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Effects of Intragastric Balloon on Gastric Emptying and Plasma Ghrelin Levels in Non-morbid Obese Patients

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Background: Intragastric balloons have been proposed to induce weight loss in obese subjects. The consequences of the balloon on gastric physiology remain poorly studied. We studied the influence of an intragastric balloon on gastric emptying and ghrelin secretion in non-morbid obese patients.

Patients and Methods: 17 patients were included in the study, with mean BMI of 34.4 (range 30.1-40.0). The balloon was inserted under general anaesthesia and endoscopic control, inflated with 600 ml saline, and removed 6 months later. Body weight and gastric emptying (^{13}C-octanoic acid breath test) were monitored while the balloon was in place and 1 month after removal. Ghrelin levels were measured just before balloon insertion and removal.

Results: Mean weight loss was 8.7 kg (range 0-21). Gastric emptying rates were significantly decreased with the balloon in place, and returned to pre-implantation values after balloon removal. Plasma ghrelin levels were significantly decreased (95% CI: -3.8 to -20.7 ng/ml), despite concomitant weight loss. Weight reduction was not correlated to the effect of the balloon on gastric emptying, but was significantly correlated to the ghrelin variations (r=0.668, 95% CI: 0.212-0.885).

Conclusions: Gastric emptying rates and plasma ghrelin levels are decreased in the presence of intragastric balloon. Weight loss induced by the intragastric balloon is related to ghrelin variations, but not to gastric emptying. Ghrelin inhibition may explain part of the effect of the balloon on satiety.

Key words: Obesity, ghrelin, gastric emptying, human, intragastric balloon

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Introduction

Intragastric balloons have been proposed for treatment of obesity.[1-5] They are currently left in place for a limited period of time (4 to 6 months), to avoid the risk of deflation and subsequent migration of the balloon. Short-term efficacy of the device has been reported, with a mean weight loss of 15 kg.[6] However, some patients will not respond adequately in terms of weight loss. The tolerance of the balloon is usually acceptable, although most patients complain of nausea and vomiting for about 1 week after balloon insertion. In some cases, the balloon is not tolerated by the patients (intense nausea and vomiting, abdominal pain), with the need for early removal of the device. These differences in terms of efficacy and tolerance may be related to dietary habits of the subjects, to the volume of the inflated balloon, but also to other gastric parameters such as organ size or gastric emptying.

The mechanisms of action of the intragastric balloon remain poorly studied. The presence of a balloon in the gastric cavity may lead to a reduction of the possibility of ingesting copious meals, and also to a reduction of hunger. There are no data in the literature reporting the effects of the balloon on gastric physiology.

Furthermore, it would be of interest to predict the efficacy and the tolerance of the balloon before insertion, in order to improve patient selection. A pre-insertion predictive test could also help with determination of the optimal filling of the balloon.

The goals of this prospective study were: 1) to measure the effect of an intragastric balloon on gastric emptying and fasting plasma adiponectin, ghrelin and leptin levels (hormones involved in the regulation of alimentary intake and metabolism), in patients with non-morbid obesity (body mass index, BMI >30 and ≤40); 2) to evaluate the possibility to predict the efficacy and the tolerance of the balloon by the use of a pre-insertion gastric emptying test.

Patients and Methods

Study Design

Patients of both sexes, older than 18 and younger than 60, with a BMI between 30 and 40 were included after giving their informed consent. The study had been approved by the CCPPRB Lyon A (local independent ethics committee). Before balloon insertion, a gastric emptying test (^{13}C-octanoic acid breath-test for the measurement of gastric emptying of solids),[7] a specific quality of life questionnaire (IWQOL-Lite),[8] and blood sampling for measurements of fasting plasma adiponectin, ghrelin and leptin levels, were performed. Blood samples for hormone assays were centrifuged immediately, and plasma frozen at -20°C until analysis. All plasma samples were analyzed at the same time using commercial RIA kits (Linco Research, St. Charles, MI, USA) for total ghrelin, leptin and adiponectin. Results are expressed in ng/ml.

The test meal of the gastric emptying test was composed of a scrambled egg with the yolk enriched with 100 mg of [1-^{13}C]-octanoic acid, 2 slices of white bread and 5 mg of margarine, followed by 150 ml of water (total caloric intake: 250 kcal). The $^{13}CO_2$ excretion curves of the gastric emptying test were analyzed according to Ghoos et al,[7] with the calculation of the gastric emptying coefficient (GEC, a global index of gastric emptying rate), the half-emptying time (t1/2), and the lag phase (tlag), corresponding to the initial delayed portion of the gastric emptying curve of solids.

The Impact of Weight on Quality of Life (IWQOL-Lite) questionnaire is a specific health-related quality of life measure, in relation to obesity. Five dimensions are studied with a total of 31 questions: physical function (11 items), self-esteem (7 items), sexual life (4 items), public distress (5 items) and work (4 items). The best theoretical score is 31, and the worst 155.

Intragastric balloon insertion was performed under general anesthesia and after endoscopic control: the balloon (silicone intragastric balloon BioEnterics, Inamed Health, Santa Barbara, CA, USA) was inflated with 600 ml of saline containing 1 ml of methylene blue (to detect balloon deflation). A systematic follow-up including dietary counselling (to obtain a daily food intake of 1300 kcal), physical examination, weight measurement, abdominal X-ray to detect balloon deflation, gastric emptying test, quality of life and food habits questionnaires, was performed at 1 and 4 months after balloon insertion. Endoscopic balloon removal under general anesthesia and tracheal intubation (to avoid tracheal inhalation) was planned 6 months after balloon insertion. Blood samples for fasting plasma hormone levels were obtained on the morning before balloon removal. A final visit was planned 1 month after balloon removal, for physical examination, weight measurement, quality of life and food habits questionnaires, and a gastric emptying test. Figure 1 summarizes the main steps of the study.

Patients

Seventeen patients (3 males and 14 females), with a mean age of 34.9 years (range 19 to 57) were included in the study. The mean BMI was 34.4 ± 0.7 kg/m^2 (range 30.1 to 40.0). One patient was excluded at the time of the initial gastroscopy because of the presence of gastric ulcers related to Helicobacter pylori gastritis. The balloon had to be removed in

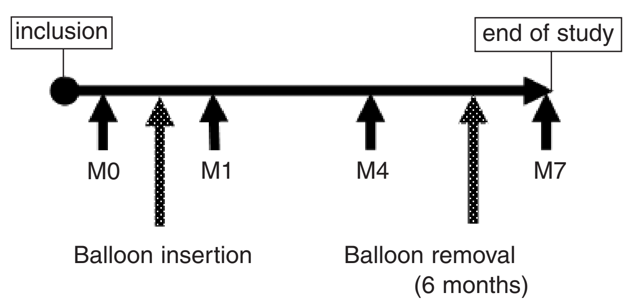

Figure 1. Schematic representation of the study design. (M0: before balloon insertion; M1, M4: 1 month and 4 months after balloon implantation; M7: 1 month after balloon removal).

one male subject 3 months after implantation, because of severe anemia and gastrointestinal bleeding due to balloon-induced gastric ulcers. The balloon was removed as planned in the 15 remaining patients: endoscopic appearance of gastric and esophageal mucosa was normal. Thus, balloon tolerance and efficacy were evaluated on 16 subjects, and the effect of intra-gastric balloon on gastric emptying parameters and hormone levels on 15 subjects.

Statistical Analyses

All results are expressed as mean ± SD, unless otherwise indicated. Temporal evolution of weight, quality of life and gastric emptying results were analyzed using ANOVA for repeated measurements. The PLSD Fischer's test was used for post-hoc comparisons. Hormone levels before and 6 months after balloon insertion were compared using t-test for paired data. Analyses were performed using Statview® for Windows software (SAS Institute Inc, v5.0, Cary, NC, USA).

Results

Balloon Tolerance

One balloon had to be removed after 3 months because of severe gastrointestinal bleeding and anemia due to gastric ulcers. Gastric biopsy specimens were negative for Helicobacter pylori infection, and the recovery after balloon removal was uneventful after a 4-week course of proton pump inhibitors: the ulcers were healed on control endoscopy. Two patients had to be hospitalized at 3 and 4 months after balloon insertion because of food intolerance, vomiting and dehydration for 3 and 5 days, respectively. On abdominal X-ray, the balloon was found in place in the gastric corpus and normally inflated; the 2 patients recovered after 2 and 3 days of I.V. rehydration, and the balloon was left in place for the planned duration. Finally, all patients reported nausea and vomiting for 2 to 14 days (median 6 days) after balloon insertion: these symptoms were treated with oral medications only. Balloon tolerance was not predicted by any of the initial parameters (weight, BMI, hormone levels, gastric emptying rates: data not shown).

Weight Loss

BMI and body weight significantly decreased at 1 and 4 months after balloon insertion, and remained stable afterwards until 1 month after balloon removal (Figure 2). The mean percentage of body weight (BW) loss was 9.4% ± 1.8. Seven patients lost more than 10% of BW with the balloon, while 8 subjects lost less than 9% of BW. Although not statistically significant, only one patient had a baseline slow gastric emptying rate among the 7 that lost more than 10% of BW, while 4 of the 8 cases with a % of BW loss <9% had a slow initial gastric emptying time (P>0.3).

Mean weight loss 1 month after balloon removal was 8.7 ± 1.6 kg (range 0-21). The mean reduction in BMI was 3.1 ± 0.7 (range 0-8.3).

Gastric Emptying Test

Before balloon insertion, ^{13}C-octanoic acid breath-test (OBT) results were within the normal range in 10 cases (half-emptying time $T^1/_2$ <90 minutes), and slow in 5 cases ($T^1/_2$ >110 minutes). ANOVA for repeated measurements disclosed a decreased gastric emptying rate at 1 and 4 months after balloon insertion (Table 1, P=0.0232 for GEC, P=0.0972 for t1/2, and P=0.0694 for tlag), with a return to normal gastric emptying rates 1 month after balloon removal. This inhibitory effect of the balloon on gastric emptying rates was more pronounced in patients with normal gastric emptying at baseline (data not shown).

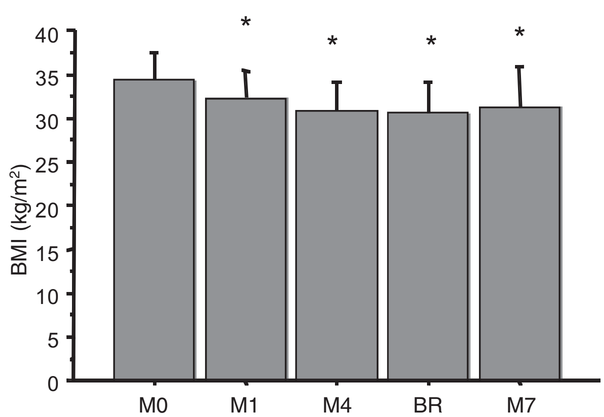

Figure 2. Evolution of BMI after balloon implantation and removal. (M0: BMI before balloon insertion; M1, M4: 1 month and 4 months after balloon implantation; BR: balloon removal; M7: 1 month after balloon removal).

Table 1. Evolution of gastric emptying parameters in presence or absence of the balloon in the stomach. M0: before balloon insertion; M1: 1 month after balloon insertion; M4: 4 months after balloon insertion; M7: 1 month after balloon removal. GEC: gastric emptying coefficient; t1/2: half-emptying time; tlag: lag phase of solid processing. *P* values indicate differences compared to baseline values (M0) with post-hoc PLSD Fischer's test

	M0	M1	M4	M7
GEC	2.58±0.63	2.25±0.65 (*P*=0.15)	1.79±0.7 (*P*=0.028)	2.15±0.75 (*P*=0.25)
t1/2 (min)	92±45	116±53 (*P*=0.21)	157±70 (*P*=0.052)	118±68 (*P*=0.443)
tlag (min)	38±34	67±32 (*P*=0.008)	76±36 (*P*=0.063)	75±42 (*P*=0.30)

Quality of Life

The IWQOL-Lite score was significantly improved at 1 and 4 months after balloon insertion and at 1 month after balloon removal, compared to pre-insertion values (Figure 3, *P*=0.0012). A similar improvement of the score was observed in all 5 dimensions (data not shown).

There was a significant correlation between the % of weight loss and the improvement of IWQOL score (r = -0.696; 95% CI: -0.908 to -0.204): this improvement was -33.7 ± 9.9 in the group of subjects that lost >10% of BW, vs -12.5 ± 4.1 in the group that lost <9% of BW. The improvement of the score was independent of the initial rate of gastric emptying (data not shown).

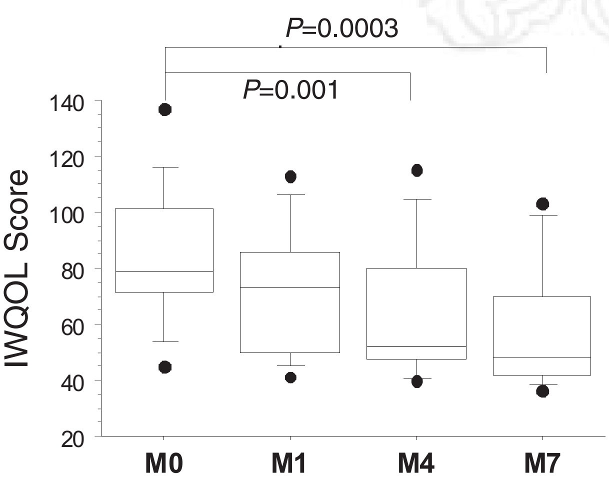

Figure 3. Evolution of the *Impact of Weight on Quality of Life* score (IWQOL-Lite) after balloon implantation and removal. (M0: IWQOL score before balloon implantation; M1, M4: scores 1 and 4 months after balloon implantation; M7: score 1 month after balloon removal).

Ghrelin, Leptin and Adiponectin Measurements

Fasting plasma ghrelin, leptin and adiponectin levels were determined on the day of balloon insertion (pre-balloon), and 6 months later on the morning before balloon removal (post-balloon). Ghrelin and leptin levels were significantly decreased before balloon removal, while adiponectin levels were significantly increased (Table 2). Variations of the levels of these hormones were independent of sex, age, initial BMI, and gastric emptying rates (data not shown).

The % of BW loss was significantly correlated with the variations of plasma ghrelin levels between balloon insertion and balloon removal (r = 0.668, 95% CI: 0.212 to 0.885, Figure 4). Such a significant correlation was not found for leptin nor adiponectin levels.

Discussion

Intragastric balloons have regained popularity for the treatment of obesity. After an initial period of interest in the early eighties,[9] the procedure was abandoned quickly because of the frequency of severe adverse events, mainly intestinal occlusion due to balloon migration out of the stomach.[10,11] The criteria for an "ideal" balloon were proposed in 1987;[12] a new balloon corresponding to these criteria has been commercialized since 1995 by Inamed Health (Bioenterics Intragastric Balloon, BIB). A recent study by Doldi et al[6] showed a mean weight loss of 13.9 kg in 281 obese subjects, with the balloon left in the stomach during 6 months. Our results are slightly lower, with a mean weight loss of 9 kg; on the whole, our patients were significantly leaner than those of Doldi's study, all being non-morbid obese patients with a BMI between 30 and 40. This weight loss was accompanied by a significant improvement in quality of life, starting 1 month after balloon implantation and remaining 1 month after balloon removal. This well-being related to weight loss may encourage patients to go on with their modified lifestyle and food habits acquired

Table 2. Fasting plasma hormone levels before balloon insertion (pre-balloon) and 6 months later, before balloon removal (post-balloon) in 15 subjects

	Pre-balloon	Post-balloon	Delta hormone between pre- and post-balloon (95% CI)	*P*
Ghrelin (ng/ml)	3.2 ± 0.4	1.9 ± 0.1	-3.8 to -20.7	0.021
Leptin (ng/ml)	27.8 ± 3.7	18.7 ± 2.7	-1.3 to -14.4	0.024
Adiponectin (ng/ml)	6.6 ± 0.5	7.8 ± 0.8	+0.12 to + 3.19	0.037

while the balloon was in place in the stomach.

However, the efficacy of this device is still a matter of debate, and its consequences on gastric physiology remain poorly studied.

One hypothesis to explain balloon-induced weight loss could be an effect on gastric emptying. The influence of obesity and weight loss on gastric emptying are far from clear in the literature.[13-15] Our findings show that gastric emptying of solids as measured by the ^{13}C-octanoic acid breath-test was within the normal range in 2/3 of the subjects, and slow in the remaining third. This difference was not related to weight or BMI. We hypothesized that these differences in the baseline gastric emptying rates may explain the variations in terms of tolerance and efficacy of the balloon. Our results demonstrate that the presence of the balloon in the stomach significantly decreased gastric emptying, and more so in the subjects with normal gastric emptying rates at baseline. Some authors have found that the intragastric balloon decreased gastric emptying in obese patients,[16] while others did not observe any significant difference.[17] The weight loss in our study was not correlated with the initial gastric emptying rates, nor to balloon-induced gastric emptying variations; thus, the balloon-induced weight loss is probably independent of its effects on gastric emptying. Similarly, the tolerance to the intragastric balloon was not predicted by the results of the baseline gastric emptying rates, or to the variations induced by the balloon.

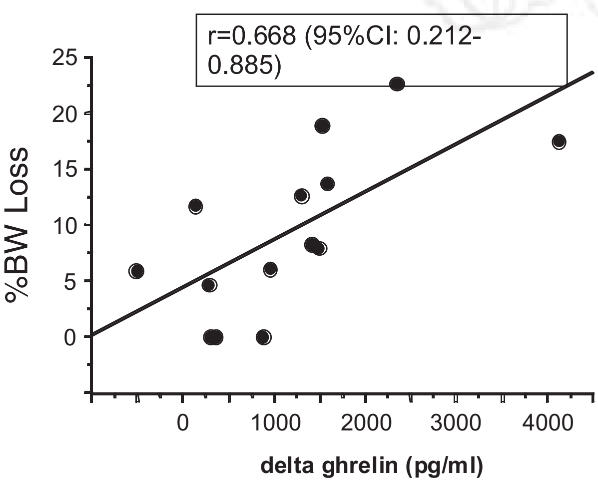

Figure 4. Correlation between the variation of plasma ghrelin levels (delta ghrelin: "before balloon insertion" minus "before balloon removal") and the percentage of body weight loss (% BWL).

Weight loss in obese patients is associated with changes in levels of hormones involved in the regulation of satiety and energy metabolism.[18] Blood levels of leptin are increased in obese subjects in relation to the adipose tissue mass, and decreased with weight loss.[19,20] Adiponectin levels are decreased in obese subjects, and its decrease parallels the development of insulin resistance.[21-24] Ghrelin, a hormone with orexigenic and adipogenic properties, primarily secreted by the fundic glands of the stomach, is usually decreased in states of excessive caloric intake.[25] Its secretion increases with diet-induced weight loss, as one of the compensatory responses of the body to an energy deficit.[26,27] This ghrelin increase in response to weight loss may be one of the factors responsible for the difficulties encountered by obese subjects to maintain their new weight after a successful diet.

Our findings are consistent with the data published, because blood leptin levels were decreased 6 months after balloon insertion, and adiponectin levels were significantly increased. However, total ghrelin levels were significantly decreased at 6 months, just before balloon removal, despite a significant weight loss at that time. This observation has not been published so far to our knowledge. Although this association does not mean a causal relationship, it may indicate a direct inhibitory effect of the balloon on gastric ghrelin secretion. It has been shown that the food-induced ghrelin inhibition observed in lean subjects is altered in obese patients.[28] Cummings et al[29] showed that gastric bypass surgery is associated with markedly reduced ghrelin levels; these authors suggested that the permanent absence of food in the stomach and the duodenum could be responsible for this observation. Our results clearly point to a different mechanism, whereby the fundic distension due to the presence of the balloon may inhibit ghrelin secretion. However, Erdman et al[30] did not find any change in ghrelin secretion after gastric distension with air. Another possibility would be a direct effect of the balloon on gastric ghrelin cells by a mechanical compression (and/or ischemia) of the fundic mucosa. Whatever the exact mechanism of the decreased ghrelin plasma levels observed with the balloon in place in the stomach, this effect may be involved in the efficacy of the balloon, because our results showed a significant correlation of individual % of weight loss with the balloon-induced ghrelin decrease. Although we agree with the conclusions of the randomized study of Mathus-Vliegen et al,[31] showing that intragastric balloon *per se* is not more efficient in terms of weight loss than severe caloric restriction, we believe that it represents a useful tool to facilitate hypocaloric diet and help patients to eat smaller quantities of food. The associated ghrelin decrease may be part of this facilitating effect.

In conclusion, our findings show that intragastric balloon has a modest inhibitory effect on gastric emptying rates. This decrease does not predict the tolerance or the efficacy of the balloon, thus suggesting that this effect on gastric emptying is not essential in balloon-induced weight loss. The presence of the balloon in the stomach is associated with a significant decrease in ghrelin secretion, despite the concomitant weight loss. This ghrelin inhibition may be part of the effect of the intragastric balloon on satiety. Further studies are needed to confirm the causal relationship between the presence of the balloon in the stomach and ghrelin inhibition.

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