiology that includes genetic, neurochemical, and physiological components for eating disorders above and beyond the more conventional theories based on psychological and sociocultural factors. Ghrelin is one of the key gut signals associated with appetite, and the only known circulating hormone that triggers a positive energy balance by stimulating food intake. This review summarizes recent findings and several conflicting reports on ghrelin in eating disorders. Understanding these findings and inconsistencies may help in developing new methods to prevent and treat patients with these disorders.

Keywords

Ghrelin; Anorexia Nervosa; Bulimia Nervosa; Binge Eating Disorder; Des-acyl Ghrelin

1. Introduction

There is now some reassuring evidence that the prevalence for anorexia nervosa (AN) has remained stable and that the prevalence has actually decreased for bulimia nervosa over the past decades (Smink et al., 2012). However, the associated mortality rate of eating disorders (EDs) particularly AN, as well as the comorbidities with other psychiatric disorders (e.g., OCD) (Altman and Shankman, 2009) and mood states (e.g., depression, anxiety) (McElroy et al., 2010) have encouraged researchers to investigate the underlying pathology of EDs. Contrary to the popular view that EDs are due solely due to psychological and sociocultural factors, new research has implicated genetic, neurochemical, and physiological substrates (Frank et al., 2005; Helder and Collier, 2011; Kaye et al., 2011; Scherag et al., 2010). Changes in hormones involved in energy balance and food intake via the neurohumoral axis may also be associated with or contribute to EDs (Prince et al., 2009; Tong and D'Alessio, 2011).

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One of the key hormones involved with appetite and food intake is ghrelin. Although there are several neuropeptides stimulating food intake, ghrelin is the only established orexigenic gut peptide to date. Its circulating levels increase during fasting and decrease following a meal (Erlanson-Albertsson, 2005). In 1996, Howard et al. cloned a G protein-coupled seven-transmembrane receptor of the rat and human pituitary gland and hypothalamus that can trigger growth hormone (GH) release (Howard et al., 1996) when bound to a ligand. The endogenous ligand for this receptor, however, was not known until 1999 (Kojima et al., 1999); when ghrelin, a 28-amino-acid peptide hormone, was confirmed to bind to the growth hormone secretagogue receptor-1A (GHS-R1A). At present, ghrelin's role in EDs has not been well elucidated, but new data suggest a link. Differences in basal fasting levels and/or meal-stimulated (postprandial) ghrelin levels have been reported in individuals with EDs (vs. normal). To improve our understanding of the neurohumoral aspects of ED's, we will review the relevant research on ghrelin associated with EDs.

2. Ghrelin Gene-Derived Products

Ghrelin is first cleaved from the 94 amino-acid preproghrelin polypeptide at the N-terminal by the prohormone convertase 1/3 (PC 1/3). A hydroxyl group of the third-N terminal amino-acid serine (Ser3) residue of the proghrelin peptide is then esterified by an octanoic acid to form acyl ghrelin. It has been discovered that ghrelin O-acyl-transferase (GOAT) enzyme is responsible for the octanoylation of the proghrelin peptide (Yang et al., 2008). In addition to GOAT and PC 1/3, several lines of evidence also suggest that prohormone convertase 2 (PC2) and furin proteases may be involved in the post-translational processing of the preproghrelin protein (Zhang et al., 2005). This post-translational octanoyl modification is required for the biological activity of ghrelin (Hosoda et al., 2000). In contrast, the non-octanoylated form, in which the acylation of Ser3 does not occur, is known as the des-acyl form of ghrelin. Ser3 acylation is necessary for the GHS-R1A binding, thus, des-acyl ghrelin cannot bind to GHS-R1A and mediates its actions via alternate receptors which have yet to be determined (Leite-Moreira and Soares, 2007).

The human ghrelin gene on chromosome 3p25-26 encodes a 117-amino-acid preproghrelin protein (Gualillo et al., 2006) that undergoes post-translational modifications to generate the two major molecular forms of ghrelin; octanoylated (acyl) which comprises <10% of circulating ghrelin, and des-*n*-octanoyl (des-acyl) ghrelin, which have different, and perhaps opposing functions in relation to energy homeostasis (Toshinai et al., 2006; Zhang et al., 2005). Although the des-acyl form of ghrelin comprises more than 90% of the total ghrelin released (Hosoda et al., 2000; Leite-Moreira and Soares, 2007), the acyl form activates the GHS-R1A to regulate several metabolic processes (Kojima et al., 1999) and promote food intake.

Des-acyl ghrelin, despite having the same precursor as acyl ghrelin, when administered intracerebroventricularly (ICV), has a tendency to decrease food intake and gastric emptying rate by acting on the paraventricular nucleus and the arcuate nucleus in the hypothalamus (Arc) in mice (Asakawa et al., 2005). Asakawa et al. (2005) also showed that mice overexpressing des-acyl ghrelin exhibited a decrease in food intake, body weight, fat pad mass, and linear growth. However, Toshinai et al. (2006) showed that during the light phase, des-acyl ghrelin stimulates feeding although to a lesser degree than total ghrelin, by activation of orexin neurons in the lateral hypothalamus in rodents (Toshinai et al., 2006). This difference may be due to the injection sites used by the two groups. Asakawa et al.'s (2005) administered des-acyl ghrelin into the third cerebral ventricle whereas Toshinai et al. (2006) injected into the lateral cerebral ventricles. Moreover, no change in food intake occurred when des-acyl ghrelin was injected peripherally [intravenous] in Toshinai et al.

(2006) whereas Asakawa et al. (2005) peripheral injections [intraperitoneal] decreased food intake.

Recently, obestatin, a 23-amino-acid peptide (as opposed to 28-amino-acid peptide ghrelin), was discovered at the preproghrelin C-terminal and found to originate from post-translational processing of the preproghrelin peptide in a similar manner as ghrelin (Zhang et al., 2005). Obestatin was originally shown to have opposing action to acyl ghrelin, as cerebroventricular and peripheral injections of obestatin appeared to reduce food intake and weight in animals (Zhang et al., 2005). However, a number of investigators were unable to replicate these findings, and some found evidence opposite to its putative anorexigenic function (De Smet et al., 2007; Depoortere et al., 2008; Gourcerol et al., 2006; Gourcerol and Tache, 2007; Kobelt et al., 2008; Mondal et al., 2008; Nogueiras et al., 2007; Samson et al., 2007; Tremblay et al., 2007; Yamamoto et al., 2007). Moreover, some published in vitro results on obestatin have been retracted because of the replication and inconsistency issues (Chartrel et al., 2007; Lagaud et al., 2007; Zhang et al., 2005). Furthermore, Qader et al. (2008) reported that acyl ghrelin and obestatin both similarly stimulate glucagon secretion and inhibit pancreatic polypeptide secretion in rodents. However, more recently after a 24h fast, albino ICR-CD1 mice had increased plasma levels of total ghrelin and obestatin with no change in preproghrelin mRNA levels and proghrelin -derived peptide secretion (Morash et al., 2010). In contrast, same study also showed that another strain, C57BL/6 mice -which have lower body weight and daily food intake than CD1 (Bachmanov et al., 2002; Atalayer and Rowland, 2009) had increased proghrelin mRNA expression, stomach acyl ghrelin peptide, and no change in plasma obestatin after a 24 h fast (Morash et al., 2010). Moreover ICV injection of obestatin did not change the 2h rate of gastric emptying of a solid nutrient meal in rats (Chen et al 2012).

Since its discovery in 1999 by Kojima et al, ghrelin has been the focus of energy homeostasis and related clinical research. In addition to its main role in energy balance via the hypothalamus, ghrelin stimulation of the pituitary gland has been implicated in a number of biological processes, including immune function (Dixit et al., 2009; Nikolopoulos et al., 2010), hormone secretion (Egido et al., 2002; Messini et al., 2011), bone physiology (Kojima and Kangawa, 2005; Pemberton and Richards, 2008), memory retention (Carlini et al., 2002), cardiovascular function (Iglesias et al., 2007; Nagaya et al., 2001), and facilitation of digestion by increasing gastric acid production, gastric motility, and emptying (Bloomgarden, 2007; Levin et al., 2005). In the next sections, we will focus on the role of ghrelin as related to food intake, energy homeostasis, and appetite, which will underscore the relevance of ghrelin to eating disorder research.

3. The Role of Ghrelin in Appetite and Body Weight Regulation

Ghrelin has been shown to be a major orexigenic and adipogenic hormone, produced mainly in the gastrointestinal tract by the endocrine X/A-cells of the oxyntic glands of the mucosa and released to the blood stream (Choi et al., 2003; Sakata et al., 2009; Thompson et al., 2004). Although all the stimuli for ghrelin release have yet to be determined, numerous studies have shown circadian fluctuation in plasma ghrelin levels, with distinct increases before food intake, and rapid reductions after meals in both animals and humans. Studies have also shown that ghrelin is produced predominantly by the stomach, where its expression is highest (Kojima et al., 1999) and to a much lesser degree, in the hypothalamus (i.e. Arc and infundibular nucleus) and the pituitary gland (Howard et al, 1996).

Ghrelin also has central action following direct synthesis within the hypothalamus (De Vriese and Delporte, 2008; Wren et al., 2001). After its release into the blood stream, ghrelin reaches the Arc by crossing the blood-brain barrier and activates neuropeptide Y and

agouti-related peptide-containing neurons (Guan et al., 2010). The stimulation of the Arc, has been shown to increase food intake (Berthoud, 2002) by increasing the number of meals rather than meal size (Chen et al., 2004; Murphy and Bloom, 2006). Another mechanism of a peripheral action via the vagal afferents as ghrelin receptors have been found on dorsal vagal complex (Holst and Schwartz, 2004). Additional ghrelin and growth hormone secretagogue receptors have been found in various peripheral organs (e.g. adrenal glands, pancreas, kidneys etc. (Date et al., 2000; Gnanapavan et al., 2002; van der Lely et al., 2004). Intravenous injections of acyl ghrelin increase appetite and food intake in humans. In a randomized double-blind cross-over study, Wren et al. (2001) reported a 28% dose-dependent increase in food intake in healthy adults (N=9) following serial intravenous ghrelin (vs. saline) infusions. Also, although the congenital deletions of gene for either ghrelin or its receptor have been shown to fail to decrease food intake (Sun et al., 2003), they resulted in diet-induced obesity-resistant phenotypes in mice (Wortley et al., 2005; Zigman et al., 2005) which supports ghrelin's orexigenic role. Normal mice fed with a valine-deficient diet that induced severe anorexia (80% lower-than-average food intake), developed a significant hyperghrelinemia (Goto et al., 2010). Thus, ghrelin levels may be affected by the eating habits and/or depleted energy stores. Moreover, subcutaneous infusions of an agent that blocks ghrelin mediated activation of GHS-R1A in vivo was shown to promote weight loss in diet-induced obese mice (Shearman et al., 2006).

Administering ghrelin intracerebroventricularly in a dose-dependent manner has been shown to promote food intake and increase body weight more than peripheral ghrelin injections in both humans and rodents (Faulconbridge et al., 2003; Tschop et al., 2000). Unilateral injections of ghrelin into the dorsal vagal complex also induced hyperphagia in mice (Faulconbridge et al., 2003). Moreover, ghrelin's central nervous system (CNS) role has been linked to the reward-related aspect of eating behavior, as ghrelin stimulates dopamine neurons in the ventral tegmental area (VTA) and promotes dopamine turnover in the nucleus accumbens of the ventral striatum (Jerlhag et al., 2007), part of the major central reward pathway. Antagonism of ghrelin receptors in the VTA in mice decreased food intake (Jerlhag et al., 2007). Thus, ghrelin's effect on reward processing in the mesolimbic dopamine system may also contribute to its orexigenic action (Abizaid et al., 2006; Malik et al., 2008) in addition to its homeostatic energy balance role. Overall, these findings indicate that a key action for ghrelin is in the hypothalamic regulation of energy balance, which is a CNS mechanism.

As noted, plasma ghrelin levels rise prior to meals and decline rapidly postprandially (Carlson et al., 2009; English et al., 2002; Zwirski-Korczala et al., 2007), suggesting a role in preprandial hunger and meal initiation (Cummings et al., 2001). Moreover, postprandial suppression has been shown to be proportional to the caloric content of the meal (Callahan et al., 2004). The majority of studies examining ghrelin levels after Roux-en-Y-gastric bypass (RYGB) -a highly effective surgical intervention for obesity, show a decrease in postsurgical circulating ghrelin levels (Foschi et al., 2008; Fruhbeck et al., 2004; Garcia de la Torre et al., 2008; Lin et al., 2004; Morinigo et al., 2004). However, other results have also been found, such as an increase (Pardina et al., 2009; Sundbom et al., 2007; Vendrell et al., 2004) as well as no change following RYGB (Korner et al., 2009; Whitson et al., 2007), and higher ghrelin concentrations following gastric banding (Fruhbeck et al., 2004; Nijhuis et al., 2004; Schindler et al., 2004).

Conditions of higher energy stores (e.g., hyperglycemia, insulin resistance, obesity), on the other hand, are associated with lower ghrelin concentrations (Shiia et al., 2002; Tschop et al., 2001). Obese individuals have lower fasting plasma ghrelin levels than their lean counterparts (Shiia et al., 2002; Tschop et al., 2001). Despite this, the reduced ghrelin levels in overweight, obese, and insulin-resistant individuals do not appear to dampen their

propensity to gain weight. The lower fasting ghrelin levels in obesity suggest a down-regulation of ghrelin in response to overeating or to excess body weight. Higher ghrelin levels, on the other hand, have been observed during periods of fasting, hunger, or other conditions associated with lower energy stores, such as short-term starvation, cancer cachexia, as well as anorexia nervosa (Bloomgarden, 2007). These findings collectively demonstrate ghrelin's role as an orexigenic hormone involved in energy homeostasis and body weight regulation. Ghrelin's importance in eating behavior suggests a potential role in disordered eating behavior.

4. The Role of Ghrelin in Eating Disorders

According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM IV-TR1), EDs may be categorized as anorexia nervosa (AN), bulimia nervosa (BN), and eating disorders not otherwise specified (EDNOS) (e.g., binge-eating disorder [BED], night-eating syndrome [NES]). Common features of EDs include aberrant eating patterns and excessive concern about body shape or weight. Although EDs have a multifactorial etiology and are commonly associated with psychological factors, we selectively describe recent findings concerning ghrelin levels in EDs, while acknowledging several contradictory findings (Table 1). In addition, we will summarize various reports on the genetic aspects of the association between ghrelin and EDs (Ando et al., 2007; Monteleone et al., 2006a). Finally, although animal models to explore physiology and central mechanisms are useful to advance our understanding of eating behavior, the models have limitations for ED research, e.g., an animal model of AN induced by restriction of food intake, would differ considerably from deliberate self-starvation. Thus, while including pertinent findings from animal models, we focus on human clinical studies.

4.1. Anorexia Nervosa (AN)

Anorexia Nervosa (AN) is a severe psychiatric disorder affecting about 0.9% of women and 0.3% of men (Hudson et al., 2007) and has the highest mortality rate of any mental disorder (Sullivan, 1995). It is characterized by a marked decrease in food intake from self-induced starvation, extreme weight loss (BMI < 18.5 kg/m² for U.S.A.), and reduced body fat. AN persons exhibit an obsessive fear about becoming overweight and excessive dietary restraint (restrictive subtype, AN-R) or may be in conjunction with binge eating and subsequent purging (binge-eating/purge subtype, AN-BP) or other forms of compensatory behavior (e.g., laxative misuse, excessive exercise) to avoid weight gain (Treasure et al., 2010).

DSM IV-TR criteria for AN are (APA, 2000):

- Refusal to maintain body weight at or above a minimally normal weight less than 85% of that expected for age and height.
- Intense fear of gaining weight or becoming fat, even though underweight.
- Disturbance in the way one's body weight or shape is experienced, undue influence of body weight or shape on self evaluation, or denial of the seriousness of the current low body weight.
- For postmenarcheal females, the absence of menstruation (at least 3 consecutive cycles).

Several studies have shown that AN individuals have higher levels of fasting plasma ghrelin than normal weight (NW) healthy controls (Monteleone et al., 2008; Nedvidkova et al., 2003; Otto et al., 2001; Tsenova et al., 2007). Monteleone et al. (2008) also reported increased circulating levels of obestatin and ghrelin as well as an increased ghrelin/obestatin ratio in AN than NW women. Moreover, in AN women, positive correlations emerged

between the ghrelin/obestatin ratio and current body weight as well as BMI (Monteleone et al., 2008), suggesting an adaptive response to prolonged starvation. Although the controversy on the defined role of obestatin still exists, Monteleone et al. (2008) suggested that higher circulating levels of ghrelin and obestatin in underweight AN persons can be explained by an enhanced expression of the preproghrelin gene. This may lead to an enhanced production of ghrelin and obestatin, which results in higher ghrelin/obestatin ratio, producing a greater orexigenic signal in AN than NW women.

In addition, several researchers have compared nonpathological constitutionally thin (CT) women (BMI similar to AN) with AN patients. Tolle et al. (2003) showed that morning fasting plasma ghrelin concentrations in AN, compared to both normal weight (NW) and CT women, increased and remained higher for the rest of the day (measured every 4h in a 24h period) and subsequently normalized after renutrition. This suggests that in AN, in addition to being body weight-dependent, ghrelin levels are affected by acute nutritional status. During short-term fasting, for example, circulating ghrelin is known to increase independently of changes in body adiposity (Tschop et al., 2001). In conditions of higher energy stores, such as obesity and overeating, ghrelin levels decrease, whereas during fasting or in AN, ghrelin is up-regulated (Soriano-Guillen et al., 2004). It is likely that higher ghrelin levels in AN are adaptive responses to stimulate eating and thereby increase body weight and fat. In addition, although AN and CT women had similar BMIs, AN women still had significantly lower body fat than CT women. Thus, intermediate ghrelin levels in CT (compared to AN and NW) indicate that ghrelin levels may be inversely related to body fat. However, the circadian rhythm of ghrelin levels in CT women was comparable to that of NW controls and AN patients, with ghrelin levels peaking at night in all groups (Tolle et al., 2003). These findings suggest that altered levels of ghrelin may be a consequence of disordered eating rather than a cause for AN.

Differences in ghrelin levels among specific subtypes of AN have also been reported. An AN-R subgroup, compared to NW control, had higher levels of ghrelin (Janas-Kozik et al., 2007; Nakahara et al., 2007) and reduced growth hormone release following ghrelin administration. This may be due to AN individuals adapting to the higher (than normal) ghrelin levels (Broglia et al., 2004). Recently, Germain et al. (2010) measured the 24h circulating levels of plasma ghrelin and showed that the area under the curve (AUC) of acyl ghrelin levels was greater for AN-R than for controls, also AN-BP subgroup had lower AUC of acyl ghrelin levels than the AN-R or the control group (Germain et al., 2010). Germain et al. (2010) also measured the ratio of mean circadian plasma acyl ghrelin to total ghrelin, which was similar in AN-R and control women, but lower in AN-BP women. Also, Nedvickova et al. (2003) reported no decrease in postprandial ghrelin levels in AN after a standardized breakfast or noncaloric fiber meal (Psyllium), whereas ghrelin levels significantly decreased in healthy controls after both meals.

Monteleone et al. (2008) however, found no difference between AN-BP and AN-R women in fasting plasma ghrelin, obestatin, or in the ghrelin/obestatin ratio. Other varied results have been reported: Troisi et al. (2005) found higher levels of fasting ghrelin in AN-R than in AN-BP, in contrast to Tanaka et al.'s (2003) findings of higher fasting plasma ghrelin in AN-BP than AN-R. Troisi, et al. (2005), however, combined data from the AN-BP and BN purging patients, who likely had higher BMIs, which could explain why the results differed from Tanaka et al. (2003). Tanaka's group replicated their results in a subsequent study and included a third AN subgroup, requiring emergency hospitalization (AN-E), who were unable to eat and had extreme weight loss (Tanaka et al., 2004). They showed that AN-E had higher fasting plasma ghrelin than AN-BP, and that AN-BP had higher levels than AN-R. The three AN groups also had gradually decreasing plasma ghrelin levels following inpatient treatment. At the end of the nutritional rehabilitation, AN-BP patients still showed

higher plasma ghrelin values than the control group (Tanaka et al., 2004). Others have also shown that ghrelin levels in AN-R patients after treatment did not completely normalize (Janas-Kozik et al., 2007; Nakahara et al., 2007; Soriano-Guillen et al., 2004). A likely explanation is that AN individuals, despite rehabilitation, did not reach their target BMI, and thus still displayed higher ghrelin values than controls (Janas-Kozik et al., 2007; Nakahara et al., 2007; Soriano-Guillen et al., 2004). Consistent with this, circulating ghrelin normalized after a renutrition intervention regimen in adolescents with AN following a 25% increase in BMI, which was their target goal (Soriano-Guillen et al., 2004; Tolle et al., 2003). Moreover, Otto et al. (2001) (including AN-R and AN-BP) and Nedvidkova et al. (2003) (subtype unspecified) reported a negative correlation between BMI and fasting plasma ghrelin levels in AN females. Shiiya et al. (2002) reported negative correlations between BMI and fasting plasma ghrelin in AN, obese, and normal weight control groups, while others reported no correlations (Janas-Kozik et al., 2007; Tanaka et al., 2003). On the other hand, body fat rather than BMI may better explain ghrelin levels (Monteleone et al., 2008) as some of the groups who had contradictory results regarding the correlation between BMI and ghrelin, showed consistent results for body fat (Tanaka et al., 2002; Nedvidkova et al., 2003; Monteleone et al., 2003; Monteleone et al., 2005).

Although assays to distinguish between acyl and des-acyl ghrelin moieties have improved recently (Prudom et al., 2010), there are still conflicting findings. For example, Hotta et al. (2004) found lower fasting levels of acyl ghrelin in AN than controls and no correlations between fasting levels of acyl ghrelin and BMI using immunocomplex transfer-enzyme immunoassay (ICT-EIA). However, using enzyme-linked immunosorbent assay (ELISA) kits, Hotta et al. (2004) reported no difference in fasting levels of acyl ghrelin between AN and controls, and also no correlation between fasting acyl ghrelin levels and BMI. Opposite to this, when using a radioimmunoassay (RIA) kit, they observed significantly higher plasma levels of fasting acyl ghrelin, as well as des-acyl (ELISA kit), and total ghrelin (RIA kit) in AN than the controls, which all negatively correlated with BMI.

Moreover, postprandial ghrelin levels in patients with AN remain high after consumption of a 585 kcal solid mixed meal (32.6 g fat, 17.6 g protein, 50 g carbohydrate) and do not fall even two hours after meal consumption (Nedvidkova et al. 2003), whereas 250 ml fluid meal of 250 kcal (8.3 g fat, 9.4 g protein, 34.4 g carbohydrate) (Otto et al. 2005) as well as a 400 kcal (10.4 g fat, 19.2 g protein, and 54.2 g carbohydrate) standard test meal (Nakahara et al. 2007) suppressed plasma ghrelin in AN. One study using RIA reported that fasting plasma acyl ghrelin levels were higher in AN than the controls and remained high after an oral glucose tolerance test (OGTT) (75 g/225 ml glucose solution) (Nakai et al., 2003). Similarly, Misra et al. (2005) using an RIA kit reported that fasting plasma ghrelin levels were higher in AN adolescents than healthy controls ($p<0.01$) and remained higher following oral glucose (100 g glucose ingested over 10 min) at 30 min ($p=0.0002$) and 60 min ($p=0.008$). In addition, plasma acyl ghrelin after an intravenous infusion of 500 ml of 10% glucose solution displayed suppression in both AN and controls using ICT-EIA or ELISA kits, whereas des-acyl ghrelin (ELISA kit) did not decrease after glucose infusions in AN patients (Hotta et al., 2004). Although similar results on postprandial ghrelin levels have been reported, studies not differentiating the active and inactive forms of ghrelin make it difficult to interpret the findings.

Lastly, the role of genetic factors related to the ghrelin gene associated with the EDs is under active investigation. Twin and family trio (father, mother, child) studies as well as case-control designs have shown that genetic factors play a role in the etiology of AN. The three preproghrelin gene single nucleotide polymorphisms (SNPs), Leu72Met, Gln90Leu, and Arg51Gln, are thought to be associated with a tendency to develop EDs (Dardennes et al., 2007). The Leu72Met variant of the preproghrelin gene and an excess of transmission of the

Gln90Leu72 preproghrelin/obestatin haplotype have been reported in patients with AN-BP (Dardennes et al., 2007). In addition, a genetic polymorphism was reported in the Leu72Met SNP of the preproghrelin gene and Ala67Thr SNP of the AgRP (Thr67AGRP) gene which was shown to be preferentially transmitted for the trios with a bingeing/purging proband for AN (Vink et al., 2001). These genetic findings support the hypothesis that polymorphisms in ghrelin and AgRP genes may lead to susceptibility to AN, especially the binge/purge subtype (Dardennes et al., 2007). However, some studies report no significant differences in the frequencies of the Leu72Met, Arg51Gln (Monteleone et al., 2006a), and Gln90Leu ghrelin gene variants among AN or BN patients (Cellini et al., 2006; Miyasaka et al., 2006; Monteleone et al., 2006a), but these studies did not distinguish among different clinical subtypes of AN. Higher baseline plasma ghrelin levels, BMI, body adiposity, waist circumference, and self-rating scores in the “drive for thinness” and “body dissatisfaction” subscales of the Eating Disorder Inventory II (EDI-2) have been reported in young healthy women carrying the C allele at the 3056 T-C SNP rather than the TT genotypes (Ando et al., 2007; Ando et al., 2010). The C allele is also associated with a higher probability and rate of recovery of normal body weight from AN-R (Ando et al., 2007; Ando et al., 2010). Overall, although polymorphisms in the preproghrelin/ghrelin gene have been previously identified in relation to obesity (Korbonits et al., 2002); no candidate genes for ghrelin that predispose people to EDs have been identified to date.

4.2. Bulimia Nervosa (BN)

Bulimia nervosa is characterized by recurrent episodes of binge eating followed by inappropriate compensatory behaviors to avoid weight gain. The binge eating and inappropriate compensatory behavior both occur, on average, at least twice a week for 3 months. Self evaluation is unduly influenced by body shape and weight.

DSM IV-TR (APA, 2000) describes the recurrent episodes of binge eating by:

- Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.
- A sense of lack of control over eating during the episode (such as a feeling that one cannot stop eating or control what or how much one is eating).

and describes the recurrent inappropriate compensatory behavior to prevent weight gain by:

- Self-induced vomiting and misuse of laxatives diuretics, enemas, or other medications (purging subtype, BN-P), fasting and overexercising (nonpurging subtype, BN-NP).

Food intake is highly variable in BN, and unlike patients with AN, most patients with BN tend to be of normal weight (Weltzin et al., 1991). Many studies have been conducted to investigate psychological and cognitive factors related to BN (Rowe et al., 2010; Woldt et al., 2010). Several physiological factors associated with BN have also been described, such as enlarged stomach capacity (Geliebter et al., 1992), rare cardiac complications (Suri et al., 1999), stomach ruptures (Abdu et al., 1987), and neurochemical alterations (Kaye et al., 2005). However, neurohumoral pathogenesis associated with BN has not been adequately studied.

Tanaka et al. (2002) showed that mean fasting (08:00 am) plasma ghrelin concentration in female BN subjects were significantly higher than controls with similar BMIs. They also showed that ghrelin levels in both groups were negatively correlated with BMI and body fat percentage. Elevated basal plasma ghrelin levels in BN patients were also reported by Kojima et al. (2005). In addition to fasting ghrelin, the postprandial ghrelin decline was

found to be significantly blunted in BN women compared to controls (Kojima et al., 2005; Monteleone et al., 2005b). On the other hand, Nakazato et al. (2004) reported that ghrelin levels did not differ significantly between healthy controls and female BN patients. In addition, they reported no significant correlation between ghrelin levels and BMI, in contrast to the Tanaka et al. (2002) study. One possible explanation for the differential reports would be that Nakazato et al. (2004) measured serum ghrelin levels randomly between 11:00 am–12:00 pm (non-fasting) instead of fasting plasma ghrelin that was measured by Tanaka et al. (2002). Peripheral ghrelin has been assayed from serum as well as plasma; however Espelund et al. (2003) showed that serum yielded higher results than heparinized plasma EDTA (Ethylenediaminetetraacetic acid) plasma, and EDTA-plasma with aprotinin ($p<0.05$). Thus, preference for use of plasma versus serum may affect levels obtained in different studies. Nevertheless, Monteleone et al. (2008) measuring fasting plasma ghrelin as did Tanaka et al. (2002), found results similar to Nakazato et al. (2004): no difference in plasma ghrelin between BN women and controls, and no correlation between BMI and ghrelin. It should be noted that Monteleone et al. (2008) used ELISA whereas Tanaka et al. (2002) used RIA to measure ghrelin. This could also help account for the discrepancy because the sensitivity between the two methods may vary and detect different fragments of ghrelin (Hotta et al., 2004). Monteleone et al. (2010) when using RIA, noted enhanced fasting plasma ghrelin increase after a modified sham feeding (chewing and spitting each bite over the 15 min time period) in BN patients, which may result in greater potentiation of peripheral hunger signals in BN compared to healthy controls. They hypothesize that BN patients have greater ghrelin secretion in the cephalic phase of vagal stimulation, which might contribute to their binge eating episodes. These findings are similar to those in patients with binge-eating disorder (BED) (Monteleone et al., 2003). Thus, when using the RIA kits, Monteleone et al. (2010) reported similar results to that of Tanaka et al. (2002) study showing higher fasting plasma ghrelin levels in BN than controls. This indicates that the difference between Nakazato et al.'s (2004) and these two studies may be due to the nonfasting ghrelin measured by Nakazato et al.

Analyzing the ghrelin levels of the two subtypes of BN (purging vs. nonpurging) separately has also been done. A study by Germain et al. (2010) measured ghrelin levels in patients with purging type BN (BN-P) at twelve time points during a 24h period, which included three standard meals at 0815 h (400 kcal), 1215 h (800 kcal), and 1915 h (800 kcal) after an overnight fast, and obtained an area under the curve (AUC) for analysis. In contrast to the above reports (Tanaka et al., 2002; Nakazato et al., 2004; Monteleone et al., 2008; Monteleone et al., 2010), Germain et al. (2010) found that patients with BN-P had significantly lower AUC total and acyl ghrelin levels than healthy controls. However, in the above reports, the different subtypes of BN were not separated. Although this may help explain the discrepancy, a study by Troisi et al. (2005) reported no difference in fasting plasma ghrelin between the purging and nonpurging BN (BN-P vs. BN-NP) subtypes, suggesting that subtype may not adequately explain the different findings (Tanaka et al., 2002; Nakazato et al., 2004; Monteleone et al., 2008; Monteleone et al., 2010). Another possible explanation may be that the above studies reported fasting plasma ghrelin, whereas Germain et al. (2010) used AUC for 24h circulating plasma ghrelin which also reflects meal intake and circadian patterns. Germain et al. (2010) also showed that BN-P patients have lower AUC 24h circulating plasma obestatin and mean circulating plasma acyl-to-total ghrelin ratio than healthy controls. They additionally found that the mean circulating levels of obestatin-to-acyl ghrelin ratio was higher in BN patients than in controls. In a more recent study, Sedlackova et al. (2011) obtained similar results namely that the ratio of fasting plasma ghrelin-to-obestatin was lower in BN compared to the control group. Monteleone et al. (2008) however, found no difference in the ratio of ghrelin-to-obestatin, between BN and control women.

Besides comparing BN to healthy controls, comparing BN to AN patients is also informative. Troisi et al. (2005) found that women with AN had significantly higher fasting plasma ghrelin level than BN, BED, and control women. They also categorized the different subtypes of AN and BN, and showed that AN-R had higher ghrelin levels than BN patients regardless of the BN subtype. They reported no difference in fasting plasma ghrelin concentrations between the BN subtypes (BN-P vs. BN-NP). The restricting-type AN (AN-R) women had higher fasting plasma ghrelin levels than patients with binge-eating/purging behavior, including those with both AN (AN-BP) and BN (BN-P). Grouping AN-BP and BN-P together may be a limitation, but Germain et al. (2010) found no difference between the AN-BP and BN-P in 24 h levels of plasma ghrelin. Overall, these studies showed that patients displaying binge-eating/purging subtypes for both AN and BN (AN-BP and BN-P) had lower ghrelin levels than AN-R patients. Although the lower ghrelin levels in AN-BP and BN-P may reflect a higher energy store than in AN-R, BMI, tends to be similar between AN-BP and AN-R, and yet ghrelin was significantly lower in AN-BP than BN-P (Monteleone et al., 2003). Therefore, ghrelin level differences in AN-R versus AN-BP patients may be an indicator of acute nutritional status reflecting lower caloric intake rather than energy store (Tolle et al., 2003). It has also been shown that ghrelin concentration and secretion were negatively correlated with insulin resistance (HOMA-IR) (Misra et al., 2005) which is an indication of reduced glucose uptake. Nakahara et al. (2007) also showed that HOMA-R score in AN patients was significantly lower ($p < 0.05$) than controls which was normalized after treatment. Thus, taken together, ghrelin levels are predicted by markers of acute nutritional status in ED patients.

Ghrelin gene polymorphisms may be associated with vulnerability for BN. Several studies have examined the distribution of ghrelin gene variants in BN. The frequency of the CC type of the GHS-R gene (171T/C) was significantly higher in BN than in healthy controls and may be a risk factor for BN (Miyasaka et al., 2006). In addition, preferential transmission of the ghrelin Glu90Leu72Arg51 haplotype has been suggested as another predisposing factor for BN (Cellini et al., 2006). Ando et al. (2010) reported a more frequent C allele at the 3056 T-C SNP (CC and TC genotypes) in intron 3, and a more frequent Met allele at the Leu72Met SNP of the ghrelin gene in BN-BP. However, these studies did not confirm an established genetic variant as a risk factor for BN. Studies including larger sample sizes, different ethnic backgrounds, and extensive screening for comorbidities are needed.

4.3. Binge eating disorder (BED)

Binge eaters consume excessive food quantities in short time periods, with loss of control and lack of compensatory behaviors. The high prevalence of BED (Franko et al., 2012), which is more common in overweight and obese individuals (Yanovski et al., 1993), has led to its expected new status as a distinct clinical diagnostic entity in the DSM V (Keel et al.). However, it is currently categorized as EDNOS in DSM IV-TR.

Following are the criteria for BED in DSM IV-TR (APA, 2000):

- Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
 1. eating, in a discrete period of time (within any 2h period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances
 2. a sense of lack of control over eating during the episode (a feeling that one cannot stop eating or control what or how much one is eating)
- The binge-eating episodes are associated with three (or more) of the following:

1. eating much more rapidly than normal
 2. eating until feeling uncomfortably full
 3. eating large amounts of food when not feeling physically hungry
 4. eating alone because of being embarrassed by how much one is eating
 5. feeling disgusted with oneself, depressed, or very guilty after overeating
- Marked distress regarding binge eating is present.
 - The binge eating occurs, on average, at least 2 days a week for 6 months.

Researchers have investigated various genes and neuropeptides associated with BED to determine possible predictors of binge eating behavior. Higher ghrelin levels could help explain greater food intake, reduced fuel utilization, and subsequent weight gain in BED. Although one study showed that fasting and postprandial ghrelin levels did not differ between overweight/obese BED persons and BMI-matched controls (Munsch et al., 2009), the majority of studies report that plasma ghrelin concentrations are decreased in obese BED, which is contrary to the expected higher levels (Geliebter et al., 2005; Monteleone et al., 2005a; Troisi et al., 2005). Despite decreased ghrelin levels, there does not appear to be a reduced propensity to gain weight in BED. The lower ghrelin, as also seen in the obese relative to lean individuals, may be due to down-regulation of ghrelin release in response to overeating or excess body weight. The initial smaller decline in ghrelin following a meal has been noted in obese BED patients (Geliebter et al., 2005), and conceivably, the blunted postprandial decline in ghrelin levels may act to maintain hunger.

Ghrelin-encoding genes potentially may be contributing to BED. For example, Monteleone et al. (2006) assessed the 196G/A SNP of the human BDNF gene in BN and BED women and found no differences in gene variant frequencies between groups, yet persons with the 196G/A SNP as compared with 196A/G and 196G/G genotypes, had greater frequency of binge eating episodes. Monteleone et al. also found greater expression of the Leu72Met ghrelin gene variant in obese and normal-weight persons with BED relative to healthy, normal weight women (Monteleone et al., 2007). The Leu72Met ghrelin gene may therefore be associated with a genetic susceptibility for BED (Monteleone et al., 2007), whereas the AA variant of the 196G/A SNP of the human BDNF gene may predispose individuals to higher frequency of binge eating (Monteleone et al., 2006b).

4.4. Night eating syndrome (NES)

Night eating syndrome (NES) is currently categorized as EDNOS in DSM IV-TR (APA, 2000); however there is a proposed upgrading of NES in DSM V NES is characterized by recurrent episodes of evening hyperphagia and nocturnal food intake that is not accounted for by BED, other EDs, or insomnia. NES is associated with significant distress and/or impairment in functioning. A small number of studies have assessed ghrelin levels in NES individuals. Allison et al. (2005) measured circulating ghrelin levels over 25 hours in obese NES and found that ghrelin was significantly lower in the NES group compared to healthy, obese controls from 1 am to 9 am. Studies have shown that ghrelin helps regulate the sleep-wake cycle to promote sleep (Schussler et al., 2006; Steiger, 2007), and lower levels may contribute to the tendency for frequent awakenings in persons with NES. However, another group found no significant difference in nocturnal ghrelin concentrations in women with and without NES (Goel et al., 2009), but the ghrelin secretory pattern was phase-advanced by 5.2 hours, suggesting a dissociation between the circadian rhythm associated with food intake and the sleep-wake cycle. Elevated ghrelin levels in a NES patient before and also after 8 weeks of treatment, relative to normal weight controls, were reported by Rosenhagen et al. (2005), suggesting that higher ghrelin levels may disrupt sleep due to increased hunger

(Rosenhagen et al., 2005). Collectively, these findings suggest that variations in nocturnal ghrelin secretion may contribute to the onset or maintenance of NES (O'Reardon et al., 2005). A ghrelin concentration above a certain threshold may stimulate hunger vs. sleep in humans (Schuessler et al., 2005), and abnormal elevations in nocturnal ghrelin secretion could increase the risk of developing NES.

4.5. Prader-Willi syndrome (PWS)

Prader-Willi syndrome (PWS) is a genetic form of obesity, associated with the loss or silencing of several paternal genes in the q11-13 region of chromosome 15. Infants with PWS typically exhibit poor feeding and failure to thrive, with the hallmark hyperphagia beginning between the ages of 18 months and 6 years. PWS is characterized by endocrine disturbances, neurocognitive disabilities, and severe hyperphagia leading to obesity. Although not classified as an eating disorder, PWS merits inclusion in this review because of the coincidence of obesity, hyperphagia, and abnormal ghrelin levels in this disorder (Cummings et al., 2002).

Moreover, PWS is included in DSM IV-TR (APA, 2000) in Axis I Diagnosis of *Personality Change Due to a Medical Condition* as follows:

- Overeating of typical food
- Eating atypical food (frozen, raw, spoiled food or pet food)
- Sneaking food in the home
- Night time foraging in the home
- Arguing or manipulating to get food
- Throwing tantrums to get food
- Opportunistic food theft (shoplifting from a store or stealing food from school or work)
- Planned food foraging expeditions in the neighborhood or community
- Nonconfrontational, invasive food access (breaking locks on cabinets, refrigerator or freezer, trespassing)
- Confrontational food access (using verbal or physical threats or actual aggression to access food)

Total ghrelin levels in PWS individuals are elevated relative to healthy as well as adiposity-matched controls, in both the fasting and fed states. This elevated ghrelin level has been postulated to be a cause for the hyperphagia and resultant obesity associated with PWS. PWS individuals experience markedly reduced meal-induced suppression of hunger, as compared with adiposity-matched and lean controls (Purtell et al., 2011). However, another recent study found that the childhood transition from poor feeding to hyperphagia is not associated with a change in ghrelin levels (Goldstone et al., 2012). Also not all PWS individuals have increased ghrelin. Furthermore, suppression of ghrelin release by octreotide does not appear to reduce hyperphagia, appetite, or body adiposity (De Waele et al., 2008; Haqq et al., 2003; Tan et al., 2004). However, octreotide would have suppressed all hormonal output, including the satiety inducing gut peptides, which might have canceled the effects on ghrelin. Exenatide, an incretin analogue that suppresses appetite, increases pancreatic insulin secretion, and has been approved for the treatment of type 2 diabetes mellitus, increased satiety in PWS individuals, without affecting ghrelin levels. The data from these studies indicates that while ghrelin appears to play a role in the hyperphagia and resulting obesity of PWS, more investigation is required before causation can be established.

5. Discussion

The etiological factors of ED may not solely be psychological and include the interplay of genetic and environmental factors. Although the causal direction remains unclear, metabolic and endocrine alterations in EDs have been reported indicating altered ghrelin levels. Some inconsistencies (Table 2) between studies by different groups may be due to methodological differences, sample differences such as, duration of illness, sample size, ED subtypes, serum vs. plasma ghrelin, acyl vs. des-acyl vs. total ghrelin, age, and BMI. Nevertheless, one common finding is the inverse relation between BMI and ghrelin levels, and there is even more consistency across studies when percentage or absolute body fat is used rather BMI.

Thus, although genetic factors have been reported on ghrelin levels in patients with EDs, it is possible that altered ghrelin levels (relative to the healthy controls) may be a results of an under/overweight status of those with these disorders. Studies show that after a BMI increase of ~15% following treatment of AN patients, circulating and fasting ghrelin levels decreased towards normal (Otto et al. 2001; Janas-Kozik et al., 2007; *respectively*).

Moreover, following treatment, patients with AN who gain more weight exhibit a faster insulin and glucose responses than patients who gain less weight (Yasuhara et al., 2003). It is known that ghrelin levels are suppressed by glucose administration in healthy humans (Shiya et al., 2002). Thus, examining other metabolic hormones that are regulated by body fat, such as leptin (Rowland and Morien, 1996; Berthoud, 2002) is also informative.

It is known that ghrelin and leptin exert opposite metabolic actions in relation to energy homeostasis (Berthoud, 2002), and that ghrelin is orexigenic, whereas leptin is anorexigenic. In conditions of positive energy balance such as obesity, overeating (except PWS), plasma ghrelin levels decrease (Soriano-Guillen et al., 2004), whereas plasma leptin levels move in the opposite direction and increase (Rowland and Morien, 1996). On the other hand, during fasting or in AN, which entails a lower body fat, leptin is down-regulated (Miljic et al., 2006) while ghrelin is up-regulated (Soriano-Guillen et al., 2004). Monteleone et al., (2008) showed that AN patients had lower leptin and higher ghrelin than healthy controls whereas BN had ghrelin and leptin levels similar to healthy controls. They also found no difference in plasma levels of leptin, ghrelin and BMI between AN-R and AN-BP patients. However, findings from studies in BED patients suggest that binge eating may lead to a decrease in ghrelin levels despite similar BMI. Moreover, caloric restriction may have a direct effect beyond body energy stores in increasing ghrelin as in AN-R. However, purging which induces a lower energy store may also stimulate ghrelin. Nevertheless, AN-BP patients had higher fasting ghrelin levels than BN-P, which is likely due to weight differences. It would be worthwhile to examine ghrelin over a period of time following purging in AN-BP vs. BN-P patients to differentiate the effect of purging from body weight. It is likely that higher ghrelin levels in AN are adaptive responses to a state of negative energy store, to induce eating and increase body weight and fat. Normalizing or partially normalizing circulating ghrelin levels following weight gain via renutrition in AN supports the hypothesis that altered levels of ghrelin are consequences of the disorder. Reduced food intake in patients AN with low BMI and body fat as well as chronically higher ghrelin levels may also reflect insensitivity to the effects of ghrelin (Misra et al., 2005). Several studies have shown that patients with AN had reduced growth hormone secretion after ghrelin administration than the controls which may be an adaptation to the high ghrelin levels (Broglia et al., 2004; Miljic et al., 2006). Future research should examine the relationship among hormones associated with body fat, including ghrelin and leptin.

To improve consistency across studies, researchers should examinedifferent moieties of ghrelin in their hormone analyses. The blood collection time and methods, including the hormone assay kits used are also relevant to replicate results. In addition, the subtypes of

EDs should be considered separately, as their phenotypes and genotypes may differ. Investigation of genetic markers associated with different subtypes of EDs (Dardennes et al., 2007) may also be helpful because initial ED diagnosis may vary over time. For example, some reports have noted that 62% of patients initially diagnosed with AN-R are later diagnosed as AN-BP, and 21–36% are later diagnosed as BN (Nishimura et al., 2008). It has been suggested that preproghrelin gene expression may be altered by energy store imbalance over prolonged periods, and genetic polymorphisms may therefore be potential predictors of subtypes as well as changes over time in EDs. Since obestatin and ghrelin are produced from the same preproghrelin gene, regardless of the obestatin's questioned function, measuring obestatin levels and obestatin to ghrelin ratio may help discriminate between EDs. Few recent studies have reported obestatin levels in patients with EDs (Germain et al., 2010; Sedlackova et al., 2011) and most reported total obestatin, that is both amidated and nonamidated peptide. Similar to the acylation of the peptide, amidation of obestatin is necessary for its bioactivity (Monteleone et al., 2008).

The duration of the ED may contribute to the degree of metabolic alterations and endocrinological changes, resulting in inconsistency between different studies. For instance, in AN the postprandial decrease in ghrelin has been reported by several groups (Nakai et al., 2003; Nakahara et al., 2007) while others reported that the postprandial response is impaired (Nedvidkova et al., 2003). All of these studies are missing the information about duration of the illness. Thus, another possible factor contributing to the inconsistency among these studies may be variation in the duration of illness.

In conclusion, the key factor influencing ghrelin levels may be the under or overweight status (Tolle et al., 2003; Misra et al., 2005) in EDs in humans. Thus, ghrelin dysregulation could be involved in the maintenance of EDs, but without being a causal factor. The complex interplay among central and peripheral signals involved in normal eating behavior, may be even more complex in its disordered forms. Although ghrelin has been a topic of ED research for over 10 years, the causal direction has still not been resolved. Future research on ED's should examine the interplay of multiple food intake signals including ghrelin in longitudinal and treatment studies as well as considering the aforementioned methodological issues.

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Highlights

1. Ghrelin in eating disorders has been the topic of recent investigations.
2. There are inconsistent reports on ghrelin levels in eating disorder patients.
3. Different forms of ghrelin used may explain these inconsistencies.
4. Body weight may be an important factor on determining ghrelin levels in eating disorders.

Table 1

Studies measuring ghrelin levels in individuals with eating disorders.

Study	Duration	Sample size (m ± SD)	Age (m ± SD)	BMI (kg/m ²) (m ± SD)	Condition	Ghrelin/Assay kit	Results	Basal fasting levels (m ± SEM)	Correlations
Otto et al 2001		AN,36 C,24	AN,25±1.2 C,31±1.4	AN,15.2 ±0.2 C,22.9± 0.5	o/n fast fast (post-tre)	plas RIA	AN>C (p<0.02) ↓AN (p<0.001)	AN,1057±95pg/ml; C,514±63	ΔGhrelin (−) corr. w/ ΔBMI in AN (r=−0.47; p=0.005).
Tanaka et al 2002	3.2±2. 9	BN,15 C,11	BN,23.3±5.3 C,24±1.9	BN,20±2.9 C,21.1±1.2	o/n fast	plas RIA	BN>C (p<0.0005)	BN,298.4±136p mol/l; C,126.9±28.2	Ghrelin (−) corr. w/BMI (r= −0.5; p<0.01), BF % (r=−0.54; p<0.005) in BN&C.
Nedvidkova et al 2003		AN,5 C,6	AN,24.3±2.7 C,23±4.8	AN,15.2±1.5 C,21.6±1.2	o/n fast postPr (breakfast) postPr (fiber)	plas(acyl) RIA	AN>C (p<0.001) ↓C (p<0.05), [↔] in AN ↓C (p<0.05), [↔] in AN	AN,1800±47pmol/l; C,795.9±24.3	Fasting ghrelin (−) corr. w/BF% in AN(r= −0.54; p<0.05) and C(r=−0.49; p<0.05).
Monteleone et al 2003	4.7±1.7	BNp,9 C,12	BNp,24.2±2.3 C,24.5±2.6	BNp, 21.7±3.4 C,21.5±1.8	o/n fast postPr	plas RIA	BNp=C [↔] in BNp, ↓C, BNp>C (p<0.0002)	BNp,1250pg/ml; C,1350	Fasting ghrelin (−) corr. w/BW (r=− 0.61, P<0.002) and BF (r= −0.5, P<0.01) in all S' s.
Nakai et al 2003		AN _R ,5 C,7	age-matched	AN _R ,13.9±1 C,20.4± 0.5	o/n fast post-OGTT	plas(acyl) N-RIA	AN _R >C (p<0.01) ↓AN _R >↓C in 2h	AN _R ,52.1±10.5f mol/ml; C,21.2±3.1	N/A
Tanaka et al 2003	AN _R ,2.5±1.5 AN _{BP} ,3.3±3	AN _R ,19 AN _{BP} , 20 C,11	AN _R ,20.1±5 AN _{BP} ,22±4.7 C,21±2	AN _R , 13.6±1.5 AN _{BP} ,13. 7±2 C,21.4± 1.2	o/n fast	plas RIA	AN _{BP} >AN _R >C (p<0.01)	AN _{BP} ,350pM, AN _R ,250, C,150	Ghrelin (−) corr. w/BMI in AN _R (r= −0.47, p<0.05) AN _{BP} (r= −0.51, p<0.05)
Tanaka et al 2004	AN _E ,3.2±1 AN _R ,2±.4 AN _{BP} ,5.2±1	AN _E ,7 AN _R ,14 AN _{BP} ,13 C,9	AN _E ,18±1.2 AN _R ,18.4±1.3AN _{BP} ,25±1.3 C,21.5±0.9	AN _E ,11± 0.3 AN _R ,13± 0.2 AN _{BP} ,14.5±0.3 C,21.5±0.4	o/n fast fast (treatment) fast (post-tre) (68.7±3. 1 dys)	plas RIA plas RIA plas RIA	AN _E >AN _R >AN _{BP} >C (p<0.05) ↑AN _R AN _R >AN _E =AN _{BP} =C	AN _{BP} ,346.7±21.8pmol/l; AN _E ,520.7±27.8; AN _R ,254.3±25.9; C, 139.2±20	Ghrelin (−) corr. w/BMI in all S' s (r=

Study	Duration	Sample size (m ± SD)	Age (m ± SD)	BMI (kg/m ²) (m ± SD)	Condition	Ghrelin/Assay kit	Results	Basal fasting levels (m ± SEM)	Correlations
							↓AN _R AN _{BP} >AN _E =AN _R =C		−0.64, p<0.01) (post-tre) no corr. bet. ghrelin and BMI in all S' s
Nakazato et al 2004	BN,3.7±2.4	BN _P ,16 BN _{NP} , 2 C,21	BN,21.6±4 C,21.4±1.7	BN,20.4±2.1 C,20±1.5	1100am – 1200pm	Serum ELISA	BN _P =BN _{NP} =C	BN,2.89±3.97ng/ml; C,2.84±3.77	No corr. bet. ghrelin and BMI in all S' s
Hotta et al 2004		AN,30 C,16 AN,6 C,6	AN,24±3 C,25.6±2 AN,23–29 C,21–33	AN,15.5±2.6 C,20.3±2 AN, 10.2–14 C,18.4– 21.5	o/n fast postPr-glucose	plas ICT-EIA plas(acyl) ELISA plas(des-acyl) RIA plas(acyl)RIA plas RIA plas ICT-EIA	AN<C(p=0.043) AN=C AN>C(p<0.0001) AN>C(p=0.048) AN>C(p<0.0001) ↓AN (9.8%) and ↓C (3.3%) (P=0.206)	AN,49.2±3pmol/l; C, 65±5 AN,34.7±3.2; C,30±3 AN,223.5±37.3; C,94±7.5 AN,136.7±13; C,104±10 AN,2.87±0.2513 nmol/l; C,1.85±0.13	No corr. bet. BMI and ghrelin (ICT- EIA), acyl ghrelin (ELISA) in AN and C. (–) corr. bet. des-acyl ghrelin (ELISA), acyl (RIA), and ghrelin total (RIA)
Kojima et al 2005	4.8±1.1	BN _P ,10 C,12	BN _P ,24.7±1.5 C,24.8±0.8	BN _P ,20±0.6 C,20.2±0.5	o/n fast postPr(A UC)	plas RIA plas RIA	BN _P >C (p=0.04) ↓BN _P <↓C	BN _P ,265±25.5p mol/l; C, 199.3±18.4	N/A
Troisi et al 2005	AN,8.9±6.9 BN,8.6±4.2 BED,9±8.8	AN _R , 13 AN _{BP} , 2 BN _P ,14 BN _{NP} , 8 BED, 13 C,23	AN,26.7±6.8 BN,29.2±11.5 BED,38±12 C,25.6±3.2	AN,16± 2.3 BN,26.1 ±7.5 BED,33 ±7.9 C,21.24 ±1.9	o/n fast	plas RIA	AN>BN=BED= C (p<0.0001), AN _R >BN _P &AN _B , AN _R >BED&B _{NP} , AN _R >C, BN _P =BN _{NP}	AN,4624±2182p g/ml; BN,2357±1132; BED,2405±1452; C,2897±8953	Ghrelin (–) corr. w/BMI in all ED S' s (r=−0.49, p<0.0001). No corr. in C
Monteleone et al 2005	BED[OB], 14±9.6 BED[No], 6.2±3 Ob[non BE], 11.7±9.1 BN _P ,5.2±4.2	BED(OB),34 BED(No),13 Ob(no-binge),28 BN _P ,56 C(lean),51	BED(OB),33.6±9 BED(No),27±8 Ob(no-binge), 38.4±14.1 BN _P ,23.4±4.3 C(lean),22.6±3.1	BED(OB), fast 39.8±4.9 BED(No), 25.8±2.5 No(no-binge), 38±6.3; BN _P , 22±3.8 C(lean), 21.7±2.3	o/n	plas RIA	BED<C(lean)= BN (p<0.0001) C(lean),1150	BED(OB),850pg/ml; BED(No),850; Ob(no-binge),875; BN _P ,1200, C(lean),1150	Ghrelin (–) corr. w/BW (r=−0.44, p<0.0001), BMI (r=−0.41, p<0.0001), BF (r=−0.37, p<0.0001) in all S' s but not groups alone
Geliebter et al 2005	N/A	C(OB),12 BED(OB),11 BE(OB), 14	C(OB),33.1±8.7 BED(OB), 29±8.4 BE(OB), 28.6±6.7	C(OB), fast 35.3±5.5 BED(OB), 36.6±6.2	o/n	plas RIA plas RIA	BED<C (p=0.03) ↓BED<↓C (p=0.004)	C(OB),65793±6764pg/ml; BED(OB),39,242±3257; BE(OB),51,389±6909	N/A

Study	Duration	Sample size (m ± SD)	Age (m ± SD)	BMI (kg/m ²) (m ± SD)	Condition	Ghrelin/Assay kit	Results	Basal fasting levels (m ± SEM)	Correlations
postPr BE(Ob), 35±5.3									
Janas-Kozik et al 2007	11.5±7	AN _R ,30;C,20	AN _R ,18±2 C,18.5±0.5	AN _R , 15.1±1.4 C,21.4±2.1	fast fast(post-tre) (6 mo)	plas	AN _R >C (p=0.002)	AN _R ,6500pg/ml; C,5000	No corr. in AN _R and C S' s Δ Ghrelin (+)corr. w/ ΔBMI in AN _R (r=0.52, p=0.0054)
						plas	AN _R <C (p<0.001)		
Harada et al 2007	N/A	AN _R , 10 C,10	AN _R ,21.9±1.8 C,23.5±0.8	AN _R ,13.43±0.3 C,21.6±1.2	o/n fast post-OGTT (AUC)	plas[acyl] ELISA	AN _R =C (p=0.05)	AN _R , 28.6±2pg/ml; C,22.3±2.2 AN _R ,340±39;C,231±20 AN _R ,65±2.2;C,49.2±2.1	N/A
						plas(des-acyl) plas(obest.) plas(des-acyl/ acyl) plas(acyl) plas(des-acyl) plas(obest.)	AN _R >C (p<0.01) AN _R >C (p<0.05) AN _R >C (p<0.05) AN _R >C (p<0.01) AN _R >C (p<0.01) AN _R >C (p<0.01)		
Nakahara et al 2007	N/A	AN _R , 14 C,12	AN _R ,24.6±6 C,25.7±6.7	AN _R , 125±1.7 C,22.3± 2.2	o/n fast postPr fast(post-tre) postPr(post-tre)	plas RIA plas plas	AN _R >C (p<0.01) AN _R >C (p<0.01) AN _R =C	AN _R ,433.1±124. 8pmol/l; C,215.6±90.7	No corr.
						plas	AN _R >C (p<0.05)		
Monteleone et al 2008	N/A	AN _R , 7 AN _{BP} , 13 BN _p ,21 C,20	AN,23.4±7.5 BN _p ,26.2±7.1 C,23.6±5.5	AN,16.6±1.6 BN _p , 21.4±3.3 C,21.1±2.2	o/n fast	plas ELISA plas(obest.) ELISA plas ELISA (ghrelin/obest.)	AN>BN=C(p<0.0016) AN _R =AN _{BP} AN>BN=C (p<0.009) AN _R =AN _{BP} AN>BN=C (p<0.045) AN _R =AN _{BP}	AN,370.6±164pg/ml; C,221±96; BN,217±112 AN,86.2±24.4; C,68.3±15; BN,80±22.4	Ghrelin/obest. (+)corr. w/BMI (r=0.48, p=0.03), BW (r=0.53, p=0.01) in AN. No other corr.
Munsch et al 2009	N/A	BED(Ob),18 C,20	BED(Ob), 50.2±9.5 C,48.6±9.7	BED(Ob), 32.4±5.4 C,34.3±7.6	o/n fast + postPr(AUC) AUC(post -tre)	plas RIA plas RIA	BED=C BED=C	BED,139176pg* min/mol; C,115418	No corr.
Germain et al 2010	N/A	AN _R , 22 AN _{BP} , 10 BN _p ,16 C,9	AN _R ,23±6 AN _{BP} ,24±8 BN _p ,22.5±5 C,24±5	AN _R , 15.2±1. 6 AN _{BP} , 15.4±1. 4 BN _p , 21.9±2. 2 C,20.9±1.9	24h(AUC) μ circadian μ circadian μ circadian	plas (total, acyl, obest.) RIA plas (total, acyl, obest.) RIA plas (acyl)/total) RIA plas (obest./acyl) RIA	AN _{BP} =BN _p <AN _R =C (p<0.001) AN _R >C (p<0.05) BN=AN _{BP} <AN _R =C C<AN _R <BN=AN _{BP}	N/A	N/A

Study	Duration	Sample size (m ± SD)	Age (m ± SD)	BMI (kg/m ²) (m ± SD)	Condition	Ghrelin/Assay kit	Results	Basal fasting levels (m ± SEM)	Correlations
Sedlackova et al 2011	AN,6.8 BN,5.5	AN _R , 5 AN _{BP} , 3 BN,13 C,11	AN,25.4±2 BN,22±1 C,25±1.2	AN,15.8±0.5 BN,20±0.4 C,21±0.4	o/n fast postPr	plas RIA plas(obest.) RIA plas RIA (ghrelin/ obest.) plas RIA plas(obest.) RIA plas(ghrelin/ obest.) RIA	AN>BN=C (p<0.0001) AN>BN>C (p<0.0001) C>AN>BN (p<0.0001) AN>BN=C AN>BN>C C>AN>BN	AN,1700ng/ml; BN=C,1000 AN,400; BN,275; C,200	N/A

Table 2

Summary of the results from the studies in Table 1.

Variable	# of studies
Correlation bet. ghrelin and BMI	
[-] corr.	6
[+] corr.	3
No corr.	7
Correlation bet. ghrelin and BF	
[-] corr.	4
[+] corr.	0
No corr.	1
Ghrelin levels AN vs. C	
AN>C	11
AN=C	3
AN<C	2
Ghrelin levels BN vs. C	
BN>C	2
BN=C	6
BN<C	1
Ghrelin levels BED vs. C	
BED>C	0
BED=C	2
BED<C	2

Table 3

Abbreviations used in Tables 1 and 2.

Abbreviation	Definition
Acyl/total	Acyl ghrelin/total ghrelin ratio
AN	Anorexia Nervosa (all types)
AN_E	Anorexia Nervosa, requiring Emergent Hospitalization
AN_{BP}	Anorexia Nervosa, Binge-eating/Purge subtype
AN_R	Anorexia Nervosa, Restricting subtype
AUC	Area Under the Curve
BE	Binge Eater (not full BED criteria)
BED	Binge Eating Disorder
bet.	between
BN	Bulimia Nervosa (all types)
BN_P	Bulimia Nervosa, Purging subtype
BN_{NP}	Bulimia Nervosa, Non-Purging subtype
BMI	Body Mass Index
BW	Body weight
BF	Body Fat
C	Control group
corr.	Correlation
dys	Days
ELISA	Enzyme-Linked Immunosorbent Assay
Ghrelin/obest.	Ghrelin/Obestatin Ratio
H	Hours
mo	Months
N/A	Not Applicable
No	Non-obese
NW	Normal Weight
Ob	Obese
obest.	Obestatin
OGTT	Oral Glucose Tolerance Test
Obest./acyl	Obestatin/Acyl ghrelin ratio
o/n fast	Overnight Fast
obest./acyl	Obestatin/Acyl ghrelin ratio
plas	Plasma
PostPr	Postprandial
Post-tre	Post-treatment
RIA	Radioimmuno Assay
SEM	Standard Error of the Mean
S's	Subjects
w/	With
yrs	Years

Abbreviation	Definition
Δ Ghrelin	Change in Ghrelin
[−] corr.	Negative correlation
[+] corr.	Positive correlation
[↔]	No change
↓	Decrease
↑	Increase
&	Combined
μ	Mean