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ORIGINAL CONTRIBUTIONS

Fasting and Meal-Induced CCK and PP Secretion Following Intragastric Balloon Treatment for Obesity

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Abstract
Background Satiety is centrally and peripherally mediated by gastrointestinal peptides and the vagal nerve. We aimed to investigate whether intragastric balloon treatment affects satiety through effects on fasting and meal-stimulated cholecystokinin (CCK) and pancreatic polypeptide (PP) secretion.
Methods Patients referred for obesity treatment were randomised to 13 weeks of sham treatment followed by 13 weeks of balloon treatment (group 1; sham/balloon) or to twice a 13-week period of balloon treatment (group 2; balloon/balloon). Blood samples were taken for fasting and meal-stimulated CCK and PP levels at the start (T0) and after 13 (T1) and 26 (T2) weeks. Patients filled out visual analogue scales (VAS) to assess satiety.
Results Forty-two patients (35 females, body weight 125.1 kg, BMI 43.3 kg/m^2) participated. In group 1, basal CCK levels decreased but meal-stimulated response remained unchanged after 13 weeks of sham treatment. In group 2, basal and meal-stimulated CCK levels decreased after 13 weeks of balloon treatment. At the end of the second 13-week period, when group 1 had their first balloon treatment, they duplicated the initial 13-week results of group 2, whereas group 2 continued their balloon treatment and reduced meal-stimulated CCK release. Both groups showed reduced meal-stimulated PP secretions at T1 and T2 compared to T0. Changes in diet composition and VAS scores were similar. Improvements in glucose homeostasis partly explained the PP results.
Conclusions The reduced CCK and PP secretion after balloon positioning was unexpected and may reflect delayed gastric emptying induced by the balloon. Improved glucose metabolism partly explained the reduced PP secretion. Satiety and weight loss were not adversely influenced by these hormonal changes.

Keywords Cholecystokinin · Pancreatic polypeptide · Intragastric balloons · Obesity · Gastric emptying · Satiety

Introduction

Obesity, defined by an excess of body fat, is a chronic disease which aggravates or predisposes to many clinical disorders such as diabetes, cardiovascular disease and several cancers. Treatment algorithms have been proposed by authoritative institutes (WHO, NIH) which include a first step of a combined intensive lifestyle treatment, a second step of drug treatment and a final step of surgery for subjects suffering from severe obesity.

Evidence-based guidelines for treating obesity do not include endoscopic procedures such as intragastric balloon therapy. This is partly because ineffective and hazardous balloons were used in the 1980s. Because of concerns about the design, construction and integrity of previous balloons, experts formulated the fundamental requirements for an optimal balloon design in 1987 [1]. Years of research finally resulted in the development of a balloon (Bioenterics Intragastric Balloon®, Allergan, Irvine, CA, USA) which fulfilled the specified requirements. In contrast to an unfavourable Cochrane review on intragastric balloons which

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included many studies using the earlier mentioned hazardous balloons, more recent reviews discussed these newly designed balloons and concluded that they were effective in promoting short-term weight loss in two thirds of patients with significant improvements in co-morbidities in the short term [2–4]. Treatment was safe provided that contraindications were taken into account. Yet, intolerance in 7 % and a non-response rate in 15 % have to be considered [3]. However, more data regarding the mode of action of intragastric balloons are needed [5].

Intragastric balloons occupy a portion of the gastric volume and this theoretically reduces the stomach's capacity. These devices physically impede the intake of nutrients and, through outlet obstruction, may delay gastric emptying. In addition to this peripherally mediated sensation of satiety, distension of the gastric wall may activate the vagal nerve, the nucleus of the tractus solitarius and the paraventricular nucleus, resulting in a centrally mediated feeling of satiety. Studies with inflatable balloons have shown that acute stomach distension stimulates cholecystokinin (CCK) release [6–8]. Gastrointestinal peptides such as CCK and pancreatic polypeptide (PP) are involved in the peripheral mediation of satiety. We hypothesised that their release, stimulated by gastric distension, would contribute to the mode of action of intragastric balloons. Therefore, we decided to compare a 13-week of sham treatment with a 13-week period of balloon treatment and to investigate—by a second 13-week period of balloon treatment in every subject—the effects of change from sham to balloon treatment and to study the effects of prolonged balloon treatment on fasting and meal-stimulated secretion of CCK and PP. As changes in diet composition and glucose homeostasis may affect gastrointestinal peptide secretion, these factors were taken into consideration as well [9, 10].

Patients

Patients referred for the treatment of obesity were asked to participate in an explorative study examining the mechanism of action of intragastric balloons. The study was approved by the Medical Ethical Committee. They all conformed to the criteria of eligibility as described previously and gave their informed consent [3, 11]. Patients were seen biweekly by the physician, the dietician and the behavioural therapist. The dietician supported adherence to a calorie-restricted diet (1,000–1,500 kcal; 4.2–6.3 MJ). Self-help groups were organised for aerobic fitness training and aqua jogging.

Patients were randomised to receive a sham–balloon (group 1) or a verum–balloon (group 2) for the first 13 weeks. In the second 13 weeks, all subjects received an intragastric balloon. Group 1 patients thus first received a sham–balloon and thereafter a verum–balloon (sham/balloon) and group 2 patients a verum–balloon in both periods (balloon/balloon).

Balloon Insertion

After intravenous administration of midazolam, endoscopy was performed to rule out abnormalities that would preclude the patient from participation in the study. Also, the distance between the incisor teeth and gastro-oesophageal junction was measured. Thereafter, patients were randomised by a computerised random model to sham or balloon treatment. After removal of the endoscope, the balloon placement assembly was inserted 10 cm distal to the measured distance between the incisor teeth and gastro-oesophageal junction. The placement assembly consisted of a sheath, with the collapsed balloon and a balloon fill tube. For patients randomised to sham treatment, the collapsed balloon was not present in the assembly. The design was such that neither the patient nor the investigator could perceive a difference between sham– and verum–balloon placement. A syringe was attached to the balloon fill tube and the balloon (or the stomach, if sham procedure) was filled with the recommended initial volume of 500 mL of saline solution. After filling the balloon, gentle suction exerted by withdrawing the plunger of the syringe created a vacuum, which sealed the valve. The balloon was released by a short pull on the fill tube, whereupon the fill tube and empty placement assembly were removed. For safety reasons, the balloon was exchanged after 13 weeks as the balloon had a newly developed valve that could be re-intubated to adjust the fill volume of the balloon in case of intolerance or insufficient weight loss. At the exchange procedure after 13 weeks, the balloon, if present, was punctured, removed and exchanged for a new balloon.

Methods

At three different occasions, i.e. before the randomisation (T0) and 13 weeks after having a sham–balloon or verum–balloon treatment (T1), and again 13 weeks later at 26 weeks (T2), when every patient had completed a 13-week balloon treatment, patients fasted from midnight onwards and came to the hospital where they received a standard breakfast meal consisting of a pancake with butter and jelly and 150 mL orange juice (671 kcal, 2,818 kJ; 79 g carbohydrates (47 %kcal, the proportion of total energy); 19 g protein (11 %kcal); 31 g fat (42 %kcal)). Fasting blood samples were taken for haematology, electrolytes, liver and kidney function, glucose and insulin. The updated Homeostasis Assessment model (HOMA2) was used to calculate insulin resistance (HOMA-IR) [12]. Blood for CCK and PP measurement was collected in tubes containing EDTA

15 min before (−15), immediately before (0), and 15, 30, 45 and 60 min after breakfast and stored on ice until further work up. After centrifugation, the plasma was stored at −20 °C until measurement. All samples for one patient were measured in duplicate and in one run. Plasma concentrations of CCK were measured using a sensitive and specific radioimmunoassay (RIA) using antibody T204. This antibody binds to all carboxy-terminal CCK peptides containing the sulfated tyrosyl region without binding to sulfated and unsulfated gastrin or structurally unrelated regulatory peptides such as insulin, glucagon, PP, somatostatin, secretin, gastric inhibitory peptide (GIP), vasoactive intestinal polypeptide (VIP), neurotensin or motilin. The detection limit of the assay is 0.5 pmol/L [13]. The intra-assay variation was between 4.6 and 11.5 %. Plasma concentrations of PP were measured by radioimmunoassay using a rabbit antihuman PP antiserum showing no cross reactivity with insulin, glucagon, gastrin, CCK, secretin, GIP, VIP or bombesin. The intra-assay variation was between 4.4 and 7.2 %. The detection limit of the assay was 5 pmol/L [14]. Both RIAs were developed and commercialised by the University of Leiden (Leiden, the Netherlands) [13, 14]. To prevent an olfactory response to the test meal, which could lead to early peptide release, the meals were prepared and stored elsewhere.

At 13 weeks, satiety was evaluated by using visual analogue scales (VAS) before and 60 min after breakfast. On a 10-cm horizontal line anchoring the most positive or negative sensation, they indicated the desire to eat (very small to very strong), feeling hungry (not hungry at all to very hungry), feeling full (not at all full to very full) and how much they thought they could eat (nothing to very much) [15]. At 26 weeks, these satiety scores were measured at each time of the blood sampling.

After the test, they returned home and kept a diary of the meals, snacks and drinks taken that day. Also, each time of the breakfast test, patients entered a 4-day diary of foods and drinks. The intake of energy and macronutrients was calculated by dieticians with the help of the Dutch Food Composition Tables 2011.

Statistical Analysis

Patient characteristics are given as means±SD (standard deviation). Because of a non-Gaussian distribution of most of the peptide values, the Mann–Whitney *U* test was used for the comparison between groups and the Wilcoxon signed-rank test for comparison within groups. To compare the release of CCK and PP, the area under the curve (AUC; pM*75) was calculated by the trapezoidal rule [16]. The integrated postprandial CCK and PP secretion was determined by calculating the area under the curve after subtracting the basal value (integrated AUC; AUCi, pM*75). Similarly, the AUCs for the four appetite scores at T2 were calculated.

The highest CCK and PP level and the time of occurrence were analysed. Also, the influence of the balloon position in the stomach on the release of CCK and PP was investigated. The effect of glucose homeostasis was investigated by grouping the patients at the start according to their fasting glucose levels (< or ≥7 mmol/L for diabetes and < or ≥5.6 mmol/L for impaired fasting glucose) and HOMA-IR (< or ≥2.7) and the median levels of glucose, insulin and HOMA-IR. Correlations between hormone release and satiety and glucose homeostasis measures were investigated by Spearman ρ statistics. A p value of <0.05 was considered significant.

Results

Forty-two patients (35 women; mean age 41.0 years, range 22–64 years) with severe obesity (body weight 125.1 (range 93.2–186.7) kg; BMI 43.3 (range 33.9–61.3) kg/m^2) entered the study. Twenty-three patients were randomised to sham treatment (group 1) and 19 to balloon treatment (group 2). In both groups, age, body weight, BMI, glucose, insulin, HOMA-IR, basal CCK and PP values were similar at the start (Table 1). Also, the CCK secretion in response to the breakfast meal was similar. The PP secretion differed as the PP values at 30, 45 and 60 min and the AUC, but not the integrated AUC, corrected for the basal value (AUCi), were slightly higher in group 1 subjects. Thirty-seven subjects remained available after 26 weeks, 21 patients in group 1 and 16 in group 2. Two patients could not tolerate the balloon, one patient was not cooperative at balloon positioning, one patient was disappointed by the rate of weight loss and one patient could not attend the study appointments for personal reasons. Patients in both groups were very compliant as to the dietary advice, physical exercise and behavioural therapy; they reduced the energy and macronutrient intake substantially and to a similar extent (Table 2). The weight loss was not different in the first 13 weeks: 11.2 kg in group 1 and 13.1 kg in group 2. In the second period of 13 weeks, the weight loss in group 1 subjects, who then had their first balloon, was significantly greater (9.9 kg) than in group 2 patients (4.5 kg, $p=0.003$).

CCK Values

Group 1 Patients Pairwise comparison of patients in group 1 who had first a 13-week sham treatment showed higher fasting values and a higher 15-min value at T0 compared with T1 with similar values 30–60 min after the meal. The AUC was higher but the AUCi, the AUC corrected for the basal value, was lower at T0. After the second period of 13 weeks, when group 1 patients had completed their first balloon treatment, fasting values were back to values at the

Table 1 Characteristics of the whole group and according to randomisation at the start, group 1 being randomised to sham and group 2 to verum–balloon treatment

	Whole group	Group 1	Group 2
N (M/F)	42 (7 M/ 35 F)	23 (3 M/20 F)	19 (4 M/15 F)
Age (years)	41.0±10.8	43.7±10.1	37.7±10.9
Body weight (kg)	125.1±21.7	125.9±22.6	124.0±21.1
BMI (kg/m^2)	43.3±6.6	43.6±7.6	43.0±5.5
Glucose (mmol/L)	6.26±2.00	6.12±1.14	6.42±2.74
Glucose (≥7 mmol/L), *N*	6	4	2
Insulin (pmol/L)	170.2±99.2	157.9±75.5	185.0±122.6
HOMA-IR	3.20±1.81	3.00±1.43	3.45±2.20
CCK −15 min	1.81±0.87	1.96±0.86	1.63±0.88
CCK 0 min	1.83±0.98	1.99±0.98	1.63±0.98
CCK 15 min	3.16±1.73	3.19±1.26	3.13±2.22
CCK 30 min	3.62±1.75	3.74±1.53	3.47±2.02
CCK 45 min	3.54±1.71	3.73±1.66	3.31±1.79
CCK 60 min	2.94±1.35	3.23±1.35	2.60±1.29
CCK AUC	217.9±94.1	228.7±84.5	204.9±105.5
CCK AUCi	82.0±70.5	81.6±58.1	82.5±84.9
Peak CCK	4.18±2.03	4.30±1.64	4.04±2.46
Time of peak CCK	35.0±13.5	37.2±14.2	32.4±12.5
PP −15 min	46.4±31.1	54.2±33.1	37.0±26.2
PP 0 min	47.1±33.6	51.5±33.1	41.7±34.4
PP 15 min	170.2±71.7	186.8±82.6	150.0±50.9
PP 30 min	153.9±64.3	177.8±64.3	125.0±52.6**
PP 45 min	139.7±66.0	157.5±62.1	118.2±65.7*
PP 60 min	137.3±71.5	160.0±76.9	109.7±54.4*
PP AUC	9,040.7±3,883.6	10,211.4±3,943.2	7,623.6±3,388.2*
PP AUCi	5,562.1±3,030.9	6,148.4±3,543.0	4,852.5±2,147.5
Peak PP	180.0±77.6	200.7±88.0	154.8±55.04*
Time of peak PP	22.9±13.8	24.1±14.1	21.3±13.5

*$p<0.05$; **$p<0.01$ for comparison between group 1 and 2 (Mann–Whitney *U* test)

start but the meal-stimulated CCK secretion and the AUC and AUCi were significantly lower when compared to T0. When T1, 13 weeks after a sham period, was compared to T2, 13 weeks after balloon positioning, the fasting CCK values were significantly higher after the balloon period at T2, whereas meal-stimulated CCK secretion was lower after the balloon period, significantly for the 30- and 45-min values and the AUCi. As to the peak CCK, the value was significantly lower at T2 when compared with T0 and also significantly lower when compared with T1. The time of the peak value did not change (Table 3, Fig. 1).

Group 2 Patients In group 2, patients showed significantly higher values for fasting and meal-stimulated values at T0 when compared to the values after 13 weeks of balloon treatment (T1). No difference was present at 60 min. The AUC and the AUCi at T0 were greater but only significantly greater for the AUC. After 26 weeks at T2, after a second episode of balloon treatment, the values were intermediate between those of T0 and T1 without significant differences between the values of T2 and T0 except for a lower T2-CCK value after 15 min. When T1 and T2 were compared, slightly higher values were noticed at T2, significant for the fasting and 60-min value and for the AUC. The peak CCK value was significantly lower at T1 when compared with T0 and T2, whereas the T0 and T2 value did not differ. The timing of the peak value did not change (Table 3, Fig. 2).

Comparison of Group 1 and Group 2 Subjects Comparison of group 1 and group 2 patients showed significantly lower values for the meal-stimulated CCK secretion in group 2 subjects after 13 weeks and no differences after 26 weeks. There was no difference between the groups in CCK peaks and timing of the peaks.

PP Values

Group 1 Patients In group 1 patients, the fasting PP at T0 and at T1 was not different but after 13 weeks of sham treatment the meal-induced PP secretion and the AUC and

Table 2 Energy and macronutrient intakes as calculated from the 4-day diary entered before the randomisation and at the end of each 13-week treatment period

	Group 1	Group 2
Start		
kJ	8,625±2,743	10,339±3,204
kcal	2,062±656	2,471±766
Protein g	79.4±21.2	92.8±27.5
Protein %kcal	15.8±2.7	15.2±2.5
Fat g	97.8±36.4	111.1±38.2
Fat %kcal	41.8±6.0	40.2±4.7
Carbohydrates g	205.7±72.3	269.2±93.8#
Carbohydrates %kcal	40.6±7.5	43.2±3.9
Week 13	After 13 weeks sham	After 13 weeks balloon
kJ	4,941±1,237***	5,145±1,556***
kcal	1,181±296***	1,230±372***
Protein g	61.6±13.0**	68.9±14.0**
Protein %kcal	21.2±3.8***	23.4±5.6***
Fat g	46.0±19.9***	43.9±17.2***
Fat %kcal	34.1±7.92**	31.6±7.2**
Carbohydrates g	127.2±30.0***	138.7±50.2***
Carbohydrates %kcal	43.5±6.4	44.6±5.9
Week 26	After 13 weeks balloon	After 2nd 13 weeks balloon
kJ	4,907±1,233***	5,187±1,629**
kcal	1,173±295***	1,240±389**
Protein g	62.0±9.8*	61.6±16.9**
Protein %kcal	22.0±4.8***	20.6±4.8**
Fat g	44.6±21.9***	45.4±22.0**
Fat %kcal	32.8±8.5**	32.6±7.4*
Carbohydrates g	127.8±33.5***	134.8±37.5**
Carbohydrates %kcal	44.0±7.4	43.9±5.9

%kcal proportion of total energy

*$p<0.05$; **$p<0.01$; ***$p<0.001$ pairwise comparison within the groups T1 with T0 and T2 with T0 (Wilcoxon signed-rank test) with no significant differences when comparing T1 with T2. #$p<0.05$ comparison between group 1 and group 2 (Mann–Whitney *U* test)

AUCi were significantly lower when compared with the start. At T2, after a 13-week period of balloon placement, fasting values were higher, but the meal-stimulated PP and AUC and AUCi remained significantly lower compared with T0. When T1, 13 weeks after a sham period, was compared to T2, 13 weeks after balloon positioning, the fasting PP values were significantly higher at T2, whereas the meal-stimulated PP secretion at each 15-min period and the AUC were similar. The AUCi, corrected for the basal value, was significantly lower at T2. Peak PP values were lower both at T1 and T2. The peaks occurred later in time, although this was not significant (Table 4, Fig. 3).

Group 2 Patients After the first period of 13-week balloon treatment, the fasting values were higher, but the meal-stimulated PP values were significantly lower except for the 60-min value. Both the AUC and the AUCi were lower after 13 weeks. After 26 weeks, the meal-stimulated values remained lower at 15 and 30 min, as did the AUC and AUCi. The peak levels at T1 and T2 were lower and occurred significantly later in time (Table 4, Fig. 4).

Comparison of Group 1 and Group 2 Subjects Significantly lower values for the meal-stimulated secretion of PP were seen in group 2 subjects after 13 weeks with a significantly lower peak PP value. The AUC was not different but the AUCi was significantly lower in group 2 subjects. At T2, both groups were similar and only the fasting value and 15-min values were higher in group 1 subjects.

VAS Scores and Subsequent Energy Intake After the Breakfast Test Meal

After 13 weeks, group 1 and group 2 patients did not differ in VAS satiety scores and prospective food consumption before the meal (Table 5). After the meal, both groups decreased their desire to eat, hunger feelings and prospective food consumption significantly with increased feelings of fullness. The changes in satiety induced by the meal were not different between the groups. The energy intakes during the first meal after the test meal and during the remainder of the day were also similar in both groups. The same applied to the VAS scores at the 26-week investigation: a significant decrease in appetite, hunger and prospective food consumption and increase in fullness in both groups without a difference between the two groups. Only the energy intake at the subsequent meal was significantly higher in group 2 patients without an effect on the total daily energy intake.

There was a significant correlation between the changes in feeling full and the area under the curve for CCK (Spearman's rho (ρ)=0.362, p=0.028) and the peak of CCK (ρ=0.376, p=0.022) at week 26. As to PP, there was a significant correlation between the change in prospective food consumption and the area under the curve for PP at 13 weeks (ρ=0.334, p=0.033).

Other Possible Contributing Factors

Age Age correlated with peak CCK values (ρ=0.323, p=0.037). It also correlated with fasting PP values (ρ=0.437, p=0.004), with peak PP value (ρ=0.346, p=0.025) and with PP AUC (ρ=0.384, p=0.012).

BMI BMI did not correlate with fasting or meal-stimulated CCK and PP values.

Table 3 Data of CCK values (pmol/L) over time in group 1 (sham/balloon) and group 2 (balloon/balloon) patients

	T0	T1	T2
Group 1	(*N*=23)	(*N*=23) after 13 weeks sham	(*N*=21) after 13 weeks balloon
CCK −15 min	1.96±0.86	0.79±0.63***	1.77±1.05##
CCK 0 min	1.99±0.98	1.05±0.88***	1.72±1.29#
CCK 15 min	3.19±1.26	2.59±1.62*,$	1.99±1.15**
CCK 30 min	3.74±1.53	3.70±1.60$$	2.38±1.10***,###
CCK 45 min	3.73±1.66	3.34±1.28$$	2.46±1.01***,##
CCK 60 min	3.23±1.35	3.05±1.22$	2.63±1.08*
CCK AUC	228.7±84.5	189.0±80.5**,$$	161.2±70.3***
CCK AUCi	81.6±58.1	130.0±61.0**,$$$	28.7±47.4***,###
Peak value CCK	4.30±1.64	4.1±1.68$$	3.09±0.97**,##
Time of peak value	37.2±14.2	40.4±13.1	33.6±21.2
Glucose (mmol/L)	6.12±1.14	5.82±0.88*	5.71±0.70*
Insulin (pmol/L)	157.9±75.5	108.7±63.1***	104.8±61.1***
HOMA-IR	3.00±1.43	2.10±1.18***	2.00±1.15***
Glucose (>5.6 mmol/L)	*N*=15	*N*=11	*N*=7
Glucose (>7.0 mmol/L)	*N*=4	*N*=1	*N*=2
HOMA-IR >2.7	*N*=12	*N*=5	*N*=3
Group 2	(*N*=19)	(*N*=19) after 13 weeks balloon	(*N*=16) after 2nd 13 weeks balloon
CCK −15 min	1.63±0.88	1.07±0.57**	1.56±1.05#
CCK 0 min	1.63±0.98	1.03±0.65**	1.49±0.87#
CCK 15 min	3.13±2.22	1.60±0.85***,$	1.88±1.14*
CCK 30 min	3.47±2.02	2.35±1.29**,$$	2.86±1.41
CCK 45 min	3.31±1.79	2.18±1.37***,$$	2.56±1.20
CCK 60 min	2.60±1.29	2.38±1.68$	2.85±1.08#
CCK AUC	204.9±105.5	135.6±66.6***,$$	164.9±69.0#
CCK AUCi	82.5±84.9	55.5±60.9$$$	47.7±53.0
Peak value CCK	4.04±2.46	2.87±1.68**,$$	3.31±1.32#
Time of peak value	32.4±12.5	41.1±17.2	40.3±17.1
Glucose (mmol/L)	6.42±2.74	6.15±2.59	5.86±1.57
Insulin (pmol/L)	185.0±122.6	117.3±60.7***	99.0±42.5**
HOMA-IR	3.45±2.20	2.29±1.26***	1.91±0.87**
Glucose (>5.6 mmol/L)	*N*=7	*N*=8	*N*=4
Glucose (>7.0 mmol/L)	*N*=2	*N*=1	*N*=1
HOMA-IR >2.7	*N*=10	*N*=5	*N*=3

*$p<0.05$; **$p<0.01$; ***$p<0.001$ pairwise comparison within the groups T1 with T0 and T2 with T0 (Wilcoxon signed-rank test). #$p<0.05$; ##$p<0.01$; ###$p<0.001$ pairwise comparison within the groups T1 with T2 (Wilcoxon signed-rank test). \$$p<0.05$; \$\$$p<0.01$; \$\$\$$p<0.001$ comparison between group 1 and group 2 (Mann–Whitney *U* test)

Glucose Homeostasis Comparison of patients with a fasting glucose value ≥7 or <7 mmol/L and ≥5.6 or <5.6 mmol/L showed no differences in fasting CCK and PP values and no differences in CCK secretion at T0. The meal-stimulated PP secretion was significantly higher in patients with a fasting glucose value ≥7 and ≥5.6 mmol/L. There was no difference when patients with HOMA-IR above or equal and below 2.7 were compared. A similar increased PP secretion was found when the 42 patients were divided into groups above or below the median value of glucose of 5.75 mmol/L. No differences as to fasting or meal-stimulated CCK and PP values were found between patients divided according to the median value of insulin (146 pmol/L) or HOMA-IR (2.80). Insulin levels correlated with the peak CCK value ($\rho=0.346$, $p=0.025$) and fasting glucose and HOMA values with peak PP values ($\rho=0.466$, $p=0.002$ and $\rho=0.352$, $p=0.022$, respectively) and integrated PP secretion ($\rho=0.545$, $p<0.001$ and $\rho=0.314$, $p=0.043$, respectively).

Over the total period of treatment, glucose metabolism and insulin sensitivity improved substantially (Table 3). Proportional changes in glucose, insulin and HOMA-IR levels over time were not different between the groups and

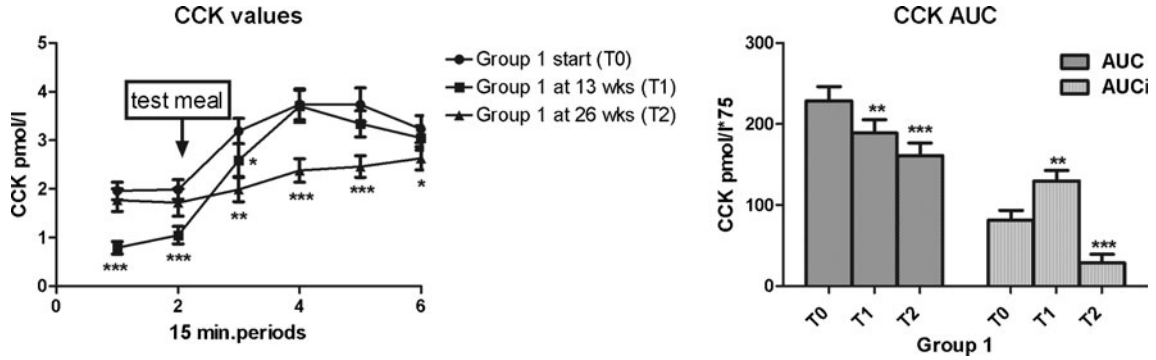

Fig. 1 Fasting and meal-stimulated CCK values at the start (T0), after 13 weeks (T1) and after 26 weeks (T2) in patients of group 1 (sham treatment followed by balloon treatment), depicted as curves (*left panel*) and area under the curve (*right panel*) (AUC pM*75) and integrated AUC (pM*75), corrected for the basal value; *$p<0.05$, **$p<0.01$; ***$p<0.001$ compared with T0

did not correlate with changes in CCK secretion except for the proportional changes in glucose which correlated with the changes in CCK AUCi over the total period of 26 weeks ($\rho=0.338$, $p=0.041$). Proportional changes in glucose over the first 13 weeks correlated with changes in PP secretion (PP AUC, $\rho=0.335$, $p=0.030$). Changes in insulin and HOMA-IR over the 26 weeks correlated negatively with PP AUCi ($\rho=-0.352$, $p=0.032$ and $\rho=-0.389$, $p=0.017$, respectively).

Diet Prescription Both groups significantly changed their diets in both 13-week periods of treatment compared to the diet before the randomisation. Proportional changes in energy (38.6 % in group 1 and 47.9 % in group 2), protein (16.2 and 18.9 %, respectively), fat (45.4 and 57.5 %, respectively) and carbohydrates (30.0 and 47.2 %, respectively) were not statistically different.

Balloon Position In the first period, balloon location was evaluated in 15 of the 19 subjects and balloons were located in the antrum (four), corpus (eight) and fundus (three). In the second period, balloon location was known in every subject, i.e. in the antrum in 9, corpus in 18 and fundus in 10. Balloon location did not correlate with meal-stimulated CCK or PP secretion nor with fasting CCK and PP values.

Discussion

Intragastric balloons are supposed to have an effect on food intake and satiety by a reduction in the capacity of the stomach and by gastric distension which may activate the vagal nerve and its brain centres, resulting in a centrally mediated feeling of satiety. Our hypothesis that stomach distension may also stimulate CCK and PP release, both involved in the peripheral mediation of satiety, is not supported by the present study. Fortunately, the design of our study allowed us to differentiate between the effects of dietary restrictions, the presence of a balloon and changes in glucose homeostasis.

The CCK response remained unchanged in the group who had sham treatment, although the fasting levels were significantly lower after 13 weeks which might be the result of the diet, which was severely restricted in fat and energy. A previous diet might influence the regulation of gastric

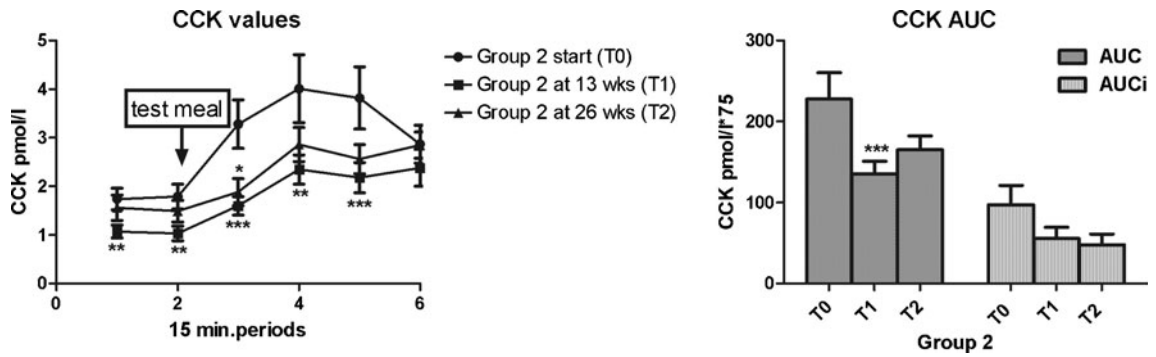

Fig. 2 Fasting and meal-stimulated CCK values at the start (T0), after 13 weeks (T1) and after 26 weeks (T2) in patients of group 2 (balloon treatment followed by balloon treatment), depicted as curves (*left panel*) and area under the curve (*right panel*) (AUC pM*75) and integrated AUC (pM*75), corrected for the basal value; *$p<0.05$, **$p<0.01$; ***$p<0.001$ compared with T0

Table 4 Data of PP values (pmol/L) over time in group 1 (sham/balloon) patients and group 2 (balloon/balloon) patients

	T0	T1	T2
Group 1	(*N*=23)	(*N*=23) after 13 weeks sham	(*N*=21) after 13 weeks balloon
PP −15 min	54.2±33.1	43.2±24.1	71.5±37.9$,###
PP 0 min	51.5±33.1	42.7±20.4	76.5±44.3**,$$, ###
PP 15 min	186.8±82.6	127.2±35.5***,$$	121.0±46.4***,$
PP 30 min	177.8±64.3$	117.9±35.2***,$	112.9±47.2***
PP 45 min	157.5±62.1	112.4±37.4***	114.4±44.4***
PP 60 min	160.0±76.9$	113.2±32.6***,$	115.7±41.9***
PP AUC	10,211.4±3,943.2	7,175.5±2,131.2***	7,775.7±3,090.8**,$
PP AUCi	6,148.4±3,543.0	3,937.5±1,457.3**,$$$	2,411.4±1,421.5***,###
Peak value PP	200.7±88.0	134.7±34.2***,$$	132.7±49.3***
Time of peak value	24.1±14.1	26.1±15.2	32.9±18.8
Group 2	(*N*=19)	(*N*=19) after 13 weeks balloon	(*N*=16) after 2nd 13 weeks balloon
PP −15 min	37.0±26.2	50.5±19.4*	48.3±32.1$
PP 0 min	41.7±34.4	53.2±22.8*	45.3±23.5$$
PP 15 min	150.0±50.9	93.9±33.8***,$$	86.4±41.2***,$
PP 30 min	125.0±52.6$	94.2±27.6**,$	94.8±41.4*
PP 45 min	172.3±250.2	88.6±26.9*	95.2±49.1
PP 60 min	164.3±249.5$	91.2±28.3$	96.3±43.2
PP AUC	10,491.4±13,242.5	6,009.1±1,786.0*	5,904.8±2,529.4*,$
PP AUCi	7,206.4±10,732.4	2,223.6±1,186.2***,$$$	2,281.4±1,548.7***
Peak value PP	222.1±305.5	102.4±31.7***,$$	104.4±41.2***
Time of peak value	21.8±13.3	33.2±17.0*	40.3±17.1**

*$p<0.05$; **$p<0.01$; ***$p<0.001$ pairwise comparison within the groups T1 with T0 and T2 with T0 (Wilcoxon signed-rank test). #$p<0.05$; ##$p<0.01$; ###$p<0.001$ pairwise comparison within the groups T1 with T2 (Wilcoxon signed-rank test). $$p<0.05$; $$$p<0.01$; $$$$p<0.001$ comparison between group 1 and group 2 (Mann–Whitney *U* test)

emptying and gastrointestinal hormone secretion by underexposure or overexposure of small intestinal receptors to nutrients [17–19].

Patients who received a verum–balloon started from a similar low CCK level as the sham-treated group as they followed the same diet restricted in energy and fat, but subsequently showed a significantly impaired CCK response. This effect was duplicated by group 1 when they received their first balloon in the second 13 weeks and did not extinguish in subjects of group 2, while having a second balloon for another 13 weeks. Yet, some adaptation might have occurred as the CCK secretion after 26 weeks was in between the pretreatment and 13-week results. Following nutrient ingestion, circulating CCK levels start to increase biphasically in response to vagal cephalic stimulation and in response to nutrients in the intestines, in particular fat- and

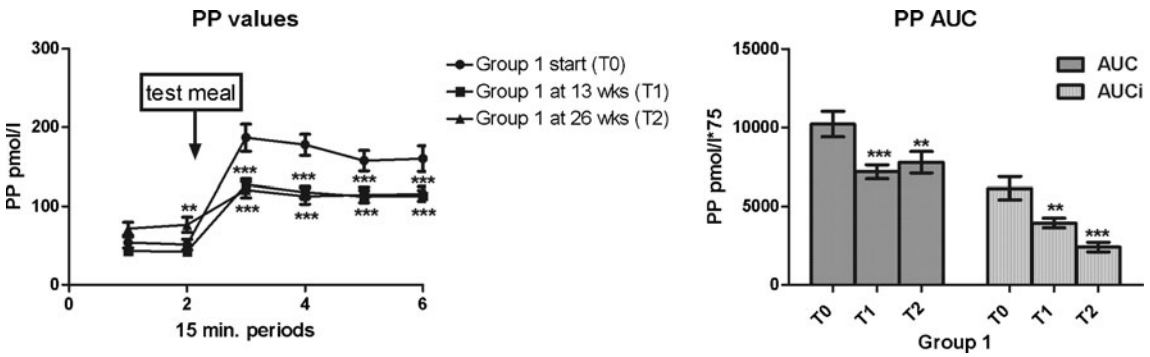

Fig. 3 Fasting and meal-stimulated PP values at the start (T0), after 13 weeks (T1) and after 26 weeks (T2) in patients of group 1 (sham treatment followed by balloon treatment), depicted as curves (*left panel*) and area under the curve (*right panel*) (AUC pM*75) and integrated AUC (pM*75), corrected for the basal value; *$p<0.05$, **$p<0.01$; ***$p<0.001$ compared with T0

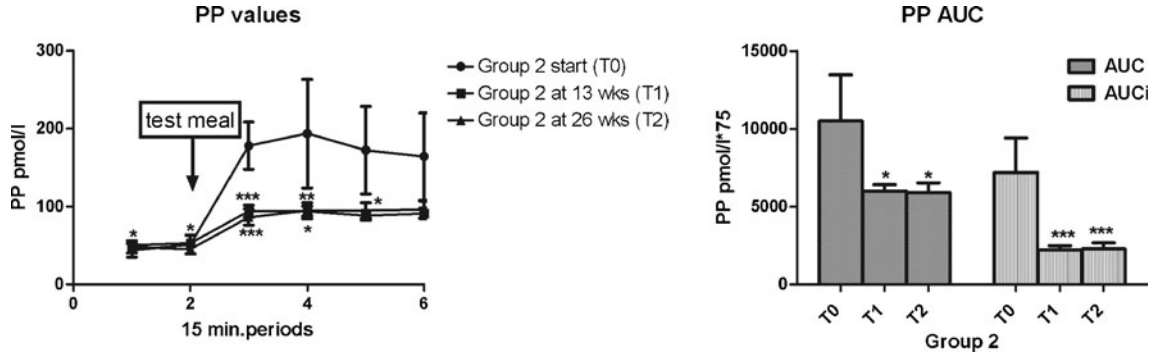

Fig. 4 Fasting and meal-stimulated PP secretion at the start (T0), after 13 weeks (T1) and after 26 weeks (T2) in patients of group 2 (balloon treatment followed by balloon treatment), depicted as curves (*left panel*) and area under the curve (*right panel*) (AUC pM*75) and integrated AUC (pM*75), corrected for the basal value; *$p<0.05$, **$p<0.01$; ***$p<0.001$ compared with T0

protein-rich meals [20, 21]. Our results are thus compatible with a delayed gastric emptying by outlet obstruction caused by the intragastric balloon as has been demonstrated by Mion et al. [22]. Delayed gastric emptying is also compatible with our findings of residual food in the stomach and food firmly adherent to the balloon at the endoscopy, needed for balloon removal or balloon exchange, despite a 1-day clear liquid diet [11]. So, our results differ from the results reported in other studies which showed that acute stomach distension with inflatable balloons stimulates CCK release [6–8]. Chronic gastric distension as present in our study may thus differ from the acute experiment. Geliebter et al. did not find an effect on fasting CCK levels by 1-month, chronic balloon distension, but they discovered a significantly lower CCK level 30 min after a lunch meal, confirming our results [23]. Oesch et al. demonstrated that CCK levels remained unchanged during balloon distension of the fundus or the antrum [24]. We could not demonstrate a difference between balloons located in the proximal or distal stomach.

In the literature, the CCK secretion in response to a meal in obese subjects was similar to that of a lean person [25–28], but a lower [29, 30] or higher [31] response was occasionally reported. To some extent, this discrepancy might be explained by the effects of diabetes type 2, hyperinsulinaemia and free fatty acids on CCK secretion [10]. Therefore, insulin resistance might be a confounding factor. We could not find any difference in CCK secretion despite an impaired fasting glucose level in 22 patients, a diabetic glucose level in 6 and insulin resistance by HOMA-IR in 22 subjects.

The PP findings are more difficult to interpret. In the untreated obese, we could not confirm an absent or blunted response to a meal as reported by others [28, 32–36], though a few authors reported a normal response [26, 27]. In patients who received a balloon, an impaired PP secretion was found which could be explained by a decreased gastric emptying, thus impairing the contact of the gut wall with nutrients, mainly protein and fat, needed to elicit a PP response, and by a decreased CCK secretion, known to stimulate PP secretion [37, 38]. This effect remained present in the second balloon episode. A similar, albeit less impressive response, however, was seen in sham patients not having a balloon, which did not decrease further when they received their first balloon in the second period of 13 weeks. The PP response while following a fat- and energy-restricted diet in the sham condition may reflect an unresponsiveness of PP secreting pancreatic islets due to the diet. We speculate that a breakfast meal higher in protein would have elicited a larger PP response. Another explanation for the blunted reaction in groups 1 and 2 is a difference in autonomic activity and reduced vagal tone due to weight loss or chronic gastric distension [39, 40]. Pancreatic polypeptide is secreted in a biphasic manner [37, 38]. While the first phase of secretion is under vagal control, the second phase would depend not only on vagal control but also on metabolic and hormonal factors such as the presence of food in the gut and on CCK [37, 38]. A third explanation might be that our finding of increased PP secretion before treatment in glucose-intolerant obese subjects is abnormal which in both groups normalised as a result of weight loss and improvement of the glucose tolerance. Unfortunately, the groups were too small to analyse this further into detail, but proof of the latter is provided to some extent by the study of Berger et al., which showed a reduction of PP secretion after normalisation of glucose values in type 2 diabetes [41]. Indeed, Glaser et al. demonstrated that obesity per se was associated with impaired PP responses but that the advent of diabetes confounded the picture since PP levels in diabetics were generally raised [36]. An increased parasympathetic drive to the pancreas has been reported resulting in increased insulin and PP secretion [42–44].

The appetite and fullness scores, before and after the breakfast meal, were not different between the groups at 13 weeks despite a different meal-stimulated CCK and PP secretion. The stomach itself can produce satiation after gastric distension and this signal is vagally mediated

Table 5 VAS scores before and after the test meal (and at 26 weeks also every 15 min after the test meal with AUC and integrated AUC (AUCi) calculation) and energy intakes at the next meal and during the remainder of the day in group 1 (sham/balloon) and group 2 (balloon/balloon) patients

	Group 1	Group 2
Test at 13 weeks	*N*=23	*N*=19
Before the test meal		
Desire to eat	4.03±2.07**	4.16±2.14***
Feeling hungry	4.40±2.07*	4.21±1.88***
Feeling full	3.74±2.81**	3.99±2.41**
Prospective food consumption	4.89±1.95***	4.39±1.94*
After the test meal		
Desire to eat	2.40±2.27**	1.84±2.46***
Feeling hungry	3.24±2.42*	2.60±2.11***
Feeling full	6.01±2.93**	6.13±2.55**
Prospective food consumption	2.35±1.90***	2.94±3.01*
Energy intake next meal (kJ)	1,495±1,039	1,570±838
Energy intake next meal (kJ)	334±225	372±201
Energy intake day (kJ)	4,493±1,829	4,274±1,977
Energy intake day (kcal)	949±445	1,007±477
Test at 26 weeks	*N*=21	*N*=16
Before the test meal		
Desire to eat	4.96±2.03***	4.77±2.51**
Feeling hungry	4.56±1.97**	4.14±2.13**
Feeling full	4.47±2.52**	4.54±2.35*
Prospective food consumption	4.20±1.76*	5.09±2.24**
After the test meal		
Desire to eat	2.31±2.25***	2.53±1.70**
Feeling hungry	2.46±2.11**	2.83±1.69**
Feeling full	7.27±2.72**	6.70±2.44*
Prospective food consumption	2.58±2.30*	2.75±1.87**
AUC Desire to eat	204.5±121.4	202.9±114.8
AUC Feeling hungry	214.5±122.9	214.5±122.8
AUC Feeling full	494.9±143.2	447.4±132.3
AUC Prospective consumption	213.0±98.7	243.4±124.8
AUCi Desire to eat	−167.3±132.4	−154.8±125.2
AUCi Feeling hungry	−127.6±127.8	−118.4±101.8
AUCi Feeling full	159.5±187.1	106.6±166.1
AUCi Prospective consumption	−102.0±149.3	−138.2±121.3
Energy intake next meal (kJ)	1,226±996#	2,098±1,210#
Energy intake next meal (kcal)	262±245#	496±291#
Energy intake day (kJ)	4,114±1,624	4,832±2,033
Energy intake day (kcal)	960±391	1,143±490

*$p<0.05$; **$p<0.01$; ***$p<0.001$ pairwise comparison of the satiety measures before and after the test meal within the group at 13 and 26 weeks (Wilcoxon signed-rank test). #$p<0.05$ comparison between group 1 and group 2 (Mann–Whitney *U* test)

[7, 8, 45]. Moreover, the effects of CCK and stomach distension combine to reduce food intake in humans [6, 46]. Gastric distension might be different for the fundus (receptive relaxation), the corpus and the antrum. We could not demonstrate a difference between balloons located in the fundus, corpus or antrum. It has been suggested that the less compliant distal antral area is probably more important than the fundus in inducing appetite-related sensations [47–49].

The limitations of our study should be acknowledged. The breakfast meal provided one third of the calculated daily energy requirements, and a relatively high proportion of fat (40 % of total energy) was selected to adequately stimulate CCK secretion. For an adequate PP secretion, the proportion of protein (11 % of total energy) might have been too low. Another aspect that should be taken into account in further studies is a more prolonged blood sampling and VAS scoring, as the intestines might be exposed to nutrients over a more prolonged period related to the delayed gastric emptying. This might result in a more prolonged secretion of CCK and PP, thus contributing more to a prolonged period of satiety and less to an immediate effect on satiation [21, 25, 46]. Also, the small size of the study did not allow a further analysis of the PP results in glucose-intolerant patients.

In conclusion, we demonstrated a lower meal-stimulated CCK and PP secretion due to delayed gastric emptying induced by the balloon, an impressive weight loss and the herewith associated improved glucose homeostasis. We could not demonstrate an adaptation to the balloon as after 26 weeks CCK and PP secretion did not return to starting values although it can be argued that in group 2 patients with a 26-week balloon period, the CCK secretion after 26 weeks was in between the pretreatment and 13-week results. Whether the prolonged satiety is due to a prolonged contact of intestinal receptors with an ongoing stream of nutrients, being slowly released from the stomach and resulting in a more sustained release of CCK and PP and a more prolonged inhibition of ghrelin, is a matter of further investigation.

Conflict of Interest Both authors, EMH Mathus-Vliegen and GH de Groot, had no conflicts of interest.

References

1. Schapiro M, Benjamin S, Blackburn G, et al. Obesity and the gastric balloon: a comprehensive workshop. Tarpon Springs, Florida. Gastrointest Endosc. 1987;33:323–7.
2. Fernandes M, Atallah AN, Soares BG, et al. Intragastric balloon for obesity. Cochrane Database Syst Rev 2007;(1):CD004931.
3. Mathus-Vliegen EM. Intragastric balloon treatment for obesity: what does it really offer? Dig Dis. 2008;26:40–4.
4. Imaz I, Martinez-Cervell C, Garcia-Alvarez EE, et al. Safety and effectiveness of the intragastric balloon for obesity. A meta-analysis. Obes Surg. 2008;18:841–6.

5. Evans JT, Delegge MH. Intragastric balloon therapy in the management of obesity: why the bad wrap? JPEN J Parenter Enteral Nutr. 2011;35:25–31.
6. Melton PM, Kissileff HR, Pi-Sunyer FX. Cholecystokinin (CCK-8) affects gastric pressure and ratings of hunger and fullness in women. Am J Physiol. 1992;263(2 Pt 2):R452–6.
7. Rigaud D, Trostler N, Rozen R, et al. Gastric distension, hunger and energy intake after balloon implantation in severe obesity. Int J Obes Relat Metab Disord. 1995;19:489–95.
8. Feinle C, Christen M, Grundy D, et al. Effects of duodenal fat, protein or mixed-nutrient infusions on epigastric sensations during sustained gastric distension in healthy humans. Neurogastroenterol Motil. 2002;14:205–13.
9. Rushakoff RA, Goldfine ID, Beccaria LJ, et al. Reduced postprandial cholecystokinin (CCK) secretion in patients with non-insulin-dependent diabetes mellitus: evidence for a role for CCK in regulating postprandial hyperglycemia. J Clin Endocrinol Metab. 1993;76:489–93.
10. Weickert MO, Möhlig M, Spranger J, et al. Effects of euglycemic hyerinsulinemia and lipid infusion on circulating cholecystokin. J Clin Endocrinol Metab. 2008;93:2328–33.
11. Mathus-Vliegen EM, Tytgat GN. Intragastric balloon for treatment-resistant obesity: safety, tolerance, and efficacy of 1-year balloon treatment followed by a 1-year balloon-free follow-up. Gastrointest Endosc. 2005;61:19–27.
12. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care. 1998;21:2191–2.
13. Jansen JB, Lamers CB. Radioimmunoassay of cholecystokinin in human tissue and plasma. Clin Chim Acta. 1983;131:305–16.
14. Lamers CB, Diemel CM, van Leer E, et al. Mechanism of elevated serum pancreatic polypeptide concentrations in chronic renal failure. J Clin Endocrinol Metab. 1982;55:922–6.
15. Blundell J, de Graaf C, Hulshof T, et al. Appetite control: methodological aspects of the evaluation of foods. Obes Rev. 2010;11:251–70.
16. Matthews JN, Altman DG, Campbell MJ, et al. Analysis of serial measurements in medical research. BMJ. 1990;300:230–5.
17. Cunningham KM, Baker RJ, Horowitz M, et al. Use of technetium-99 m(V)thiocyanate to measure gastric emptying of fat. J Nucl Med. 1991;32:878–81.
18. French SJ. The effects of specific nutrients on the regulation of feeding behaviour in human subjects. Proc Nutr Soc. 1999;58:533–9.
19. Lieverse RJ, van Seters AP, Jansen JB, et al. Relationship between hunger and plasma cholecystokinin during weight reduction with a very low calorie diet. Int J Obes Relat Metab Disord. 1993;17:177–9.
20. Chandra R, Liddle RA. Cholecystokinin. Curr Opin Endocrinol Diabetes Obes. 2007;14:63–7.
21. Wren AM, Bloom SR. Gut hormones and appetite control. Gastroenterology. 2007;132:2116–30.
22. Mion F, Napoleon B, Roman S, et al. Effects of intragastric balloon on gastric emptying and plasma ghrelin levels in non-morbid obese patients. Obes Surg. 2005;15:510–6.
23. Geliebter A, Melton PM, Gage D, et al. Gastric balloon to treat obesity: a double-blind study in nondieting subjects. Am J Clin Nutr. 1990;51:584–8.
24. Oesch S, Ruegg C, Fischer B, et al. Effect of gastric distension prior to eating on food intake and feelings of satiety in humans. Physiol Behav. 2006;30(87):903–10.
25. Hill P, Garbaczewski L, Koppeschaar H, et al. Peptide and steroid hormones in subjects at different risk for diet-related diseases. Am J Clin Nutr. 1988;48(3 Suppl):782–6.
26. Tomita T, Greeley Jr G, Watt L, et al. Protein meal-stimulated pancreatic polypeptide secretion in Prader-Willi syndrome of adults. Pancreas. 1989;4:395–400.
27. Wisen O, Bjorvell H, Cantor P, et al. Plasma concentrations of regulatory peptides in obesity following modified sham feeding (MSF) and a liquid test meal. Regul Pept. 1992;39:43–54.
28. Lieverse RJ, Masclee AA, Jansen JB, et al. Plasma cholecystokinin and pancreatic polypeptide secretion in response to bombesin, meal ingestion and modified sham feeding in lean and obese persons. Int J Obes Relat Metab Disord. 1994;18:123–7.
29. Zwirska-Korczala K, Konturek SJ, Sodowski M, et al. Basal and postprandial plasma levels of PYY, ghrelin, cholecystokinin, gastrin and insulin in women with moderate and morbid obesity and metabolic syndrome. J Physiol Pharmacol. 2007;58 Suppl 1:13–35.
30. Goedecke JH, Barsdorf M, Beglinger C, et al. Effects of a lipase inhibitor (Orlistat) on cholecystokinin and appetite in response to a high-fat meal. Int J Obes Relat Metab Disord. 2003;27:1479–85.
31. Burhol PG, Jenssen TG, Jorde R, et al. Plasma cholecystokinin (CCK) before and after a jejunoileal bypass operation in obese patients with reference to appetite regulation. Int J Obes. 1984;8:233–6.
32. Lassmann V, Vague P, Vialettes B, et al. Low plasma levels of pancreatic polypeptide in obesity. Diabetes. 1980;29:428–30.
33. Marco J, Zulueta MA, Correas I, et al. Reduced pancreatic polypeptide secretion in obese subjects. J Clin Endocrinol Metab. 1980;50:744–7.
34. Holst JJ, Schwartz TW, Lovgreen NA, et al. Diurnal profile of pancreatic polypeptide, pancreatic glucagon, gut glucagon and insulin in human morbid obesity. Int J Obes. 1983;7:529–38.
35. Lawson MJ, Gehling RN, Butler RN, et al. Human pancreatic polypeptide release and gallbladder response after amino acid and cephal vagal stimuli in obese and non-obese subjects. Med Sci Res. 1987;15:183–4.
36. Glaser B, Zoghlin G, Pienta K, et al. Pancreatic polypeptide response to secretin in obesity: effects of glucose intolerance. Horm Metab Res. 1988;20:288–92.
37. Asakawa A, Inui A, Yuzuriha H, et al. Characterization of the effects of pancreatic polypeptide in the regulation of energy balance. Gastroenterology. 2003;124:1325–36.
38. Kojima S, Ueno N, Asakawa A, et al. A role for pancreatic polypeptide in feeding and body weight regulation. Peptides. 2007;28:459–63.
39. Peterson HR, Rothschild M, Weinberg CR, et al. Body fat and the activity of the autonomic nervous system. N Engl J Med. 1988;318:1077–83.
40. Teff K. Learning hunger: conditioned anticipatory ghrelin responses in energy homeostasis. Endocrinology. 2006;147:20–2.
41. Berger D, Floyd JC, Pek SB. The effect of treatment of type 2 (insulin independent) diabetes mellitus on plasma concentrations of pancreatic polypeptide and glucagon. Diabetologia. 1981;21:120–5.
42. Gingerich RL, Nagulesparan L, Bennion L, et al. Pancreatic polypeptide in Pima Indians: the influence of obesity and diabetes. Metabolism. 1985;34:25–9.
43. Weyer C, Salbe AD, Lindsay RS, et al. Exaggerated pancreatic polypeptide secretion in Pima Indians: can an increased parasympathetic drive to the pancreas contribute to hyperinsulinemia, obesity, and diabetes in humans? Metabolism. 2001;50:223–30.
44. Vozarova de Courten B, Weyer C, et al. Parasympathetic blockade attenuates augmented pancreatic polypeptide but not insulin secretion in Pima Indians. Diabetes. 2004;53:663–71.
45. Powley TL, Phillips RJ. Gastric satiation is volumetric, intestinal satiation is nutritive. Physiol Behav. 2004;82:69–74.

46. Kissileff HR, Carretta JC, Geliebter A, et al. Cholecystokinin and stomach distension combine to reduce food intake in humans. Am J Physiol Regul Integr Comp Physiol. 2003;285:R992–8.
47. Jones KL, Doran SM, Hveem K, et al. Relation between postprandial satiation and antral area in normal subjects. Am J Clin Nutr. 1997;66:127–32.
48. Sturm K, Parker B, Wishart J, et al. Energy intake and appetite are related to antral area in healthy young and older subjects. Am J Clin Nutr. 2004;80:656–67.
49. Mundt MW, Hausken T, Smout AJ, et al. Relationships between gastric accommodation and gastrointestinal sensations in healthy volunteers. A study using the barostat technique and two- and three-dimensional ultrasonography. Dig Dis Sci. 2005;50:1654–60.