Systematic review and meta-analysis of the baseline concentrations and physiologic responses of gut hormones to food in eating disorders\textsuperscript{1,2}

Alexis C Prince, Samantha J Brooks, Daniel Stahl, and Janet Treasure

\textbf{ABSTRACT}

\textbf{Background:} Disturbances in gastrointestinal hormones have been widely identified in persons with eating disorders (EDs) and have been implicated in their clinical pathologies.

\textbf{Objective:} The objective was to identify, critically examine, and summarize studies investigating the short-term response of gastrointestinal hormones to food in persons with an ED, including the subtypes anorexia nervosa and bulimia nervosa.

\textbf{Design:} A priori inclusion and exclusion criteria were set and included a procedure in which a test meal or glucose load was given and blood hormone concentrations measured. All studies included a healthy control group for comparison. The outcome variable was defined as the mean difference between fasting plasma hormone concentrations and the maximum postprandial peak or nadir. The difference in baseline values between groups was also examined. Pooled standardized mean differences were calculated and analyzed where possible.

\textbf{Results:} A total of 28 studies were identified, including sufficient studies to perform a meta-analysis for ghrelin, peptide YY, cholecystokinin, insulin, and pancreatic polypeptide. Persons with an ED had higher baseline concentrations of ghrelin (large effect), peptide YY (medium effect), and cholecystokinin (medium effect for ED, large effect for anorexia nervosa). The response of insulin to food was decreased in persons with an ED (medium effect). No further differences were found in the release of gut peptides to a standardized test meal.

\textbf{Conclusions:} All of the studies had low power for the different subtypes of EDs. High heterogeneity among the studies was observed, and limitations are discussed. The findings suggest that the physiologic changes observed in patients with EDs are highly variable and subject to multiple confounding factors.

\textbf{INTRODUCTION}

The study of biological factors involved in the pathophysiology of eating disorders (EDs), such as neurotransmitters and gastrointestinal (GI) peptides, is an area of active interest. It has been widely hypothesized that disturbances in one or more of these agents could, in part, contribute to the development of ED and be implicated in their clinical pathologies (1). Previous reviews of the data on the neurobiological disturbances associated with ED have, in the main, concluded that there is little evidence to suggest that these abnormalities are primary and trait related (2–4). However, there is increasing evidence, although not conclusive, that some of these changes may contribute to the maintenance of some symptomatic aspects of EDs, even when secondary to malnutrition and aberrant eating behaviors (3).

It is therefore of great interest to examine the differential release of GI hormones in the spectrum of EDs, including anorexia nervosa (AN) and bulimia nervosa (BN), because their dysregulation may act to initiate, maintain, or exacerbate cycles of food restriction or binge-purge behaviors observed in these disorders. The brain regulates energy homeostasis and appetite via central signaling pathways in the hypothalamus and brainstem in response to peripheral signals released from adipose tissue and the GI tract (5, 6). The focus of the current review is specific GI hormones involved in this process and their disturbance in EDs. To our knowledge, no meta-analyses of the literature concerning this topic have been conducted. Therefore, our aim was to identify, critically examine, and summarize such studies investigating the short-term physiologic response of GI hormones in persons with an ED and to examine whether they, and the AN or BN subtypes with extremes of eating behavior, would show contrasting and discordant blood hormone concentrations before and after a test meal. Where possible, meta-analyses of the data were undertaken.

Specifically, our first hypothesis was that fasting hormone concentrations would be abnormal in the subgroup with restricting AN, as a secondary result of the disturbance in weight homeostasis, and hormones that stimulate eating (eg, ghrelin) and hormones associated with satiation [eg, peptide YY (PYY) and cholecystokinin (CCK)] would be elevated. A second hypothesis was that persons exhibiting binge-eating behaviors would also...
show an increase in ghrelin and PYY at baseline. However, the expected outcome for CCK was less clear in the binge-eating groups. The third hypothesis was that persons with AN would have a normal or increased release of hormones associated with satiation after a test meal, but that persons with binge-eating would have a reduced response and that these changes might explain their abnormal pattern of eating at normal weight.

METHODS

The aim of this study was to summarize the research that has examined the release of GI hormones in patients with EDs as compared with healthy control (HC) subjects within a test meal paradigm. The QUOROM (Quality of Reporting Meta-Analyses) statement for meta-analyses was followed.

Literature search

The literature search was conducted by using the electronic databases PubMed, Ovid, Embase, and Google Scholar and by additional hand searches through the reference lists obtained from the articles found. Journals were searched up to January 2008. The search included combinations of the following keywords and phrases: anorexia nervosa, bulimia nervosa, eating disorder, appetite, control, regulation, gastrointestinal, hormone, pancreatic peptides, cholecystokinin, CCK, ghrelin, gastric inhibitory peptide, GIP, glucagon-like peptide-1, GLP-1, insulin, peptide YY, PYY, postprandial, preprandial, test meal, and food. Studies investigating hormonal responses to a test meal in patients with an ED, specifically the AN and BN subtypes, as compared with HC subjects were eligible for inclusion. Eleven factors implicated in short-term response to food were identified during the search that had been studied in EDs: ghrelin, PYY, CCK, insulin, gastric inhibitory peptide (GIP), glucagon-like peptide-1 (GLP-1), somatostatin, glucagon, pancreatic polypeptide (PP), gastrin, and vasoactive intestinal peptide (VIP). However, only ghrelin, PYY, CCK, insulin, and PP had been investigated in a sufficient number of studies to be suitable for a meta-analysis.

Paper retrieval

The search was conducted on the basis of the following inclusion criteria:

1) Population: subjects suffering from an ED (inpatients and outpatients) and an HC group
2) Sample size: studies with >5 subjects in the test group
3) Publication date: articles from 1988 to January 2008
4) Language: English-language articles only
5) Study designs: test meal (solid or liquid) or glucose load protocol with pre- and postprandial analysis of gastrointestinal hormone concentrations
6) Measures: baseline hormone concentrations and short-term plasma hormone response to a test meal or glucose load
7) Outcome variable: baseline hormone concentrations and mean maximal changes in hormone concentrations after consumption of a test meal or glucose load

Selection

A total of 28 studies were found during the search phase; 24 studies were selected following the search criteria and 4 studies were excluded. In the first of the excluded studies, the test group consisted of recovered AN subjects (7). Data from the second excluded study could not be obtained in full (8). Two additional studies were excluded on the basis of insufficient test group sample sizes (9, 10). One study included in the review examined multiple gut hormones, but was excluded from all but one meta-analysis for PP because of a lack of raw data (11). Three studies were included in the review but were excluded from all meta-analyses because of an insufficient number of studies examining the same outcome measures, specifically GIP, GLP-1, somatostatin, glucagons, and gastrin (12–14). All included studies contained age- and sex-matched HC groups. In summary, this review examined a total of 24 studies, 21 of which were included in the meta-analyses.

Data abstraction

Descriptive statistics (mean, SD, sample size, and subtype of ED sample) for the ED and HC groups were extracted from all articles. The primary measure for hormone response was the mean maximal change (MMC) in plasma hormone concentration from baseline before consumption of the test meal to the maximum reported postprandial peak or nadir, regardless of when this occurred. The MMC was selected as the sole criterion for the purposes and ease of standardizing the data across studies for statistical analysis of the findings. The pattern of hormone release was also considered of interest, and the timing of the maximum hormone response is shown in Table 1. Some of the original publications omitted the raw data; therefore, attempts were made to contact the corresponding authors for these data. If no response was received, the appropriate published graphs were used, when possible, to extract the data and provide an approximation of the results.

Study characteristics

Most of the studies included in this review adopted an experimental cross-sectional design with measures taken before and after intervention. The measures are blood plasma concentrations of the hormones under investigation analyzed using radioimmunoassay commercial kits and the interventions were standardized test meals of known composition and energy content or glucose loads of known glucose concentration. The HC groups were selected on the basis of at least one or more of the following criteria: within 10–15% of ideal body weight or normal body mass index (BMI); normal eating behavior; no history of EDs, other psychiatric disorders, mental illness, alcohol abuse, or major affective disorders or in first-degree relatives; mentally and physically healthy; no history of metabolic diseases, obesity, hypertension, gastrointestinal disease, or surgery; no use of medications known to affect gastric motility; and regular menstruation or premenarcheal.

Description of the study protocols

Of the studies included in the review, 7 used a solid test meal protocol, 9 used a liquid test meal protocol, 5 used an oral-glucose-load protocol, and 3 used both a solid test meal and a glucose-load protocol. Details of the study samples, test meal, and oral-glucose-load characteristics, timing of the blood sampling for each study, and timing of the hormonal peak or nadir are shown in Table 1.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>n</th>
<th>Age x</th>
<th>BMI y</th>
<th>Measure</th>
<th>Test meal characteristics</th>
<th>Measurements</th>
<th>Timing</th>
<th>MMC z</th>
<th>Unit</th>
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<tbody>
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<td>Monteleone et al, 2003 (20)</td>
<td>BN 9</td>
<td>24.5 ± 2.3</td>
<td>18.3 ± 0.4</td>
<td>21.7 ± 3.4</td>
<td>Ghrelin Solid test meal: 1207 kcal, 60% CHO, 23% fat, 17% protein</td>
<td>Blood sampling at 0, 45, 60, 90, and 180 min after test meal</td>
<td>Nadir: 45</td>
<td>235.9 ± 97.9</td>
<td>pg/mL</td>
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<td>BN 12</td>
<td>24.5 ± 2.6</td>
<td>18.3 ± 0.4</td>
<td>21.7 ± 3.4</td>
<td>Ghrelin Oral glucose load: 75 g/225 mL</td>
<td>Blood sampling at 0, 45, 60, 90, and 180 min after test meal</td>
<td>Nadir: ≥ 180</td>
<td>514 ± 119.5</td>
<td>pg/mL</td>
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<td>AN-BP 9</td>
<td>20.9 ± 1.4</td>
<td>18.3 ± 0.4</td>
<td>21.7 ± 3.4</td>
<td>Ghrelin Oral glucose load: 100 g</td>
<td>Blood sampling at 0, 30, 60, 120, and 180 min after test meal</td>
<td>Nadir: 60</td>
<td>491 ± 23.2</td>
<td>pg/mL</td>
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<td>Tanaka et al, 2003 (23)</td>
<td>AN-R 11</td>
<td>18.5 ± 1.4</td>
<td>21.0 ± 0.6</td>
<td>21.4 ± 0.4</td>
<td>Ghrelin Oral glucose load: 100 g</td>
<td>Blood sampling at 0, 30, and 60 min after glucose load</td>
<td>Nadir: 30</td>
<td>123.0 ± 195.9</td>
<td>pg/mL</td>
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<td>AN-R 19</td>
<td>16.1 ± 1.1</td>
<td>18.5 ± 1.4</td>
<td>21.0 ± 0.6</td>
<td>21.4 ± 0.4</td>
<td>Ghrelin Solid test meal, breakfast: 58% CHO, 22% fat, 20% protein</td>
<td>Blood sampling at 0, 30, 60, 120, and 180 min after test meal</td>
<td>Nadir: 60</td>
<td>192.0 ± 522.9</td>
<td>pg/mL</td>
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<tr>
<td>Misra et al, 2004 (24)</td>
<td>HC 20</td>
<td>15.8 ± 1.8</td>
<td>21.6 ± 0.6</td>
<td>21.4 ± 0.4</td>
<td>Ghrelin Solid test meal: 201 kcal, 55% CHO, 30% fat, 15% protein; lunch, 1304 kcal, 15% CHO, 75% fat, 10% protein</td>
<td>Blood sampling at 0, 60, 90, 120, and 180 min after test meal</td>
<td>Nadir: 60</td>
<td>271.5 ± 84.7</td>
<td>pg/mL</td>
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<td>Kojima et al, 2005 (21)</td>
<td>BN 10</td>
<td>24.7 ± 1.5</td>
<td>20.0 ± 0.6</td>
<td>20.2 ± 0.5</td>
<td>Ghrelin Solid test meal: 201 kcal, 55% CHO, 30% fat, 15% protein; lunch, 1304 kcal, 15% CHO, 75% fat, 10% protein</td>
<td>Blood sampling at 0, 60, 90, 120, and 180 min after test meal</td>
<td>Nadir: 60</td>
<td>178.2 ± 89.0</td>
<td>pg/mL</td>
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<td>Monteleone et al, 2005 (22)</td>
<td>HC 10</td>
<td>24.2 ± 3.9</td>
<td>21.7 ± 3.4</td>
<td>21.7 ± 3.4</td>
<td>Ghrelin Solid test meal: 201 kcal, 55% CHO, 30% fat, 15% protein; lunch, 1304 kcal, 15% CHO, 75% fat, 10% protein</td>
<td>Blood sampling at 0, 60, 90, 120, and 180 min after test meal</td>
<td>Nadir: 60</td>
<td>660.0 ± 362.0</td>
<td>pg/mL</td>
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<td>Otta et al, 2005 (25)</td>
<td>AN(Ad) 20</td>
<td>25.6 ± 1.0</td>
<td>15.1 ± 0.3</td>
<td>21.7 ± 3.4</td>
<td>Ghrelin Solid test meal (250 mL, Salvimulsin Standard, Nestlé, Frankfurt am Main, Germany): 250 kcal, 55%, CHO, 30% fat, 15% protein</td>
<td>Blood sampling at 0, 20, and 60 min after liquid test meal</td>
<td>Nadir: 60</td>
<td>291.2 ± 24.6</td>
<td>% change</td>
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<td>HC 6</td>
<td>28.8 ± 1.0</td>
<td>15.1 ± 0.3</td>
<td>21.7 ± 3.4</td>
<td>Ghrelin Liquid test meal: 55% CHO, 40% glucose solution</td>
<td>Blood sampling at 0, 20, and 60 min after liquid test meal</td>
<td>Nadir: 60</td>
<td>201.6 ± 64.4</td>
<td>% change</td>
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<td>Stock et al, 2005 (26)</td>
<td>AN 10</td>
<td>16.5 ± 0.4</td>
<td>16.3 ± 0.4</td>
<td>20.2 ± 0.4</td>
<td>Ghrelin Liquid test meal: 55% CHO, 20% fat, 25% protein</td>
<td>Blood sampling at 0, 15, 60, 90, 120, and 180 min after liquid test meal</td>
<td>Nadir: 90</td>
<td>238 ± 88.5</td>
<td>pg/mL</td>
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<tr>
<td>HC 10</td>
<td>14.8 ± 0.3</td>
<td>16.3 ± 0.4</td>
<td>20.2 ± 0.4</td>
<td>Ghrelin Liquid test meal: 55% CHO, 20% fat, 25% protein</td>
<td>Blood sampling at 0, 15, 60, 90, 120, and 180 min after liquid test meal</td>
<td>Nadir: 90</td>
<td>236 ± 240.3</td>
<td>pg/mL</td>
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<td>Nakahara et al, 2007 (27)</td>
<td>AN-R 14</td>
<td>24.6 ± 6.0</td>
<td>12.4 ± 1.7</td>
<td>20.2 ± 0.4</td>
<td>Ghrelin Solid test meal: 58% CHO, 22% fat, 20% protein</td>
<td>Blood sampling at 0, 30, 60, 120, and 180 min after test meal</td>
<td>Nadir: 120</td>
<td>138.9 ± 138.3</td>
<td>pg/mL</td>
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<td>HC 12</td>
<td>25.7 ± 6.7</td>
<td>12.4 ± 1.7</td>
<td>20.2 ± 0.4</td>
<td>Ghrelin Solid test meal: 58% CHO, 22% fat, 20% protein</td>
<td>Blood sampling at 0, 30, 60, 120, and 180 min after test meal</td>
<td>Nadir: 120</td>
<td>283 ± 70.4</td>
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<td>Kojima et al, 2005 (21)</td>
<td>BN 10</td>
<td>24.7 ± 1.5</td>
<td>20.0 ± 0.6</td>
<td>20.2 ± 0.5</td>
<td>Ghrelin Solid test meal: 58% CHO, 22% fat, 20% protein</td>
<td>Blood sampling at 0, 30, 60, 120, and 180 min after test meal</td>
<td>Peak: 30</td>
<td>9.2 ± 8.2</td>
<td>pg/mL</td>
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<td>HC 12</td>
<td>24.8 ± 0.8</td>
<td>21.5 ± 1.8</td>
<td>21.7 ± 3.4</td>
<td>Ghrelin Solid test meal: 58% CHO, 22% fat, 20% protein</td>
<td>Blood sampling at 0, 30, 60, 120, and 180 min after test meal</td>
<td>Peak: 30</td>
<td>268 ± 11.1</td>
<td>pg/mL</td>
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<td>21.7 ± 3.4</td>
<td>21.7 ± 3.4</td>
<td>Ghrelin Solid test meal: 58% CHO, 22% fat, 20% protein</td>
<td>Blood sampling at 0, 30, 60, 120, and 180 min after test meal</td>
<td>Peak: 60</td>
<td>15.7 ± 56.2</td>
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<td>Geraciotti and Liddle, 1988 (29)</td>
<td>BN 14</td>
<td>25.1 ± 5.9</td>
<td>—</td>
<td>—</td>
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<td>Blood sampling at intervals from 0 to 90 min after test meal</td>
<td>Peak: 20</td>
<td>1.3 ± 0.65</td>
<td>pg/mL</td>
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<td>HC 10</td>
<td>25.1 ± 5.9</td>
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<td>—</td>
<td>—</td>
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<td>Blood sampling at intervals from 0 to 90 min after test meal</td>
<td>Peak: 20</td>
<td>3.2 ± 0.76</td>
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<td>Philipp et al, 1991 (32)</td>
<td>BN 7</td>
<td>21 (17–25)</td>
<td>21.7 ± 2.1</td>
<td>20.1 ± 1.1</td>
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<td>Blood sampling at intervals from 0 to 90 min after test meal</td>
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<td>HC 8</td>
<td>28 (21–39)</td>
<td>21.7 ± 2.1</td>
<td>20.1 ± 1.1</td>
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<td>Blood sampling at intervals from 0 to 90 min after test meal</td>
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<td>3.2 ± 1.21</td>
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<td>Geraciotti et al, 1992 (35)</td>
<td>AN 6</td>
<td>24 ± 5.0</td>
<td>37.3 ± 3.5</td>
<td>56.0 ± 6.2</td>
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<td>Blood sampling at various times before and after consumption of test meal</td>
<td>Peak: 20</td>
<td>1.3 ± 2.22</td>
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<td>HC 6</td>
<td>24 ± 4.0</td>
<td>37.3 ± 3.5</td>
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<td>Blood sampling at various times before and after consumption of test meal</td>
<td>Peak: 20</td>
<td>2.3 ± 1.01</td>
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<th>Study</th>
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<th>n</th>
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<th>Timing</th>
<th>Test meal</th>
<th>Meal size</th>
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<td>AN</td>
<td>13</td>
<td>20.0 ± 2.0</td>
<td>Weight</td>
<td>76.8 ± 8.0</td>
<td>BMI</td>
<td>26.5 ± 4.0</td>
<td>CCK Oral glucose load 50 g</td>
<td>Blood sampling at 0, 30, 60, 90, 120 min after glucose load</td>
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<td>Devries et al, 1997 (30)</td>
<td>AN</td>
<td>8</td>
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<td>Weight</td>
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<td>BMI</td>
<td>1.8</td>
<td>CCK Oral glucose load 175 g, solid</td>
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<td>Fujimura et al, 1997 (23)</td>
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<td>Weight</td>
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<td>BMI</td>
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<td>BMI</td>
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<td>23.7 ± 1.2</td>
<td>BMI</td>
<td>1.8</td>
<td>CCK Oral glucose load 175 g, solid</td>
<td>Blood sampling at 0, 15, 30, 60, 90 min after glucose load</td>
</tr>
<tr>
<td>Devries et al, 1997 (30)</td>
<td>AN</td>
<td>8</td>
<td>26.2 ± 2.3</td>
<td>Weight</td>
<td>23.7 ± 1.2</td>
<td>BMI</td>
<td>1.8</td>
<td>CCK Oral glucose load 175 g, solid</td>
<td>Blood sampling at 0, 15, 30, 60, 90 min after glucose load</td>
</tr>
<tr>
<td>Study</td>
<td>Sample</td>
<td>n</td>
<td>Age</td>
<td>BMI</td>
<td>Measure</td>
<td>Test meal characteristics</td>
<td>Measurements</td>
<td>Timing</td>
<td>MMC</td>
</tr>
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<tr>
<td>Uhe et al, 1992 (37)</td>
<td>AN 10</td>
<td>20.1 ± 2.1</td>
<td>14.7 ± 0.7</td>
<td>PP</td>
<td>Solid test meal: 509 kcal, 39.9% CHO, 37.6% fat, 22.5% protein</td>
<td>Blood sampling at 0, 15, 30, 45, 60, 90, 120, 150, and 180 min after test meal</td>
<td>Peak 150</td>
<td>↑ 75.00 ± 34.6  ng/L</td>
<td></td>
</tr>
<tr>
<td>Fujimoto et al, 1997 (33)</td>
<td>AN+BN 6</td>
<td>20.9 ± 2.2</td>
<td>21.0 ± 0.7</td>
<td>PP</td>
<td>Solid test meal: 504 kcal, 8.5% CHO, 71.5% fat, 20% protein</td>
<td>Blood samples taken at various time points before and after the test meal</td>
<td>Peak 20</td>
<td>↑ 120.0 ± 39.8  ng·min/mL</td>
<td></td>
</tr>
<tr>
<td>Tomasik et al, 2005 (34)</td>
<td>AN 13</td>
<td>15 ± 2.0</td>
<td>14.8 ± 1.1</td>
<td>PP</td>
<td>Oral glucose load: 1.75 g/kg; solid test meal: 555 kcal, 60% CHO, 16% fat, 24% protein</td>
<td>Blood sampling at 0, 15, 30, 60, and 120 min after test meal</td>
<td>Peak 15</td>
<td>↑ 8.32 ± 3.3  μmol/L</td>
<td></td>
</tr>
<tr>
<td>Stock et al, 2005 (26)</td>
<td>AN-R 10</td>
<td>16.5 ± 0.4</td>
<td>16.3 ± 0.4</td>
<td>GIP</td>
<td>Liquid test meal: 55% CHO, 20% fat, 25% protein</td>
<td>Blood sampling at 0, 15, 30, 60, 120, 180, and 240 min after test meal</td>
<td>Peak 60</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Tomasik et al, 2002 (12) 90</td>
<td>AN 13</td>
<td>14.8 ± 1.5</td>
<td>20.5 ± 2.0</td>
<td>GLP-1</td>
<td>Oral glucose load: 1.75 g/kg; solid test meal: 555 kcal, 60% CHO, 16% fat, 24% protein</td>
<td>Blood sampling at 0, 15, 30, 60, and 120 min after test meal</td>
<td>Peak 60</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Pirke et al, 1994 (14)</td>
<td>AN 18</td>
<td>22.9 ± 9.8</td>
<td>13.1 ± 5.4</td>
<td>Somatostatin</td>
<td>Liquid test meal (500 mL Nutricia/100 mL cream: 800 kcal, 40% CHO, 40% fat, 20% protein)</td>
<td>Blood sampling at 0, 10, 20, 30, 45, 60, 80, and 100 min after test meal</td>
<td>Peak 150</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Casper et al, 1988 (11)</td>
<td>BN 13</td>
<td>23.7 ± 1.9</td>
<td>22.7 ± 0.7</td>
<td>Glucagon</td>
<td>Oral glucose load (Oranges: 100 g)</td>
<td>Blood sampling at 0, 15- and 30 min intervals for next 4 h</td>
<td>Nadir 60</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Tomasik et al, 2005 (34)</td>
<td>AN 13</td>
<td>15 ± 2.0</td>
<td>14.8 ± 1.4</td>
<td>Glucagon</td>
<td>Oral glucose load: 1.75 g/kg; solid test meal: 555 kcal, 60% CHO, 16% fat, 24% protein</td>
<td>Blood sampling at 0, 15, 30, 60, and 120 min after test meal</td>
<td>Nadir 60</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Uhe et al, 1992 (37)</td>
<td>HC 6</td>
<td>20.9 ± 2.2</td>
<td>21.0 ± 0.7</td>
<td>Gastrin</td>
<td>Solid test meal: 509 kcal, 39.9% CHO, 37.6% fat, 22.5% protein</td>
<td>Blood sampling at 0, 15, 30, 45, 60, 90, 120, 150, and 180 min after test meal</td>
<td>Peak 120</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

HC, healthy control subjects; AN, anorexia nervosa; AN-R, anorexia nervosa restricting subtype; AN-BP, anorexia nervosa binge-purging subtype; BN, bulimia nervosa; AN(Ad), anorexia nervosa group on admission before treatment; YY, peptide YY; CCK, cholecystokinin; PP, pancreatic polypeptide; GLP-1, glucagon-like peptide 1; GIP, gastric inhibitory peptide; NA, not available; CHO, carbohydrate; MMC, mean maximal change (↑ or ↓); direction of hormone concentration change in response to test meal; M, maximum hormone peak recorded (however, concentration may have continued to increase); IBW, ideal body weight; AN(1), the specific test session from the original research (test session 1 = AN subjects before treatment and any subsequent weight gain).

1 All values are means ± SDs or ranges.
2 Data obtained from graph.
3 Data supplied as area under the curve.
4 Data from reference 13.
5 Data from reference 34.
6 Data from oral-glucose-tolerance test.
7 Data from reference 12.
8 Second peak at 240 min in HC not seen in BN because of very high concentrations in 3 subjects.
Quantitative data synthesis

Outcomes clustered by hormone response were summarized by a meta-analysis if the number of studies available was ≥5. This applied to studies investigating ghrelin, PYY, CCK, insulin, and PP response. Analyses were carried out by using STATA 10.0 (StataCorp, College Station, TX) using the user-contributed command for meta-analyses METAN (15). Forest plots are used to show the meta-analyses with all the independent data available for each measure.

The MMC in hormone concentration for each participant group in each study was calculated by subtracting the basal or preprandial concentration from the maximum postprandial concentration. The mean difference in response between the ED and HC groups was standardized by calculating Cohen’s $d$, which is the difference between the 2 raw means divided by the pooled SD (16). Cohen’s $d$ is understood as negligible ($\geq 0$ and $< 0.15$), small ($\geq 0.15$ and $< 0.4$), medium ($\geq 0.4$ and $< 0.75$), large ($\geq 0.75$ and $< 1.10$), very large ($\geq 1.10$ and $< 1.45$), and huge ($\geq 1.45$).

The standardized effect sizes were subsequently analyzed by using METAN. The SE of each study’s standardized effect size was calculated from the estimated effect and the group sizes of the 2 groups (ie, AN or BN group compared with HC group) by using the method of Cooper and Hedges (17), which is implemented in METAN. These were then pooled by using a random-effects model that allowed for between-study variation of effect sizes (18). Homogeneity between the studies was analyzed by using Cochran’s $Q$ test. Because of the relatively small sample sizes, an additional measure of heterogeneity or inconsistency, $I^2 = (Q - df)/Q$, was calculated (19). $I^2$ ranges between 0% (low heterogeneity) and 100% (high heterogeneity).

Seventeen meta-analyses were conducted for ghrelin, PYY, CCK, insulin, and PP, including basal concentrations and comparisons of the response to test meals between the ED and HC groups and, where possible, between the AN or BN group and the HC group separately. Insufficient studies were available to conduct a meta-analysis comparing PYY between the AN and HC groups or to conduct meta-analyses comparing all variables except CCK, for which there were sufficient studies, between the BN and HC groups.

RESULTS

Descriptive data for each study are shown in Table 1, including sample type, sample size, age, BMI, and test meal or glucose load characteristics. Quantitative data for the studies included in the meta-analyses are in the form of MMC in hormone concentrations from baseline preprandial concentrations to the maximum postprandial peak or nadir. These data were used to calculate the standardized effect sizes and CIs. Across the 28 included studies, the mean BMI of the AN group was significantly lower than that of the HC groups. In the BN groups, the mean BMI was not significantly different from that of the HC groups.

Ghrelin

Eight studies investigated the ghrelin response; 3 included BN and HC groups (20–22) and 5 included AN and HC groups (23–27), of which 4 identified AN subtypes, either restrictive type (AN-R), binge-purging type (AN-BP), or both (23, 24, 26, 27). All subjects were female, with an age range of 14 to 28 y. All ED patients were diagnosed according to the Diagnostic Statistical Manual IV (DSM-IV) criteria. Sample sizes varied between 9 and 20 subjects in the ED groups, with a mean of 12 subjects. Of these studies, 3 reported using total acetylated or bioactive ghrelin and non- or de-acetylated ghrelin in the biochemical assays (23, 26, 27), 1 reported using C-terminal ghrelin only (25), and 4 did not identify ghrelin type (20–22, 24).

All 8 studies were included in the meta-analysis. One study did not contain raw data for the baseline hormone concentrations and thus could only be included in the meta-analysis of the MMC in hormone concentration (25), and one study included data for both AN-R and AN-BP subjects (23). These data were subsequently treated as 2 separate studies for the purposes of the analysis.

The baseline contrasts in plasma ghrelin between patients and control subjects are shown in Figure 1. One study was an outlier with lower concentrations of ghrelin in the BN group (20). All of the other studies showed an increase in baseline ghrelin concentrations in all ED groups. A meta-analysis of these data, excluding the outlier, showed that the ED groups had higher plasma ghrelin concentrations at baseline than did the HC group, with a large effect size ($d = 1.05$, $z = 4.32$, $P < 0.0001$). Heterogeneity across the studies was moderate ($\chi^2 = 12.11$, $P = 0.059$, $I^2 = 50.5\%$). There was a suggestion that the increase in ghrelin concentrations was more robust in persons with AN ($d = 1.26$, $z = 4.82$, $P < 0.0001$). The MMC in ghrelin concentration after a test meal or glucose load is shown in Figure 2. Again, one study appeared to be an outlier (20). Overall, ghrelin release to a meal was no different in persons with ED than in the HC groups ($P = 0.968$).

Peptide YY

Five studies investigated the PYY response. Two included BN and HC groups only (21, 22), 3 included AN and HC groups (26–28), all of which identified the ED participants as AN-R (26–28). All subjects were female, ranging in age from 14 to 28 y. All ED groups and HC groups only (21, 22), 3 included AN and HC groups (26–28), all of which identified the ED participants as AN-R (26–28).

FIGURE 1. Forest plot showing the summarized results and effect sizes (with 95% CIs) for differences in mean baseline plasma ghrelin concentrations between different subtypes of eating disorder (ED) patients and healthy control (HC) subjects. , anorexia nervosa restricting type; , anorexia nervosa binge-purging type; , bulimia nervosa.
patients were diagnosed according to the DSM-IV criteria. Sample sizes varied between 9 and 16 subjects in the ED groups, with a mean of 12 subjects.

The baseline differences in PYY between ED and HC subjects are shown in Figure 3. Overall, persons with ED had higher plasma PYY concentrations at baseline with a medium effect size ($d = 0.64$, $z = 2.55$, $P < 0.05$), although the range overlapped with zero in most of the studies. Heterogeneity across the studies was low ($\chi^2 = 6.27$, $P = 0.180$, $I^2 = 36.2\%$). It was not possible to conduct a meta-analysis of either of the ED subtypes separately because of an insufficient number of studies. The MMC in PYY concentration after a meal is shown in Figure 4 ($P = 0.101$). Heterogeneity was high ($\chi^2 = 20.21$, $P = 0.000$, $I^2 = 80.2\%$). Overall, there appeared to be a large but non-significant decrease in meal-related PYY in persons with ED.

### Cholecystokinin

Eight studies investigated the CCK response. Three included BN and HC groups only (29–31); 2 included AN, BN, and HC groups (32, 33); and 3 included AN and HC groups only (34–36). Only one study identified the AN subtype AN-BP (33). All subjects were female, with the exception of one male subject in the study by Phillipp et al (32). The subjects ranged in age between 15 and 28 y. Diagnoses of ED were made according to DSM-III or DSM-III-R criteria in 4 of the studies and according to DSM-IV criteria in 2 studies. In one study, the diagnoses were made according to the criteria of Feighner et al (36), and the diagnostic criteria were not stated in one study (35). Sample sizes varied between 6 and 37 subjects in the ED groups, with a mean of 13 subjects.

The baseline concentrations of CCK are shown in Figure 5. Overall, no significant effects were found for baseline CCK concentrations between ED and HC groups ($P = 0.565$). Heterogeneity across the studies was high ($\chi^2 = 86.39$, $P = 0.000$).
In anorexia nervosa binge-purging type; anorexia nervosa; bulimia nervosa. 1Oral-glucose-tolerance test. 2Solid test meal.

Nevertheless, on removal of this study, the meta-analysis suggested that baseline CCK concentrations were increased in the ED group with a moderate effect size ($d = 0.54, z = 2.16, P < 0.04$). Heterogeneity was also reduced ($\chi^2 = 16.65, P = 0.020, I^2 = 58.0\%$). The increase in baseline CCK was stronger in studies of persons with AN ($d = 1.21, z = 4.50, P < 0.0001$).

Overall, no significant effects were found for the MMC in CCK after a test meal or glucose load in persons with ED (Figure 6; $P = 0.825$), or for either the AN or BN subtypes alone ($P = 0.140$ and $P = 0.133$, respectively). Heterogeneity across the studies was very high ($\chi^2 = 143.32, P = 0.000, I^2 = 92.3\%$).

Insulin

Ten studies investigated the insulin response, one of which could not be included in the meta-analysis because of an absence of raw data (11). Two studies included BN and HC groups (11, 21). Eight studies included AN and HC groups (23, 26, 27, 34, 36–39): 1 identified the AN subtypes AN-R and AN-BP (23) and 2 identified AN-R only (26, 27). All subjects were female, with the exception of 2 male subjects in the study by Kinzig et al (39). The subjects ranged in age between 15 and 27 y across the 9 studies. ED patients were mainly diagnosed according to DSM-IV criteria. One study did not state the diagnostic criteria (37). Sample sizes varied between 9 and 14 subjects in the ED groups, with a mean of 11 subjects.

No differences were found in baseline insulin concentrations between the ED and HC groups (Figure 7; $P = 0.339$). However, heterogeneity across the studies was high ($\chi^2 = 59.66, P = 0.000, I^2 = 83.2\%$). The MMC in insulin concentration is shown in Figure 8. One study appeared to be an outlier (38). On removal of this study, a medium effect was observed; ED groups showed a trend toward a smaller release of insulin in response to a test meal or glucose load than did HC subjects ($d = 0.54, z = 1.96, P = 0.05$). This effect was not observed in persons with AN alone ($P = 0.110$). Heterogeneity across the studies was moderately high ($\chi^2 = 32.48, P = 0.000, I^2 = 72.3\%$).

Pancreatic polypeptide

Five studies investigated the PP response: 3 in AN alone (34, 37, 39) and 1 in BN (11). Fujimoto et al (33) investigated AN and BN and identified the AN subtypes AN and AN+BN (AN-BP). However, this study did not contain raw data for the baseline hormone concentrations and thus could only be included in the meta-analysis of the MMC in hormone concentration. All subjects were female, with the exception of 2 male subjects in the study by Kinzig et al (39). The subjects ranged in age between 15 and 27 y across the 5 studies. ED patients were diagnosed according to DSM-III or DSM-IV criteria. One study did not state the diagnostic criteria (37). Sample sizes varied between 5 and 13 subjects in the ED groups, with a mean of 10 subjects. No differences were found in baseline PP concentrations between the ED and HC groups (Figure 9; $P = 0.203$).
or in postprandial release (Figure 10; \(P = 0.988\)). Heterogeneity was high in the stimulated condition (\(\chi^2 = 68.83, P = 0.000, F^2 = 89.8\%\)).

**Remainng hormones**

GIP was only investigated in ED patients with AN in 2 studies, and the findings are mixed. Stock et al (26) found that baseline GIP concentrations were significantly lower in the AN group than in the HC group, whereas, Tomasik et al (13, 34) found significantly higher GIP concentrations in the AN group. In response to the test meal, Stock et al found a significantly lower GIP peak in the AN group, although a significant (2 to 3 times) increase in GIP concentrations was observed in both the AN and HC groups. Conversely, Tomasik et al found that the integrated output of GIP in both the oral-glucose-load and test-meal conditions was significantly higher in the AN group than in the HC group.

Mean basal GLP-1 concentrations were significantly lower in the AN than in the HC group (12, 13, 34). After the oral glucose load, mean integrated GLP-1 outputs were twice as high in both groups as after the test meal; however, mean integrated outputs were significantly higher in the HC group than in the AN group in both tests (34). No other studies examined GLP-1 concentrations and the response to food. Pirke et al (14) observed that all groups showed a significant increase in somatostatin secretion after the test meal and that the AN subjects showed a significantly greater increase than both the HC and weight-restored AN subjects.

Glucagon concentrations were examined in both the BN (11) and AN (34) subjects. No significant differences were found between BN and HC for either baseline plasma glucagon concentration or the glucagon decline curve and the subsequent increase. Baseline glucagon concentrations were significantly lower in the AN group than in the HC group. The integrated output of glucagon after both the oral glucose test and the test meal was higher in the AN than in the HC group. In the AN group, glucagon increased initially 15 min after the test meal and then decreased rapidly; this was not observed in the HC group. Gastrin response was examined in one study only and was found to be significantly lower in the AN group than in the HC group (37). The AN subjects also showed significantly lower basal gastrin concentrations.

**DISCUSSION**

We synthesized the results on baseline and short-term physiologic response to food from 24 studies that fulfilled our inclusion criteria. The only hormones for which there were sufficient studies to conduct a meta-analysis were ghrelin, PYY, CCK, insulin, and PP. The results were highly heterogeneous, most of the studies were small, and the diagnostic and symptomatic subgroups were poorly defined; therefore, the conclusions are limited. Persons with ED had higher baseline concentrations of ghrelin (large effect, especially in AN) and PYY (medium effect), which agrees with our first hypothesis. These groups also showed increased baseline concentrations of CCK (medium effect for the ED group, very large effect for the AN group). There was insufficient evidence to compare differences between restricting and binge-eating groups. BMI was significantly lower in the AN groups than in the HC groups. This may have physiologic implications for the release of gut hormones at baseline. To assess the impact of a low BMI, a review of the long-term changes in plasma hormone concentrations in AN patients would be helpful, comparing values before and after weight restoration.

There was no support for the second part of our hypothesis, which was that the hormonal response to a standardized test meal would be disturbed. The lack of standardization of meals across studies is considered a limitation. The release of the gut peptides ghrelin, PYY, and CCK to a meal was within the normal range across studies, as defined by a comparison of mean hormone responses in the ED groups with those of an HC group, considered in this case to be showing “normal” responses. Although there was an insufficient number of studies that examined the ghrelin response to a test meal in BN, the data indicate that the ghrelin responses in this subtype are blunted (20–22). This may result in a diminished sensation of satiety with implications for continued binge-purge behaviors. Further study is required. Blunted or reversed PYY responses in BN were also observed in 2 studies (21, 22). Insulin was the only hormone to have
a medium effect in ED patients, which showed a trend toward a decreased release of insulin in response to a test meal or glucose load as compared with HC subjects. This observation agrees with previous reports that persons with AN have an increased sensitivity to insulin and a reduced insulin response (3, 26).

Elevated ghrelin concentrations at baseline might be expected in persons with an ED, particularly those with AN, because this hormone acts to increase food intake. The increase in baseline concentrations of CCK and PYY in AN is somewhat surprising because these gut hormones act to suppress appetite. However, in many studies, the confidence limits overlapped zero. It is possible that the baseline results are more susceptible to confounding by factors such as time since last meal and stress levels than are the results of the more standardized procedure, ie, the meal. The timing of the hormone responses to food was extremely variable across all studies, and limited conclusions could be drawn from the data.

Overall, a high degree of heterogeneity was observed between the studies. Many factors may have accounted for these highly divergent results, including differences in the clinical characteristics of the samples, technical differences in the protocol used to administer the test meals and oral glucose loads (eg, differences in the macronutrient composition of the meals and in meal patterns before the study), and technical differences in the methods used to ascertain hormone concentrations (eg, the differentiation of inactive from active ghrelin or lack thereof, timing of meals, and sample collection time points). In particular, the test meals were only standardized within studies, not between studies, and as such the variability in meal composition may act to confound the results. In addition, the collection and preservation of the samples is a critical process because they can easily denature and some (eg, PYY) are released as part of a stress response.

The baseline concentrations differed in many cases between the ED and HC groups. This may have consequences for the postprandial hormone response patterns being examined. As a result, use of the area under the curve may be a more valid measure of response. However, because of the diverse nature of the reported data across the studies it was not possible to determine the area under the curve in sufficient cases.

There were also differences in the case mix, eg, inclusion criteria, stage of illness, range of ED symptoms, vomiting, laxative and diuretic abuse, and comorbidity. Another potentially confounding factor may have been the absence of raw data for many of the studies, which resulted in values being read from the published graphs. This may have led to inaccuracies in some of the data used in the meta-analyses. Much of the data presented were also recorded, analyzed, and reported differently across the studies.

In conclusion, the data in part support our first hypothesis, which was that ED patients would have abnormal fasting hormone concentrations (ie, baseline ghrelin and PYY concentrations were elevated). The finding of elevated baseline PYY and CCK concentrations was interesting, particularly in the AN groups, because it would not be predicted as a secondary response to starvation, but the confidence in this result is limited; therefore, additional high-quality studies are needed. A review and meta-analysis of studies in patients before and after recovery would also confirm or reject the hypothesis that these disturbances are state- rather than trait-related. The data suggest that the hormonal response to food is disturbed to a greater extent in BN, which may contribute to certain behavioral aspects of the disorder. However, again, more high-quality studies are required to further explore this hypothesis.

Another area of interest is the interaction between the gut and the brain, specifically how gastrointestinal responses may not simply impact food-related pathways, but may have broader aspects of reward. Obesity-prone rats have abnormalities in their dopamine system—a key component of hedonic regulation (40). Gut hormones, such as PYY, in humans alter brain activation in these limbic areas (41). Also, links exist between feeding and emotion (42), and ghrelin may serve as a defense against depressive symptoms of chronic stress (43). Unraveling and identifying these links and the underlying mechanisms is key to our understanding of both the development, onset, and maintenance of EDs.

We acknowledge the support of the ARIADNE program (Applied Research into Anorexia Nervosa and Not Otherwise Specified Eating Disorders), which was funded by a Department of Health NIHR Programme Grant for Applied Research (reference number RP-PG-0606-1043) to U Schmidt, J Treasure, K Tchanturia, H Startup, S Ringwood, S Landau, M Grover, I Eisler, I Campbell, J Beecham, M Allen, and G Wolff. The views expressed herein are not necessarily those of DH/NIHR. We also thank Carolina Lopez for her invaluable assistance in the statistical analysis of the data and the Nina Jackson Foundation for Research into Eating Disorders who fund Samantha Brooks.

The authors’ responsibilities were as follows—ACP: main author of the manuscript; JT: initiated research topic, edited manuscript drafts, and provided invaluable guidance during paper selection, draft development, and final submission; SJB: viewed and critiqued the manuscript and provided significant input in the early stages of the review in terms of idea development, discussion of the topic, and practicalities of conducting a meta-analysis; and DS: contributed to the statistical analysis of the data. None of the authors declared a conflict of interest.

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