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Normalizing Eating Behavior Reduces Body Weight and Improves Gastrointestinal Hormonal Secretion in Obese Adolescents

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Hypothesis: Retraining obese adolescents to eat more slowly will lead to beneficial changes in circulating concentrations of gastrointestinal satiety hormones.

Methods: Ghrelin and peptide tyrosine-tyrosine were measured during an oral glucose tolerance test, at baseline and at 12 months during a randomized trial assessing the clinical effectiveness of a device (Mandometer) designed to retrain eating behavior. This computerized scale provided real-time feedback during meals in the intervention arm (n = 14) to slow down the speed of eating. The control group (n = 13) received only standard care aimed at improving lifestyle behavior. The Mandometer elicited greater improvements in weight loss than standard care.

Results: Compared with baseline, only those using the Mandometer exhibited lower mean levels of fasting ghrelin (48.14 ± 18.47 *vs.* 68.45 ± 17.78 pg/ml; $P = 0.002$) and mean ghrelin area under the curve (72.08 ± 24.11 *vs.* 125.50 ± 29.72 pg/ml × min; $P < 0.001$) at 12 months. Absolute mean suppression in ghrelin at 60 min was enhanced (−40.50 ± 21.06 *vs.* −12.14 ± 19.74 pg/ml × min; $P = 0.001$). Peptide tyrosine-tyrosine response at 90 min remained unaltered in the standard care arm, whereas those in the Mandometer arm increased ($P < 0.001$): the mean 90-min response increased by 72 pg/ml [95% confidence interval (CI) 52–92 pg/ml] between baseline and 12 months. In a partial correlation analysis adjusting for change (Δ) in body mass index SD scores, Δ meal duration correlated negatively with Δ absolute suppression in ghrelin at 60 min ($r = -0.58$; $P = 0.037$; 95% CI −0.79 to −0.27) and Δ ghrelin area under the curve ($r = -0.62$; $P = 0.025$; 95% CI −0.81 to −0.31).

Conclusions: Retraining obese adolescents to eat more slowly has a significant impact on the gastrointestinal hormone response to a carbohydrate load, suggesting that externally modifiable eating behaviors actually regulate the hormonal response to food. **(*J Clin Endocrinol Metab* 97: 0000–0000, 2012)**

Body weight is regulated by a powerful homeostatic system that controls appetite and energy expenditure through the existence of peripheral factors that communicate the status of body energy stores to the brain (1). These hormones are classified as long-acting adiposity signals (leptin and insulin), which regulate overall body weight, and short-acting gastrointestinal factors [ghrelin, peptide tyrosine-tyrosine (PYY), pancreatic polypeptide,

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Abbreviations: AUC, Area under the curve; BMI, body mass index; Δ, change in; CI, confidence interval; HOMA-IR, homeostasis model assessment for insulin resistance; OGTT, oral glucose tolerance test; PYY, peptide tyrosine-tyrosine; SDS, SD score.

glucagon-like peptide-I, oxyntomodulin, and cholecystokinin], which control appetite and are acutely affected by food consumption. With the exception of ghrelin, all these circulating factors are anorexigenic and promote reductions in food intake (1, 2).

Active ghrelin, a 28-amino acid acylated peptide secreted by the oxyntic cells in the stomach fundus, binds to the GH secretagogue receptors to increase the release of GH from the pituitary (3). It powerfully increases premeal hunger and meal initiation through the stimulation of the hypothalamic neurons that cosecrete neuropeptide Y and agouti gene-related peptide (4, 5). Its plasma levels rise in the fasted state and fall to a nadir about 1 h after eating (6). This postprandial fall is proportional to ingested calories, with fat causing less suppression than carbohydrates or proteins (7). PYY is a 36-amino acid peptide released from the endocrine L cells lining the distal small bowel and colon. Most circulating PYY is the 34-amino acid N terminally truncated form ($PYY_{3–36}$) (8). Plasma $PYY_{3–36}$ levels are low during fasting and peak in the second hour after eating. This postprandial peak level is also determined by the consumed calories and meal composition. $PYY_{3–36}$ binds to the Y2 receptor expressed on the neuropeptide Y neurons causing its inhibition and consequently disinhibiting the proopiomelanocortin neurons. All these chain reactions culminate in an increase of α-MSH, leading to a final anorectic effect (9).

Studies have demonstrated that obese and normal-weight subjects have different baseline levels of these two gut hormones as well as different dynamic responses after meals. Obese patients demonstrate lower levels of fasting ghrelin and absolute suppression in response to a glucose load (even if the percentage suppression is similar to the lean subjects) (10, 11). In obese subjects, a loss of the normal physiological reduction in postprandial ghrelin to calories ingested may contribute to an increase in the total amount of food ingested during a meal, creating a vicious obesogenic circle. Fasting and meal suppression levels appear related to insulin sensitivity (independently of adiposity): the more insulin resistant the subject, the lower the fasting ghrelin and degree of absolute suppression after a meal. On the

TABLE 1. Baseline characteristics of the study subjects

	Standard care group (n = 13)	Mandometer group (n = 14)	*P* value
Age (yr) median (range)	12.38 (9.46–16.52)	11.45 (9.27–16.66)	0.46
Female	7 (54%)	8 (57%)	0.74
British white	13 (100%)	11 (79%)	0.09
Pubertal stage			
Prepubertal	4 (31%)	7 (47%)	0.55
Pubertal	7 (54%)	5 (33%)	
Postpubertal	2 (15%)	3 (20%)	
BMI SDS mean (SD)	3.10 (0.54)	3.44 (0.48)	0.08
Percent body fat SDS mean (SD)	2.62 (0.65)	3.00 (0.69)	0.16
Meal portion size (g) mean (SD)	281 (89)	363 (121)	0.04
Meal duration (min) mean (SD)	10.28 (2.62)	10.61 (2.59)	0.71
Satiety level[a]			
Premeal mean (SD)	22.4 (10.5)	16.9 (12.2)	0.22
Postmeal mean (SD)	72.1 (23.6)	67.8 (18.3)	0.51
Glucose			
Fasting (mmol/liter) mean (SD)	4.51 (0.47)	4.66 (0.38)	0.37
30 min (mmol/liter) mean (SD)	7.82 (1.64)	7.85 (1.35)	0.91
AUC mean (SD) (mmol/liter × min)	12.38 (1.94)	12.73 (1.78)	0.66
Insulin			
Fasting (μIU/ml) geometric mean (range)	19.0 (7–74)	16.9 (7–45)	0.61
30 min (μIU/ml) geometric mean (range)	182.0 (62–1000)$^{n = 12}$	180.1 (46–768)	0.74
Ratio of 30 min to fasting value geometric mean (range)	9.64 (4.6–23.2)$^{n = 12}$	10.67 (5.1–26.5)	0.54
HOMA-IR geometric mean (range)	3.78 (1.49–15.13)	3.49 (1.34–9.80)	0.71
Ghrelin			
Fasting (pg/ml) mean (SD)	62.41 (22.13)	68.45 (17.78)	0.24
Absolute suppression at 60 min (pg/ml) mean (SD)	−15.99 (24.15)	−12.14 (19.74)	0.99
Percent suppression at 60 min mean (SD)	−17.98 (35.47)	−11.66 (28.67)	0.74
AUC (pg/ml × min) mean (SD)	104.49 (20.07)	125.50 (29.72)	0.06
PYY			
Fasting (pg/ml) median (range)	<19 (<19 to 115.4) [9][b]	<19 (<19 to 58.8) [8][b]	0.57
90 min (pg/ml) median (range)	19.0 (<19 to 77.7) [6][b]	28.4 (<19 to 59.5) [4][b]	0.40

[a] Zero being very hungry and 100 being completely satiated.

[b] Number of assays less than 19 pg/ml in brackets.

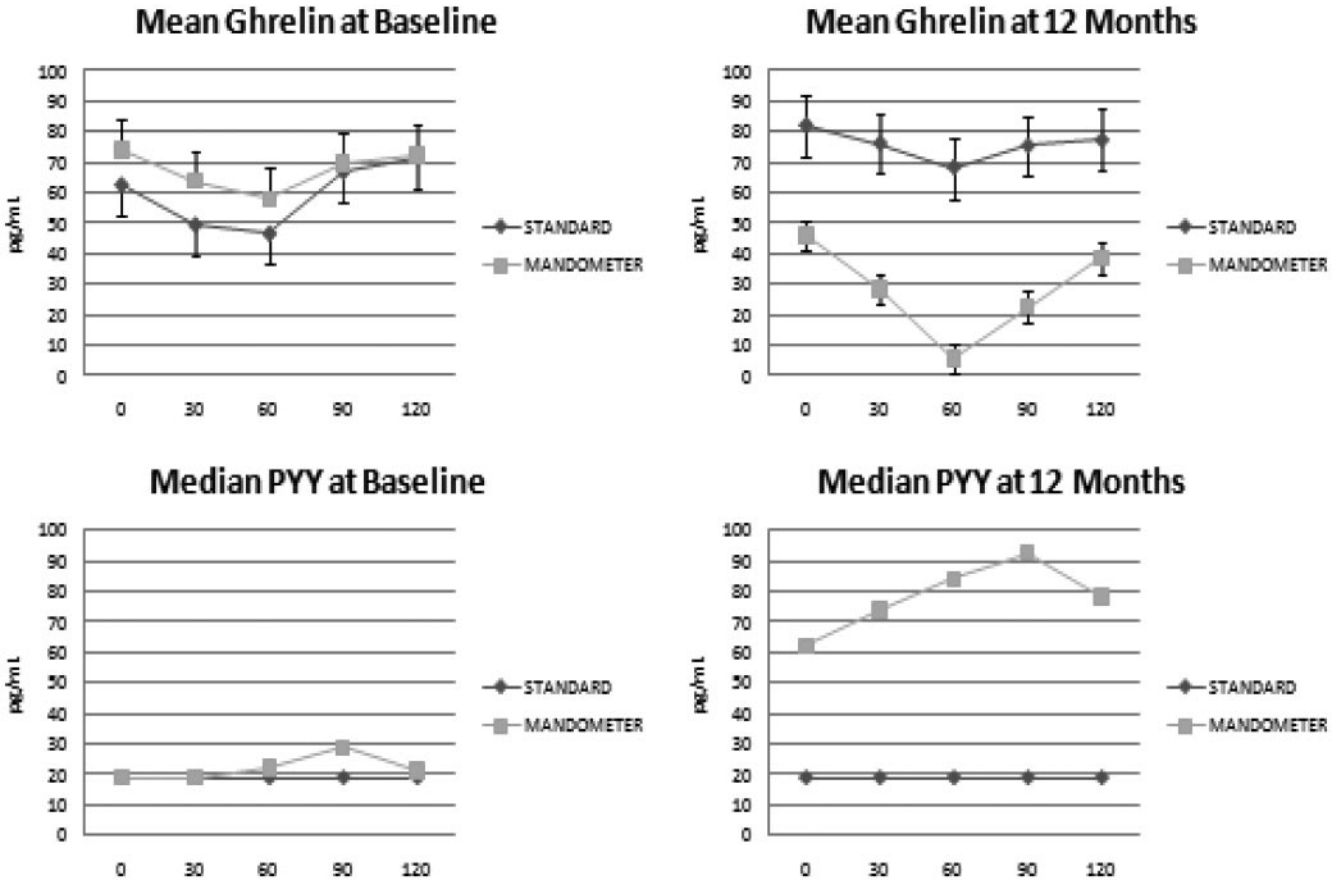

FIG. 1. Ghrelin and PYY levels during the OGTT at baseline and after 12 months of intervention.

other hand, attenuated ghrelin suppression may also act in concert with other gut hormone changes, culminating in an inhibition of satiety (12, 13). However, the true physiological role of ghrelin remains incompletely understood. For instance, children with Prader-Willi syndrome, a condition characterized by profound obesity and hyperphagia, have fasting hyperghrelinemia with an exaggerated postprandial suppression, whereas animal ghrelin knockout experiments identified no phenotypic change in growth or appetite (14, 15).

Furthermore, the obese demonstrate reduced fasting PYY levels and lower endogenous postprandial peaks. The lack of a significant postprandial PYY response may relate to reduced satiety and, thus, obese subjects may have a weaker PYY-induced signal for an equivalent meal when compared with normal-weight people (16, 17).

Eating quickly is known to be positively associated with both body weight and insulin resistance (18–20). A recent study undertaken in 17 healthy adults examining postprandial concentrations of appetite-regulating hormones provided preliminary evidence that eating similar meals at a slower pace can modify these responses with more pronounced anorexigenic PYY and glucagon-like peptide-I secretion, although ghrelin suppression did not differ significantly (21).

From 2004 to 2007, a randomized controlled trial, in 106 obese young people aged 9–17 yr, assessed whether retraining eating behaviors using a computerized scale, a Mandometer (Mikrodidakt, Lund, Sweden), which provided real-time feedback during meals, to slow down the speed of eating, was able to improve weight loss when used in combination with standard dietary and activity counseling. Compared with standard lifestyle modification therapy, the 1-yr intervention achieved a greater mean reduction in body mass index (BMI) SD score (SDS) (−0.4 *vs.* −0.14). At 12 months this weight loss was achieved in conjunction with reduced patient-determined, portion sizes during test meals without compromising levels of satiety as defined on an arbitrary scale and measured at 2-min intervals during these meals; subjects reported feeling as satiated as they did at study entry despite consuming less food. These effects were sustained at 18 months, 6 months after ending active treatment with the Mandometer device (22). Although demonstrating that retraining eating behaviors led to improved outcome in terms of weight loss, we wanted to examine potential mechanistic pathways that might underpin these encouraging results. We hypothesized that increased postprandial suppression of ghrelin and improved augmentation of circulating PYY

might be associated with improved outcome in the Mandometer intervention.

The Mandometer study was registered at www.ClinicalTrials.gov NCT00407420.

Materials and Methods

Participants

The study was conducted at Bristol Royal Hospital for Children in the United Kingdom. Eligibility criteria were ages older than 9 yr and younger than 18 yr at recruitment, a BMI greater than the 95th percentile, minimal/no learning difficulties, no underlying medical problem such as hypothyroidism, and no medication for insulin resistance. Participants were recruited from new patients at the Care of Childhood Obesity Clinic. Ethical approval was obtained from the United Bristol Hospitals Trust Research Ethics Committee (REC reference 04/Q2006/9). Written informed consent was obtained from all participating families. The last 27 patients recruited consecutively into the study [Mandometer intervention arm (n = 14) and standard intervention arm (n = 13)] had samples stored for analysis of gut peptide responses during the per-protocol oral glucose tolerance test (OGTT) at baseline and 12 months. These 27 subjects did not differ significantly from the rest of the cohort with respect to anthropometric or biochemical measurements. Hormonal analysis was undertaken by a researcher blinded to treatment allocation.

Intervention

The intervention has been described in detail elsewhere (22). Briefly, the Mandometer consists of a digital scale connected to a computer. Food is placed on a plate on the scale and as the subject eats, the weight of the plate reduces, yielding a curve for the rate of eating. In therapy, this curve is visible to the subject. During the main meal of the day (usually the evening meal) and on a daily basis, the subject aims to match their eating rate with an ideal rate shown on the monitor developed from healthy, normal-weight adult volunteers (23). At regular intervals during the meal, a rating scale also appears on the monitor asking the subject to rate their level of fullness, and the subject is encouraged to match their satiety scores with this ideal. In essence, Mandometer training helps the subject to relearn more normal patterns of eating and satiety through a program involving approximately four new training curves to gradually modify eating speed. Treatment aims to help the subject feel full after eating 300–350 g of food over 12–15 min.

Data collection

Anthropometry, early morning 12 h-fasting, and OGTT (1.75 g/kg, maximum 75 g) blood samples (0, 30, 60, 90, and 120 min) data were collected. Patient blinded test meals were undertaken at baseline and 12 months to assess changes in: patient determined portion size, grams of food consumed, meal duration, and development of satiety during meal (arbitrary visual analog scale, with zero being very hungry and 100 being completely satiated). Patient blinding was achieved by not providing

TABLE 2. Changes in eating phenotype and hormonal responses after 12 months of treatment

	Standard care group (n = 13)			
	Baseline	12 Months	Mean/median change (95% CI)	*P* value
BMI SDS mean (SD)	3.10 (0.54)	2.95 (0.60)	−0.14 (−0.36 to 0.07)	0.17
Percent body fat SDS mean (SD)	2.62 (0.65)	2.56 (0.57)	−0.06 (−0.27 to 0.15)	0.56
Meal portion size (g) mean (SD)	272 (95)[b]	254 (96)[b]	−18 (−107 to 70)[b]	0.65
Eating time (min)	10.42 (2.80)[b]	8.61 (2.36)[b]	−1.81 (−4.79 to 1.17)[b]	0.21
Premeal satiety level mean (SD)[c]	22.3 (11.4)[b]	20.5 (11.0)[b]	−1.9 (−10.0 to 6.3)[b]	0.62
Postmeal satiety level mean (SD)[c]	70.8 (24.0)[b]	60.7 (26.0)[b]	−10.1 (−32.1 to 12.0)[b]	0.33
Fasting glucose (mmol/liter) mean (SD)	4.51 (0.47)	4.55 (0.35)	0.05 (−0.22 to 0.31)	0.71
Glucose AUC (mmol/liter × min) mean (SD)	12.38 (1.94)	12.15 (2.26)	−0.23 (−1.40 to 0.95)	0.68
Fasting insulin (μIU/ml) geometric mean (range)	19.0 (7 to 74)	19.1 (6 – 64)	0.99 (0.80–1.23) (d′)	0.96
Insulin at 30 min (μIU/ml) geometric mean (range)	182.0 (62 to 1000)[e]	157.4 (31 to 657)[e]	1.16 (0.75–1.78)[d,e]	0.48
Insulin ratio of 30 min to fasting value geometric mean (range)	9.64 (4.6 to 23.2)[e]	8.41 (1.7 to 23.2)[e]	1.15 (0.74–1.77)[d,e]	0.50
HOMA-IR geometric mean (range)	3.78 (1.49 to 15.13)	3.85 (1.31 to 13.94)		0.89
Fasting ghrelin (pg/ml) mean (SD)	62.41 (22.13)	82.23 (41.87)	19.82 (−7.92 to 47.57)	0.15
Δ Ghrelin at 60 min (pg/ml) mean (SD)	−15.99 (24.15)	−14.07 (18.34)	1.92 (−14.49 to 18.33)	0.80
Percent of ghrelin suppression at 60 min mean (SD)	−17.98 (35.47)	−14.34 (14.21)	3.64 (−15.90 to 23.17)	0.69
Ghrelin AUC (pg/ml × min) mean (SD)	104.49 (20.07)	141.67 (58.51)	37.18 (−0.45 to −73.91)	0.048

[a] n = 13.

[b] n = 11.

[c] Zero indicates very hungry and 100 indicates completely satiated.

[d] Mean (and 95% CI) change was calculated using log units and backtransformed; these figures therefore relate to the mean ratio, rather than difference.

[e] n = 12.

the individualized training lines for portion size and recommended speed of eating or any visible feedback on the computer while the subject consumed their meal. The data on total food consumption in grams and meal duration were, however, recorded on the Mandometer device for later analysis.

Samples were collected in EDTA tubes containing aprotinin (100 μl per 5 ml blood), kept on ice, and centrifuged within 15 min of collection. The plasma was then separated in aliquots and acidified with 1 N HCl (50 μl per 1 ml plasma). After the addition of phenylmethylsulfonyl fluoride (10 μl per 1 ml plasma) and precipitation removed by centrifugation, the samples were immediately stored in a −80 C freezer until analysis. Serum glucose levels were determined using a two-step enzymatic assay Olympus AU640 analyzer (Olympus Diagnostic Systems, Southall, Middlesex, UK). Plasma insulin levels were measured on a COBAS Elecsys by electrochemiluminescence sandwich immunoassay (Roche Professional Diagnostics Products, Burgess Hill, West Sussex, UK).

Measurements of ghrelin and PYY were performed with the inclusion of quality controls to determine the interassay variability. Samples were always kept on ice and assayed in duplicate as quickly as possible and mean values calculated. The bioactive octanoylated form of ghrelin was measured with a single-site RIA kit (Linco Research, St. Charles, MO). It used ^{125}I-labeled ghrelin tracer and guinea pig antighrelin antibody that has less than 0.1% cross-reactivity with des-octanoylghrelin. The lower limit of detection for this assay was 7.8 pg/ml, with 7% intraassay and 13% interassay coefficients of variation. $PYY_{3–36}$ was determined by a RIA kit (Linco Research) that uses ^{125}I-labled PYY tracer and a guinea pig $PYY_{3–36}$ antibody. The lower limit of detection for this assay was 19 pg/ml, with 8.7% intraassay and 11% interassay coefficients of variation.

Plasma levels of ghrelin, PYY, glucose, and insulin were compared at each time point. Insulin sensitivity was calculated using homeostasis model assessment for insulin resistance (HOMA-IR) formula: HOMA-IR = [fasting insulin (micro-international units per milliliter) × fasting glucose (milligrams per deciliter)]/405.

Statistical analysis

Area under the curve (AUC) for postprandial glucose and ghrelin measurements was calculated using the trapezoidal rule: AUC = 0.25 × [(fasting value) + 2 × (30 min value) + 2 × (60 min value) + 2 × (90 min value) + (120 min value)]. British 1990 growth reference data from the Child Growth Foundation was used to adjust BMI and percentage of body fat for age and sex to derive SDS (24). Positively skewed variables (insulin and HOMA-IR) were logarithmically transformed (log 10) before analysis and geometric means (ranges) used for their data summary; the remaining results are reported as mean (SD).

Paired Student's *t* tests were used first to assess the 12-month changes within each of the two groups; these were followed by unpaired *t* tests to compare the two groups with respect to their mean changes.

Comparisons of PYY values were hampered by the number of measurements below the limit of detection of the assay (<19 pg/ml). Where possible, changes in PYY were assessed using sign tests. Within the Mandometer arm, it was possible to further

TABLE 2. Continued

Mandometer group (n = 14)			
Baseline	**12 Months**	**Mean/median change (95% CI)**	***P* value**
3.44 (0.48)	3.03 (0.60)	−0.41 (−0.62 to −0.19)	0.001
2.93 (0.67)[a]	2.60 (0.71)[a]	−0.33 (−0.48 to −0.18)[a]	<0.001
359 (125)[a]	246 (88)[a]	−113 (−217 to −9)[a]	0.035
10.61 (2.59)	14.92 (1.92)	4.32 (2.53 to 6.11)	<0.001
17.1 (12.7)[a]	31.3 (13.7)[a]	14.2 (2.5 to 25.9)[a]	0.021
68.5 (18.9)[a]	63.2 (18.9)[a]	−5.2 (−18.3 to 7.9)[a]	0.40
4.66 (0.38)	4.68 (0.46)	0.01 (−0.20 to 0.23)	0.89
12.73 (1.78)	11.66 (1.89)	−1.07 (−2.11 to −0.04)	0.043
16.9 (7 to 45)	17.1 (5 to 57)	0.99 (0.73–1.33) (*d'*)	0.93
180.1 (46 to 768)	144.6 (32 to 609)	1.25 (1.02–1.52)[d]	0.033
10.67 (5.1 to 26.5)	8.46 (4.7 to 17.4)	1.26 (1.01–1.58)[d]	0.042
3.49 (1.34 to 9.80)	3.54 (0.89 to 13.43)		0.92
68.45 (17.78)	48.14 (18.47)	−20.31 (−31.45 to −9.16)	0.002
−12.14 (19.74)	−41.50 (21.06)	−29.36 (−44.74 to −13.97)	0.001
−11.66 (28.67)	−83.68 (18.15)	−72.01 (−93.11 to −50.91)	<0.001
125.50 (29.72)	72.08 (24.11)	−53.41 (76.77 to −30.06)	<0.001

estimate the mean change in PYY at 90 min over the 12 months via censored normal regression.

Bivariate relationships were assessed with Pearson's correlation coefficients. Analysis of covariance was used to explore any confounding effect of change in BMI SDS on mean changes in ghrelin parameters for the two groups.

A 5% significance level was used throughout.

Results

Baseline

Baseline characteristics of the subjects are presented in Table 1. The two groups had similar demographic, pubertal stage distribution, and anthropometric measurements at baseline. There was no difference in plasma glucose, insulin, and gut hormones, both in the fasting state and during OGTT. Ghrelin levels reached a statistical nadir at 60 min, whereas insulin and PYY peaked at 30 and 90 min, respectively, after the glucose load (Fig. 1). None had diabetes mellitus or impaired glucose tolerance. Insulin sensitivity levels, expressed by HOMA-IR, were also similar in the two arms. In this cohort the Mandometer subjects by chance ate larger size meals at baseline, but there were no group differences in satiety or eating rate.

Follow-up

Table 2 shows within group 12-month changes with respect to eating phenotype and hormonal response. Participants in the Mandometer care showed a significant reduction in mean self-determined portion size, with similar perceived satiety levels at the end of meals despite the reduction in food consumption. They also had considerably reduced mean BMI SDS and mean percentage body fat SDS. Premeal satiety was significantly increased as well as meal duration. In the standard arm, self-determined portion size did not change nor did meal duration.

Neither group showed statistically significant changes in fasting glucose, fasting insulin, and HOMA-IR from baseline levels. For those using the intervention, glucose AUC was lower at 12 months than at baseline as well as the ratio of the 30 min to fasting insulin value.

Only the Mandometer arm showed a significant change at follow-up for fasting ghrelin, mean ghrelin AUC, and absolute mean ghrelin suppression at 60 min.

Comparing the mean changes between standard care and the Mandometer arm, the latter demonstrated significantly greater reductions in fasting ghrelin [40.13 pg/ml; $P = 0.006$, 95% confidence interval (CI) 12.59–67.68], absolute suppression of ghrelin at 60 min (31.28 pg/ml; $P = 0.006$, 95% CI 9.95–52.61), percentage of suppression of ghrelin at 60 min (75.65%; $P < 0.001$, 95% CI 48.21–103.08), and ghrelin AUC (90.59 (picograms per milliliter × min; $P < 0.001$, 95% CI 49.95–131.23).

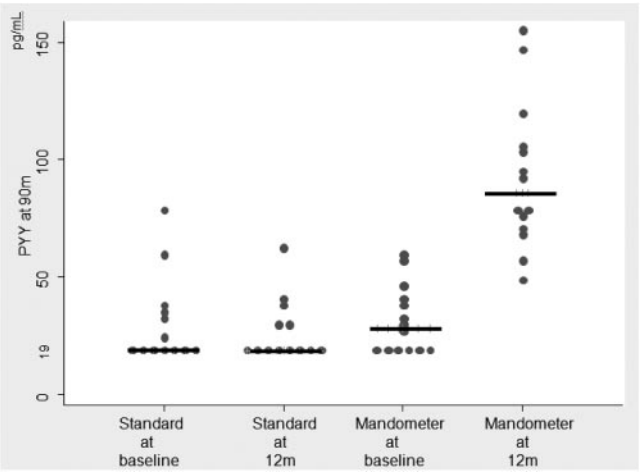

FIG. 2. Distribution of PYY values at 90 min, at baseline, and after 12 months of intervention.

Median fasting PYY was significantly enhanced in the intervention group [60.0 (range <19 to 116.8) pg/mL *vs.* <19 (<19 to 58.8) pg/ml; $P = 0.003$, sign test]. PYY response at 90 min remained unaltered in the standard care arm ($P = 0.51$, sign test), whereas all those in the Mandometer arm demonstrated a significant increase ($P < 0.001$) (Fig. 2) Assuming a normal distribution for PYY, the mean 90-min response increased by 72 pg/ml (95% CI 52–92 pg/ml) between baseline and 12 months.

Correlations

After 12 months intervention, in the Mandometer arm, the change (Δ) in the mean meal duration was inversely correlated with Δ BMI SDS ($r = -0.66$; $P = 0.01$; 95% CI −0.84 to −0.38). The Δ in absolute suppression in ghrelin at 60 min and ghrelin AUC were both inversely related to Δ meal duration (Fig. 3) and remained significant after adjustment for Δ BMI SDS (respective partial correlations −0.58; $P = 0.037$;95% CI −0.79 to −0.27 and −0.62; $P = 0.025$; 95% CI −0.81 to −0.31).

The Δ in fasting ghrelin was inversely correlated with Δ premeal satiety ($r = -0.77$; $P = 0.002$; 95% CI −0.93 to −0.37). Change in ghrelin AUC was also correlated positively with Δ portion size in the Mandometer group ($r = 0.69$, $P = 0.009$, 95% CI 0.26–0.89). None of these correlations were significant in the standard treatment group.

Taking both groups together and adjusting for Δ BMI SDS, the mean difference between the changes in the two arms was 48.0 pg/ml (95% CI 19.6–76.5) for the Δ fasting ghrelin and 63.0% (95% CI 37.3–88.7) for the Δ percentage of suppression of ghrelin at 60 min (Fig. 4).

Discussion

We have recently demonstrated that it is possible to retrain obese adolescents to eat at a slower pace, accomplishing a

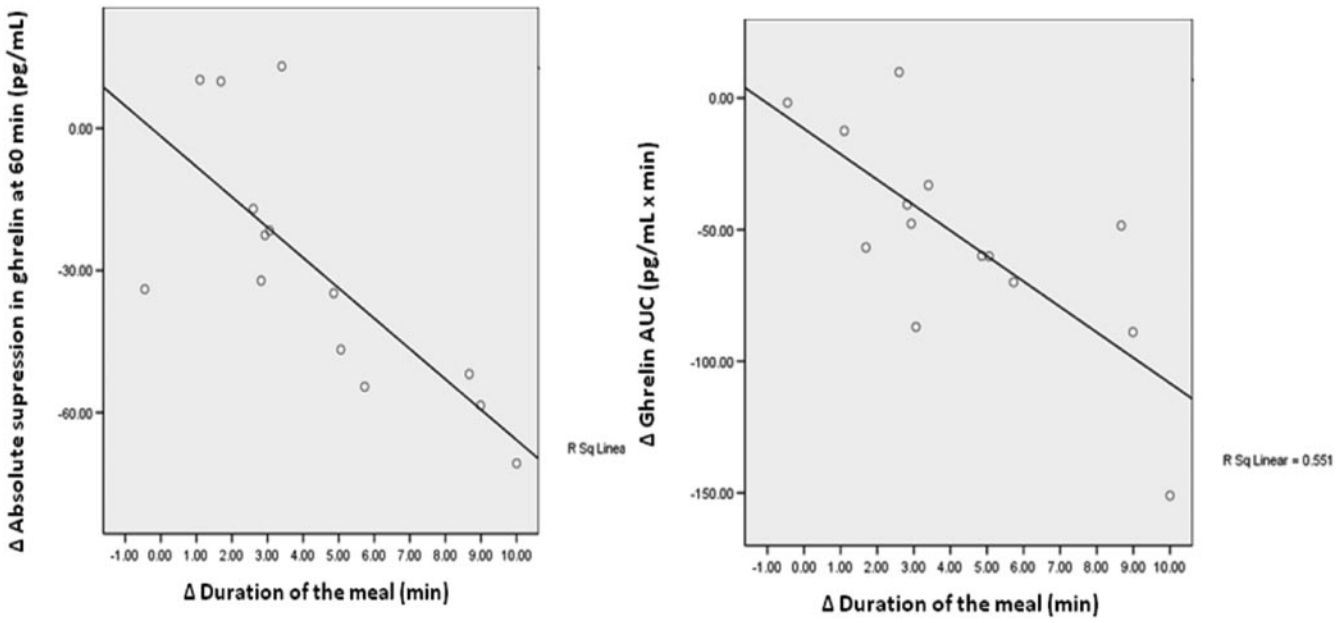

FIG. 3. Correlations between Δ duration of the meal and Δ absolute suppression of ghrelin at 60 min and Δ ghrelin AUC after 12 months of Mandometer intervention.

significantly greater improvement in age- and sex-adjusted BMI and body fat SDS compared with standard lifestyle modification. This was associated with reduced patient self-determined portion size without compromising levels of satiety (22). We believe the data herein provide important information on the mechanism underlying this effect.

We have demonstrated that retraining obese adolescents' eating behavior leads to adaptive changes in gastrointestinal hormone response, reducing orexigenic and increasing anorexigenic responses to a standard oral glucose challenge, an effect independent of reduction in adiposity. Despite the limited number of PYY values, which prevented us from comparing baseline and 12-month AUC data, the augmentation of PYY response appears similar to that described for bariatric procedures that bypass the proximal small bowel such as Roux-en-Y gastric bypass, a mechanism suggested to be responsible for the patients' ability to eat less but continue to experience satiety (25). Likewise, the reduction in fasting ghrelin levels is similar to gastric bypass responses (25, 26) rather than the response to weight loss through caloric restriction (4, 27). Calorie-restriction diets place no emphasis on eating more slowly. We believe the similarity of ghrelin responses in Mandometer therapy and bariatric surgery may relate to both therapies necessitating a reduced speed of food

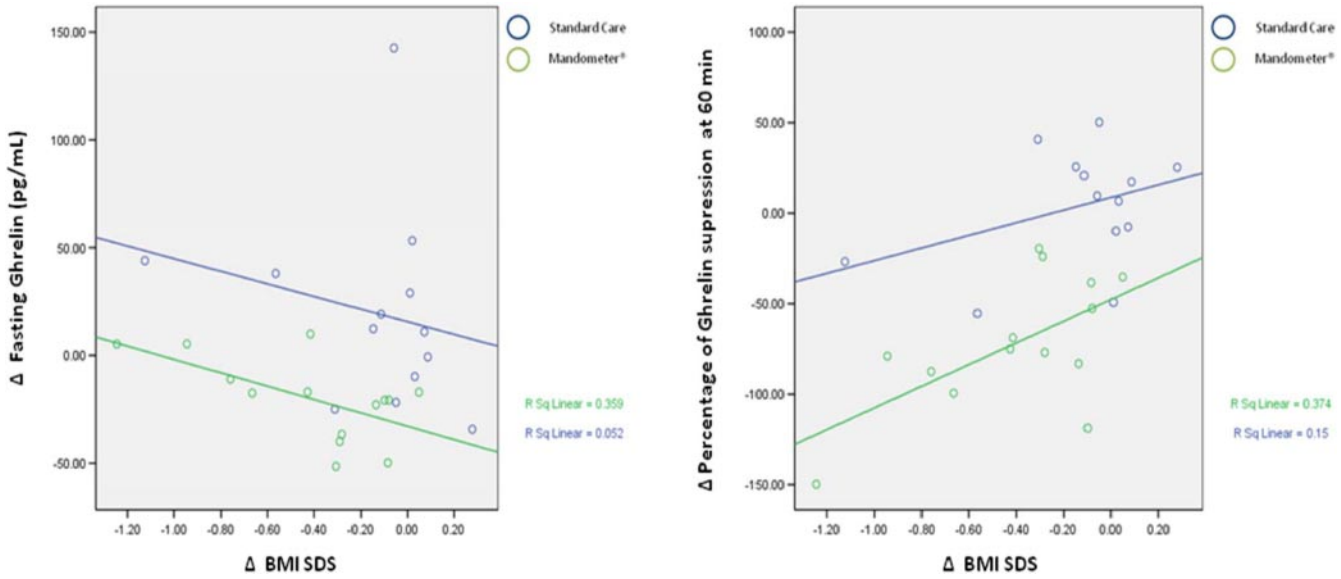

FIG. 4. Correlations between Δ BMI SDS, Δ fasting ghrelin, and percentage of suppression of ghrelin at 60 min, after 12 months of intervention.

consumption. It is plausible that the difference in fasting ghrelin levels in response to eating at a slower speed with Mandometer therapy as opposed to those elicited from calorie restriction also explain the sustained improvement in BMI after intervention.

The results differ in terms of ghrelin suppression after calorie consumption with clear suppression demonstrated in Mandometer-trained subjects compared with little sustained effect in those undergoing gastric bypass (25–28).

The results of this study suggest that the blunted gastrointestinal hormone responses to eating in obese adolescents are adaptable through changing eating behavior and encouraging slower food consumption. These data challenge the conventional paradigm in which the gastrointestinal hormonal response to meals is the key determinant of eating behavior. There are inconsistencies in this model: for instance, plasma levels of ghrelin are downregulated in the obese (10, 29), whereas patients with eating disorders such as anorexia who described exaggerated satiety have grossly elevated levels (30). We contend that our data suggest an alternative mechanism involved in obesity in which sustained, abnormal modes of eating behavior such as excessive speed of eating determine and regulate gastrointestinal response to calorie ingestion.

Although data pertaining to BMI SDS and eating behavior demonstrated a sustained effect, repeat glucose challenges were not undertaken at 18 months. Furthermore, satiety hormone profiles relate to responses to standard oral glucose challenge to allow comparison with previously published data as opposed to the blinded study test meals on which observations were made concerning speed of eating, portion size determination, and improved satiety. However, using this approach ensured that the hormone responses were to a uniform, time-delimited test as opposed to food consumption that might be influenced by individual variability such as taste preference and meal palatability. Thus, we believe the differences noted in hormonal responses to the OGTT at 12 months are likely related to eating behavior retraining.

In summary, there is little current evidence that simply addressing behavioral modification of diet and activity levels results in clinically meaningful changes in adiposity in adolescence (31). Our data suggest that a key design component of future weight management interventions should consider not only what food is consumed but the manner in which it is consumed.

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