IOP PUBLISHING PHYSIOLOGICAL MEASUREMENT

Physiol. Meas. **31** (2010) 131–144 doi:10.1088/0967-3334/31/2/001

Pilot study of temporary controllable gastric pseudobezoars for dynamic non-invasive gastric volume reduction

Martin P Mintchev[1,2,7], Marlena G Deneva[3], Bogdan I Aminkov[4], Michel Fattouche[5], Orly Yadid-Pecht[5] and Robert C Bray[6]

[1] Centre for Bioengineering, University of Calgary, Calgary, Alberta, Canada
[2] Department of Surgery, University of Alberta, Edmonton, Alberta, Canada
[3] Institute of Catalysis, Bulgarian Academy of Sciences, Sofia, Bulgaria
[4] Department of Veterinary Surgery, University of Forestry, Sofia, Bulgaria
[5] Department of Electrical and Computer Engineering, University of Calgary, Calgary, Alberta, Canada
[6] Departments of Surgery and Kinesiology, University of Calgary, Calgary, Alberta, Canada

E-mail: mintchev@ucalgary.ca

Received 15 September 2009, accepted for publication 19 November 2009
Published 11 December 2009
Online at stacks.iop.org/PM/31/131

Abstract

Invasive surgical procedures for gastric volume reduction or bypass have been considered the most effective approach to sustainable long-term weight reduction. However, non-invasive techniques for dynamic volume reduction from inside the stomach are lacking. The aim of this study was to propose temporary, permeable, controllable pseudobezoars for non-invasive, long-term sustainable gastric volume reduction and to test them in pilot human studies. Permeable sac-like carriers made from biocompatible and biodegradable material were filled with expandable superabsorbent fiber and polymer granules. The implements were designed to prevent the expulsion of the pseudobezoars through the pylorus for a controlled time period. The pseudobezoars were administered transorally to two human patients (2M, 78.9 kg/174 cm, girth 88.1 cm, and 89.7 kg/175, girth 95.2 cm). Body weight dynamics, girth, level of satiety, stools, bowel regularity and notable side effects were monitored in three distinct 1 month periods: baseline, therapy and washout. Sonographic verification of the presence of pseudobezoars in the stomachs of both subjects was performed at the end of the therapy month and was repeated at the end of the washout period to examine the clearance of the implements. During the therapy month, both individuals exhibited significant weight and girth reduction ($p < 0.05$), and substantially increased satiety levels. The patients retained their bowel regularity and did not report any notable side effects. The temporary pseudobezoars were clearly noticeable

[7] Address for correspondence: Department of Electrical and Computer Engineering, University of Calgary, 2500 University Drive NW, Calgary, Alberta, T2N 1N4, Canada.

sonographically in both patients at the end of the therapy month and cleared after its discontinuation. Controllable temporary pseudobezoars were designed and tested in pilot studies.

Keywords: besoars, food intake, satiety, obesity, bariatric surgery, gastric volume reduction

1. Introduction

1.1. The worldwide problem of obesity

Recent comprehensive statistics for the year 2005 from across the globe (106 countries, covering approximately 88% of the world population) indicate that more than 22% of the citizens of the world are overweight and more than 9% are obese, with these percentages rapidly growing. Moreover, projections for the year 2030 reveal an alarming trend, particularly for the countries with established market economies. It is projected that more than 36% of the population in these countries will be overweight, and more than 22% will be obese (Kelly *et al* 2008). In the USA alone obesity encompassed more than 30% of the adult population, and the trends are alarming (Baskin *et al* 2005, Wang and Beydoun 2007, James 2008). This is particularly significant since obesity has been implicated as the leading cause of various clinical conditions, including cardiovascular diseases, hypertension, arthritis and diabetes (Guh *et al* 2009).

Five major streams of research and development related to new treatments for obesity are currently being explored: (1) diets, dietary regiments, supplements and related treatments (Katz 2005, Dubnov-Raz and Berry 2008), including oral administration of fiber- or polymer-based substances that expand in the stomach, thus introducing temporary sensation of fullness and satiety (Matulka *et al*, Willman *et al* 2002); (2) pharmacological treatment using specifically developed medications (Bray 2008, Vincent and le Roux 2007); (3) gastric stimulation using implantable electronic devices (Wang *et al* 2006, Aelen *et al* 2008); (4) invasive surgical procedures related to gastric volume reduction (Smith *et al* 2008, Bult *et al* 2008, Miller and Hell 2003), and (5) intragastric balloons for reducing gastric volume and introducing a sensation of satiety and fullness (Genco *et al* 2008, Dumonceau 2008).

1.2. Diets, dietary regimens and dietary supplements

Currently, there are many various diets, dietary supplements, regimens and combinations thereof, and their numbers are growing dramatically (Malik and Hu 2007). However, as a rule, even the best of these weight loss strategies work in the short term only, their success often varies widely between individuals, and they are not sustainable long-term (Katz 2005, Dubnov-Raz and Berry 2008, Malik and Hu 2007, Tsai and Wadden 2005).

Combining diets and dietary supplements is a recent trend in obesity treatment which aims at improving the long-term sustainability of diets using a variety of natural supplements ranging from fibers or fiber-based substances (Eastwood 1992) to exotic plant (Cefalu *et al* 2008) and animal-based extracts (Perez-Torres and El Hafidi 2008). Of these, of particular interest are emerging dietary supplements that expand in the gastrointestinal tract and are believed to induce early satiety resulting in a diminished food intake in the framework of consistently maintained overall diet plans (Matulka *et al*, Willman *et al* 2002). Although pursuing this

avenue could be interesting, the available commercial products Appesat (sodium alginate-based, Goldshield, Croydon, Surrey, UK), and PREE (sodium acrylate-based, Wellosophy Corp., Folsom, CA) to date fail to demonstrate significant and long-term sustainable weight loss in any systematic clinical studies of a reasonable number of patients, despite the fact that an initial, double-blind, randomized, placebo-controlled study showed promising results for the first product (Willman *et al* 2002).

1.3. Pharmacological treatment

Weight-loss-related pharmacological treatment based on specifically developed and clinically tested drugs has also not led to any significant success. Numerous therapies have been associated with various side effects (Powers and Bruty 2008, Fernstrom and Choi 2008, Bray and Ryan 2007), some of which have been considered quite serious and even life-threatening (Kolanowski 1999), leading to suspension of market distribution even after governmental approvals. After numerous attempts to introduce various anti-obesity drugs to the US and the EU markets, presently only two medications remain approved for sales in the USA, orlistat (Xenical, Roche Laboratories, Nutley, NJ, USA), and sibutramine (Meridia, Abbott Laboratories, Abbott Park, IL, USA) (Gupta 2007). However, the range of side effects recently included potential liver damage for Xenical (Umemura *et al* 2005) and cardiovascular problems for Meridia (Florentin *et al* 2007).

1.4. Gastric electrical stimulation

Recently developed techniques for gastric stimulation (Hasler 2009), involving surgical implantation of miniature microelectronic devices have been proposed as an avenue to tackle more severe cases of obesity, and particularly morbid obesity. The devices can administer electrical signals to the stomach and adversely affect normal propulsive gastric peristalsis. However, the procedures used for the positioning of the stimulating electrodes as well as for the implantation of the devices are invasive, and the long-term effect of the treatment remains unknown both in terms of sustainability and safety (Aelen *et al* 2008).

1.5. Bariatric surgery and gastric banding

Surgical procedures related to significant gastric volume reduction are invasive measures to address the problem of obesity, and to date are considered the most reliable avenue for sustainable weight reduction (Snow *et al* 2005, Varela *et al* 2008). With respect to the modification of gastrointestinal anatomy, the intervention can be permanent (Roux-en-Y bypass, biliopancreatic diversion, sleeve gastrectomy, etc (le Roux and Bloom 2005, Encinosa *et al* 2009)) or temporary (gastric banding (Chau *et al* 2005)). Important changes in gut hormone profiles have been reported and have been associated to a various extent with each of these surgical procedures (le Roux *et al* 2006, 2007, Karamanakos *et al* 2008, Shak *et al* 2008, Borg *et al* 2006, Wang and Liu 2009, Diker *et al* 2006, Rubino *et al* 2004). Roux-en-Y gastric bypass and biliopancreatic diversion can be considered the most successful weight reduction techniques, reporting the highest percentage of sustainable weight loss compared to other methods, but with the price of higher mortality and morbidity (te Riele *et al* 2008, Lancaster and Hutter 2008). At the other end of the spectrum, laparoscopic gastric banding has been reported to result in more modest weight loss, but has been associated with a significantly reduced mortality and morbidity (Lancaster and Hutter 2008). Despite the relative success of these surgical methods, risk-normalized mortality rates associated with some of them can

exceed 1% (Tanner and Allen 2008), and the patients have to undergo prolonged recovery periods and dramatically abrupt changes in lifestyle, eating habits and dietary regimens (Ernst *et al* 2009). In addition, all surgical interventions and subsequent patient management can be quite expensive (Carvalho *et al* 2009).

1.6. Intragastric balloons

In the last 20 years, various designs of intragastric balloons have been proposed as an avenue to reduce gastric volume from inside the stomach and thus promote sustainable weight loss superior to diets (Genco *et al* 2008, Dumonceau 2008). Although the balloons have been found effective in promoting short-term weight loss in about two-thirds of the patients with a mean weight loss of over 17 kg, evidence for the long-term sustainability of this technique (over 2 years) is still lacking, and early digestive intolerance precludes its wider applicability (Dumonceau 2008). In addition, it has been demonstrated that the balloon positions itself in the fundus of the stomach, and thus a rather large volume is needed for any serious effect to be achieved (Carvalho *et al* 2009). Moreover, serious adverse side effects associated with the technique include cases of cardiac arrest, esophageal and gastric perforations, and even death, putting a substantial question mark over the safety of this method (Cubattoli *et al* 2009, Ruiz *et al* 2009, Koutelidakis *et al* 2009).

1.7. Temporary controllable pseudobezoars

The present limitations of non-invasive obesity treatments such as diets, dietary regiments, dietary supplements and pharmaceuticals on one hand, and invasive procedures such as bariatric surgery, laparoscopic gastric banding, gastric electrical stimulation and intragastric balloons on the other hand, leave a substantial gap in obesity research. However, a common theme could be found between these often seemingly opposing methods, and this theme inevitably leads to gastric volume reduction. Dramatically achievable surgically or with intragastric balloons, substantial volume reduction has not been reported using non-invasive techniques.

Historically, gastric bezoars, foreign bodies in the stomach formed either by tangled fruit or vegetable fibers (phytobezoars, (Zissin *et al* 2004)) or hair (trichobezoars, (Malhotra *et al* 2008)) have been reported to be difficult to diagnose, manage or remove. On the other hand, more severe cases of large intragastric bezoar formations have led to anemia, malnutrition and wasting, related to often substantial weight loss, which is usually resolved after the removal of the bezoar (Bernstein *et al* 1973, McGehee and Buchanan 1980). Although the formation of intragastric bezoars is a rare medical phenomenon, it is the focus of the present study.

It could be speculated that if we had the ability to design non-nutritional, non-invasive, ingestible implements which upon oral intake can rapidly grow in the stomach to a size and stiffness precluding their expulsion through the pylorus, substantial gastric volume reduction could be achieved without surgical or endoscopic intervention. However, several issues related to this concept emerge that need to be examined: (1) these pseudobezoar implements should retain their volume and relative stiffness for a relatively long time period (5–15 days) so that they cannot exit through the pylorus during a pre-determined time period; (2) they should remain soft enough not to injure gastric mucosa while residing in the stomach; (3) they should be permeable to fluids and gases to avoid possible gastrointestinal obstructions, and (4) they should be relatively quickly disintegratable on demand for safety reasons, a feature that we refer to as controllability. Thus, even if the individual volume of such implements is relatively small (10–50 cc), with proper and regular long-term daily intake, a dynamic but

permanent gastric volume reduction can be achieved in a far less invasive way compared to surgical interventions and intragastric balloons. The controlled disintegration and subsequent expulsion of a given pseudobezoar after residing in the stomach for several days can be compensated by the continuous intake of additional pseudobezoar capsules, thus dynamically maintaining a volume of non-nutritional pseudofood chunks in the stomach, which would stimulate the mechanoreceptors located on the mucosal side of the gastric wall. It can be hypothesized that the presence of these pseudofood chunks would lead to early satiety, the feeling of fullness and, respectively, to long-term sustainable weight loss and a gradual, but not dramatic change in the eating habits of the patient. More importantly, such an approach could lead to a wide-ranging and safe gastric volume reduction treatments accessible to far greater percentage of the population compared to the surgical gastric volume reduction techniques available today.

1.8. Aim of the study

The aim of the present study is to propose a design of temporary, permeable, controllable pseudobezoars for non-invasive but long-term sustainable gastric volume reduction and to test this design in preliminary pilot human experiments.

2. Methods

2.1. Design of the temporary controllable pseudobezoars

Although seemingly simple, the requirements for such non-nutritional pseudobezoars have proven to be quite demanding. Initially, our vision was to utilize permeable sac-like carrier or carriers, in which granules of superabsorbent fibers or polymers that rapidly swell in acid would be placed with disintegration control from outside the body and on demand (Mintchev and Yadid-Pecht 2009). Immediately after ingestion, the implement would swell to a size precluding its expulsion through the pylorus, while retaining dimensions higher than 1.5 cm in all directions even if forces higher than 1.5 N were applied on it. It has been suggested previously that gastric peristaltic forces do not exceed 1 N (Kong and Singh 2008) and that sufficiently rigid spherical particles larger than 1.5 cm in diameter cannot exit the pylorus (Kong and Singh 2008, Cargill *et al* 1988). We eventually simplified the controllability by sourcing a biocompatible, biodegradable and pH-dependent gauze carrier material for timed, pH-based disintegration, in which superabsorbent polymer granules were to be positioned.

Appropriately permeable carboxy cellulose gauze was custom-manufactured and cut into 5×8 cm rectangular pieces. Separately, the same manufacturer provided a 12-tex continuous suture also made from carboxy cellulose which was utilized to enclose the rectangular carboxy cellulose gauze piece into a pyramid-like sac. Two granulated superabsorbent products were mixed in an optimized volume ratio to fill this carboxy cellulose sac, the PolyGlycopleX® (PGX®) granules by Natural Factors (Vancouver, BC, Canada), a novel viscous dietary polysaccharide fiber (Matulka *et al*), and FAVOR PAC (Evonik Degussa, Krefeld, Germany), an inert sodium polyacrylate polymer (carbomer) (Haselbach *et al* 2000a, 2000b, 2000c).

Ultimately, the carboxy cellulose carrier containing the granulated superabsorbents was packed in a 000 gelatin capsule (Capsugel, Peapack, NJ, USA). Two thousand such capsules were manufactured in an ISO 9001 certified dietary supplement manufacturing facility and the product was registered as a dietary supplement under the name Zalak® with the Capital Inspectorate for the Protection of Public Health in Bulgaria according to the European Union and Bulgarian legislation. The product is a four-component implement, including

(a) permeable carboxy cellulose gauze sutured into a sac-like carrier using (b) carboxy cellulose sutures and containing a proprietary mixture of (c) swellable PGX® granulated fibers and (d) carbomer granules.

2.2. Laboratory testing

The pseudobezoars were laboratory tested in HCl-based solution simulating gastric liquids and were optimized for (a) maximal swelling in pH 1–2; (b) optimal hardness so that lateral forces of 1.5 N from any direction would not compress them to dimensions of less than 1.5 cm, while preventing them from bursting, and (c) maximal swelling speed. The optimization was performed by blending PGX and carbomer granules and exploring different dimensions and shapes for the carboxy cellulose gauze carrier, given the volume constraints of a standard 000 gelatin capsule.

In addition, the controllability of the pseudobezoars was examined in pH solutions of 1, 1.5, 2, 3, 4 and 5, testing the integrity of the gauze when pulled from different directions with a force of 1 N, simulating gastric peristaltic forces. Altogether, ten pseudobezoars were tested in each pH solution.

2.3. Pilot human testing

Two overweight healthy male adults (subject 1: 78.9 kg/174 cm, BMI 26.06 kg m^{-2}, girth 88.1 cm, and subject 2: 89.7 kg/175 cm, BMI 29.29 kg m^{-2}, girth 95.2 cm) consented in writing to try the registered dietary supplement Zalak® for a period of 1 month, taking two capsules half an hour before meals with 300 to 500 ml of water, three times a day. During the therapy month, the subjects were asked not to change their daily routines, eating habits and diets, and to record their weight and girth daily. During the baseline and the washout months, the volunteers monitored their weight and girth once a week. The subjects were also asked to regularly fill a sheet with the satiety scale of Haber (Haber *et al* 1977) after each meal during the therapy and for 1 month after its discontinuation. The results for each month (baseline, therapy and washout) were averaged, standard deviation was measured and the level of significance was examined using MS Excel-based two-tailed Student's *t*-test, with $p \leqslant 0.05$ considered significant. In addition, the individuals were advised to estimate, record and report any notable changes in their food and water intake patterns. In this pilot human testing, we aimed at mimicking the way an average patient would be initiated into the pseudobezoar therapy.

It has been reported before (Newman and Girdany 1990) that abdominal ultrasound can detect the presence of bezoars in the stomach. Therefore, at the end of the therapy month, and at the end of the washout month, the patients underwent a routine 3D abdominal ultrasound examination after an overnight fast, which sought to reveal the presence or the absence of the pseudobezoars in the stomachs of both subjects. The 3D feature of the ultrasonic machine (GE Voluson E8, Fairfield, CT, USA) was utilized to estimate gastric volume.

The tests were approved by the Ethics Committee of the University of Forestry in Sofia, Bulgaria.

3. Results

3.1. Laboratory tests

The optimized pseudobezoar implement swelled in simulated gastric acid (pH 1–3) in less than 10 min to a size ranging from 12 to 15 cc (figure 1), with such stiffness that a force of

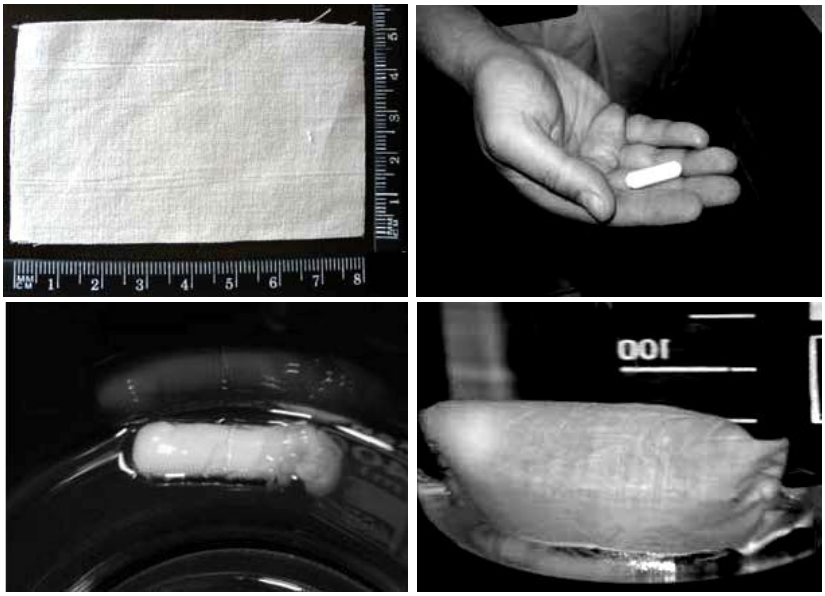


Figure 1. The 5 × 8 cm carboxy cellulose gauze piece (above, left) was sutured into a pillow-like carrier filled with a proprietary mixture and quantity of fiber and polymer granules and placed into a 000 gelatin capsule (above, right). Immediately after submerging in body temperature HCl solution (pH of 2), the gelatin capsule started disintegrating, and the permeable gauze began moisturizing (below, left). After 10–15 min, the pseudobezoar expanded fully to a 12–15 cc implement.

Figure 2. After expanding, Zalak® did not reduce its dimensions to less than 1.5 cm in any direction under force of 1.5 N (shown as a weight load on top) regardless of the pH dynamics of the simulated gastric medium.

1.5 N applied to it from any direction and on any portion of the surface area would not reduce any of its post-expansion dimensions to less than 1.5 cm (figure 2).

The swelling of the pseudobezoar started at 2–3 min after capsule submersion in the simulated gastric environment, immediately after the gelatin dissolved. The three parameters characterizing the pseudobezoar in the simulated gastric medium were monitored: the swelling velocity, the steady-state value of the expanded volume and the compliance response to external force of 1.5 N.

The longevity of the pseudobezoars in pH between 1 and 2 (typical for the stomach) ranged from 6 to 9 days. In pH of 3–4, it was reduced to 3–4 days, and in pH of 5–6 the

Table 1. Results from the pilot chronic human tests of carboxy cellulose/PGX/FAVOR PAC pseudobezoars. Significance is denoted by an asterisk (*) with respect to the first letter of the period (B = baseline, T = therapy, W = washout). Arrows denote whether the significant change was incremental or decremental.

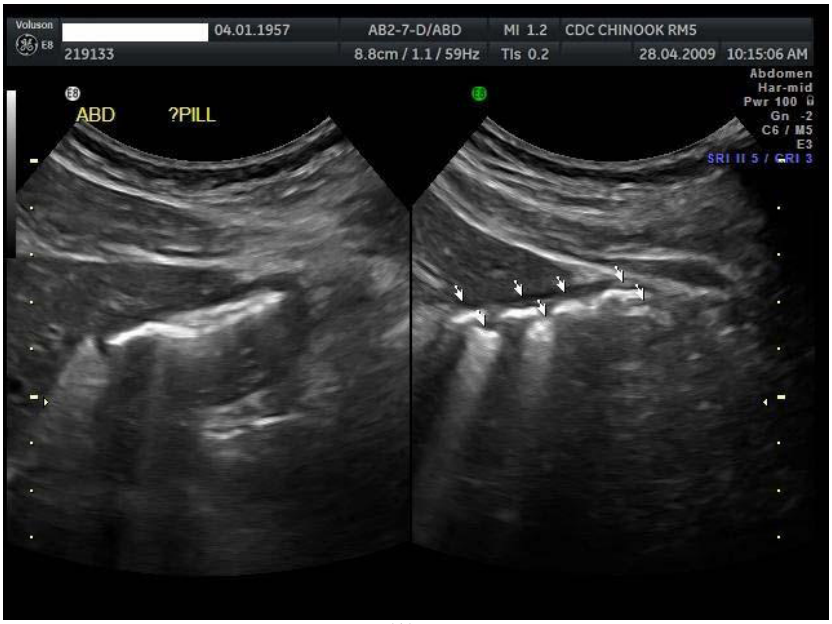
	Volunteer 1 (M)	Volunteer 2 (M)
Haber satiety scale (baseline)	6.4 ± 0.7	6.1 ± 0.9
Haber satiety scale (therapy)	8.8 ± 1.1, *B↑, *W↑	9.0 ± 0.8, *B↑, *W↑
Haber satiety scale (washout)	6.7 ± 0.7, *T↓	6.2 ± 1.1, *T↓
Girth (baseline)	88.0 ± 0.3 cm	95.2 ± 0.14 cm
Girth (therapy)	85.5 ± 1.3 cm, *B↓	91.8 ± 2.1 cm, *B↓
Girth (washout)	85.7 ± 0.6 cm, *B↓	90.9 ± 1.7 cm, *B↓
Weight (baseline)	78.7 ± 0.4 kg	89.2 ± 0.15 kg
Weight (therapy)	76.0 ± 1.7 kg, *B↓	85.8 ± 2.2 kg, *B↓
Weight (washout)	75.5 ± 0.4 kg, *B↓	83.9 ± 1.4 kg, *B↓

gauze carrier weakened and could not withstand 1 N pulling forces after 2–3 h, indicating an excellent pH-based controllability on demand. In other words, if the therapy was to be discontinued for whatever reason (patient concerns, discomfort, or any other possible issue), the administration of a strong antacid raising the pH in the stomach to above 5 would result in the destruction of the pseudobezoars in a matter of hours. Similarly, the pseudobezoars would disintegrate rapidly in the gut, where the pH is between 4 and 6, thus ensuring the safety of the method.

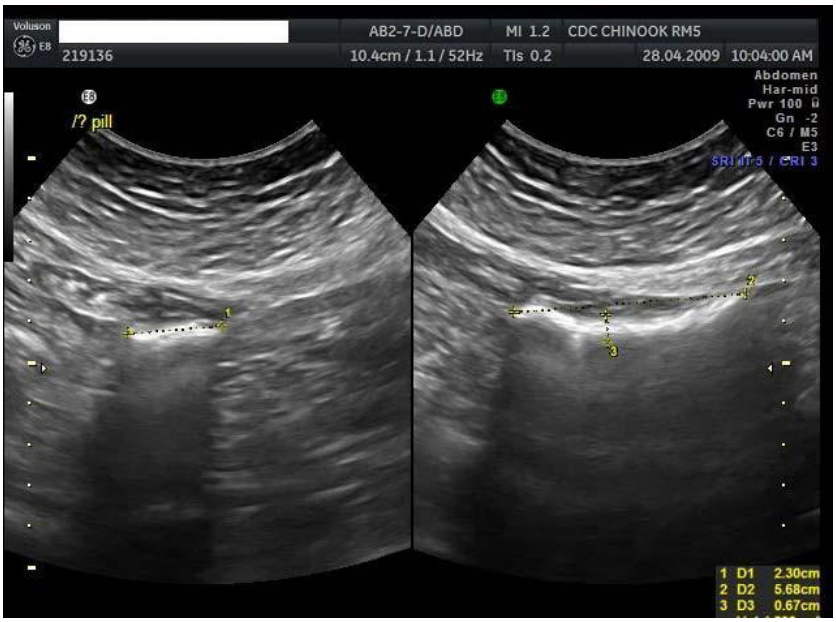
3.2. Pilot human tests

Both subjects exhibited significant weight loss and girth reduction during the therapy period, and high satiety scores on the satiety scale of Haber. These diminished gradually during the washout period. It is important to note that the subjects retained their regularity and did not report any constipation or diarrhea. Only on one single occasion during the therapy, one of the volunteers reported morning nausea, which, however, did not result in vomiting and disappeared after the breakfast meal. Otherwise, both patients reported the feeling of 'something is in my stomach', particularly during the night and in the morning, and substantially reduced appetite and volume of food consumed at mealtimes. However, they did not report any significant or notable side effects or discomfort, although they constantly experienced 'feeling full' sensation when going to bed during the therapy month. One of the subjects (initial BMI of 29.29 kg m^{-2}) started the therapy with a weight of 89.7 kg, to end it at 82.1 kg (a 1 month weight reduction of 8.5%, new BMI of 26.8 kg m^{-2}). In terms of girth, this individual started the therapy with 95.4 cm to end it with 88.6 cm, a 1 month reduction of 7.1%. The other subject started the therapy with a BMI of 26.03 kg m^{-2}, initial weight of 78.9 kg, and girth of 87.9 cm, to end it at a new BMI of 24.61 kg m^{-2}, weight of 74.5 kg (5.6% reduction), and girth of 84.5 cm (3.5% reduction). Both individuals also reported substantially diminished occurrences of incidental food consumption between meals, and substantially diminished food quantity intake during the therapy period, without any other dietary changes. Table 1 summarizes the results from the pilot chronic human tests.

The abdominal 3D ultrasound examination at the end of the therapy month revealed the presence of the pseudobezoars in the stomachs of both subjects (figure 3). In one of the



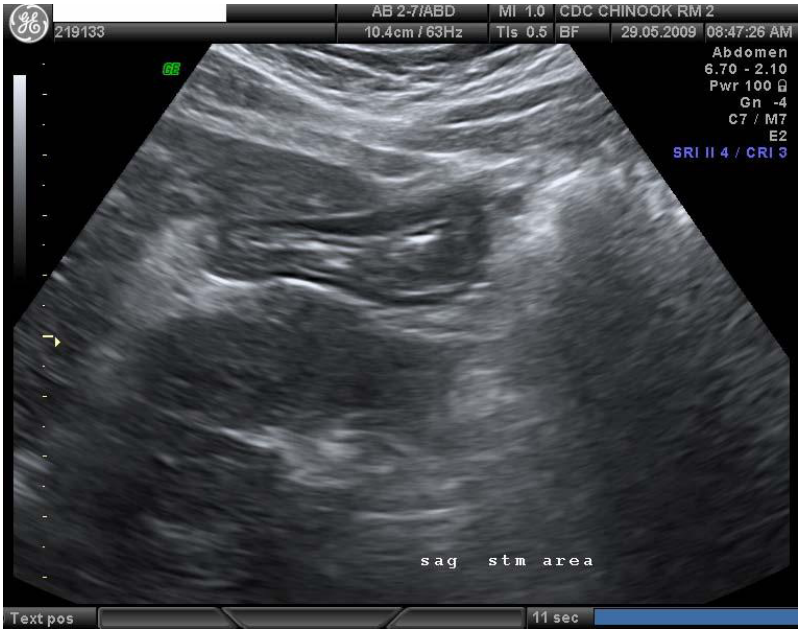
(A)



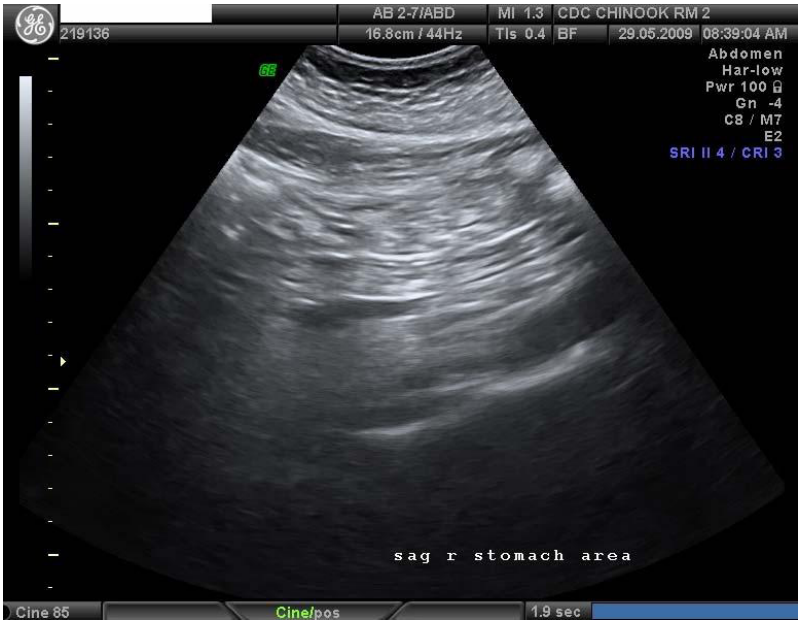
(B)

Figure 3. Abdominal ultrasonic images taken at the end of the therapy revealed the presence of the pseudobezoars in the stomachs of both subjects (A and B), which echographically manifested themselves as cast shadows (denoted with arrows). The pseudobezoars positioned themselves along the lesser curvature of the stomach in the antral and corporal area and away from the fundus.

subjects, the 3D feature of the ultrasonic machine (GE Voluson E8, Fairfield, CT, USA) estimated the gastric volume at 124 cc. In both subjects, the pseudobezoars were located in the lower half of the stomach, in the area of the lesser curvature. Otherwise, the stomachs were



(A)



(B)

Figure 4. Abdominal ultrasonic images taken 30 days after the end of the therapy revealed the absence of pseudobezoars in the stomachs of both subjects (A and B). The lack of shadowing under the lesser curvature of the stomach is obvious.

not distended but were collapsed around the pseudobezoars. At the end of the washout month (i.e. 30 days after the discontinuation of the therapy), pseudobezoars were not identified in any of the subjects (figure 4).

4. Discussion

In the quest for new and effective treatments for obesity, non-invasive alternatives to bariatric surgeries represent a challenging but luring possibility. However, diets and drugs have provided only limited alternatives to patients, and even these have been recommended to specific patient groups only (Katz 2005, Dubnov-Raz and Berry 2008, Bray 2008, Vincent and le Roux 2007).

In this pilot study of temporary controllable pseudobezoars as an alternative to bariatric surgery for the treatment of obesity, we tested this innovative concept on two patients with excellent results.

Naturally, much work needs to be done before the concept of temporary, controllable gastric pseudobezoars becomes a real and proven alternative to bariatric surgery. First and foremost, further clinical studies on a significant number of gender- and age-diversified patients are needed, which should include comparative assessment of hormonal changes that have been demonstrated with bariatric surgeries (le Roux *et al* 2006, 2007, Karamanakos *et al* 2008, Shak *et al* 2008, Borg *et al* 2006, Wang and Liu 2009, Diker *et al* 2006, Rubino *et al* 2004, Lenz and Diamond 2008), and the effect of the therapy on gastric motility and emptying, particularly with respect to the possible modifications that this pseudofood therapy would induce on the Migrating Motor Complex (MMC) in the stomach during fasting (Malagelada 1990).

A key question stemming from this line of research and development is whether this method is yet another dietary option, or it is truly a volume-reduction therapy closer to its surgical counterparts. It is also possible that the method could be a combination of both, depending on the dosage and the administration patterns.

It is worth mentioning also, that in addition to pH-based controllability being an important safety feature of this technology, the carboxy cellulose material used for the gauze carrier has proven anti-inflammatory properties (Zhu *et al* 2001), which probably would not only prevent injuring gastric mucosa after prolonged therapy, but may also have secondary benefits for gastric and even bowel mucosa, particularly if impregnated with beneficial therapeutic excipients. Naturally, on a long run, the benefits of fiber-like granules passing through the gut after the disintegration of the pseudobezoars should not be underestimated as well. In that respect, it is important to note that both subjects did not report excessive gas, bloating, diarrhea or constipation.

The present study clearly demonstrates that administration and long-term sustainability in the stomach of non-invasive, temporary, controllable pseudobesoars is entirely possible. In both subjects, this has been verified echographically, just as it has been reported for actual bezoars (Newman and Girdany 1990). It is our firm belief, therefore, that with the provided controllability of the volume, the number and the presence of such pseudobezars in the stomach, achieving the effects that have been reported for actual bezoars, including weight loss, are entirely possible, while avoiding in a controlled fashion the negative effects of naturally formed bezoars.

5. Conclusion

Controllable temporary pseudobezoars have been designed, optimized and tested in pilot chronic human trials as an alternative to bariatric surgery for the treatment of obesity. The results clearly demonstrated the feasibility of this novel alternative approach in obesity management. Studies on more patients using this technique are needed to confirm these findings.

Acknowledgment

This study was sponsored by EDF Inc., Calgary, Alberta, Canada.

Note added. The methodology described in this paper is protected by pending patents.

References

Aelen P, Neshev E, Cholette M, Cristanti K, Mitchell P, Debru E, Church N and Mintchev M P 2008 Manipulation of food intake and weigh dynamics using retrograde neural gastric electrical stimulation in a chronic canine model *Neurogastroenterol. Motil.* **20** 358–68

Baskin M L, Ard J, Franklin F and Allison D B 2005 Prevalence of obesity in the United States *Obes. Rev.* **6** 5–7

Bernstein L H, Gutstein S, Efron G, Wagie A and Graham E 1973 Trichobezoar-an unusual cause of megaloblastic anemia and hypoproteinemia in childhood *Dig. Dis.* **19** 67–71

Borg C M, le Roux C W, Ghatei M A, Bloom S R, Patel A G and Aylwin S J B 2006 Progressive rise in gut hormone levels after Roux-en-Y gastric bypass suggests gut adaptation and explains altered satiety *Br. J. Surg.* **93** 210–5

Bray G A 2008 Medications for weight reduction *Endocrinol. Metab. Clin. North Am.* **37** 923–42

Bray G A and Ryan D H 2007 Drug treatment of the overweight patient *Gastroenterology* **132** 2239–52

Bult M J F, van Dalen T and Muller A F 2008 Surgical treatment of obesity *Eur. J. Endocrinol.* **158** 135–45

Cargill R, Cadlwell L J, Engle K, Fix J A, Porter P A and Gardner C R 1988 Controlled gastric emptying: 1. Effects of physical properties on gastric residence times of nondisintegrating geometric shapes in beagle dogs *Pharm. Res.* **5** 533–6

Carvalho G L *et al* 2009 An improved intragastric balloon procedure using a new balloon: preliminary analysis of safety and efficiency *Obes. Surg.* **19** 237–42

Cefalu W T, Ye J and Wang Z Q 2008 Efficacy of dietary supplementation with botanicals on carbohydrate metabolism in humans *Endocr. Metab. Immune Disord. Drug Targets* **8** 78–81

Chau W Y, Schmidt H J, Kouli W, Davis D, Wasielewski A and Ballantyne G H 2005 Patient characteristics impacting excess weight loss following laparoscopic adjustable gastric banding *Obes. Surg.* **15** 346–50

Cubattoli L, Barneschi C, Mastrocinque E, Bonucci P and Giomarelti P P 2009 Cardiac arrest after intragastric balloon insertion in a super obese patient *Obes. Surg.* **19** 253–6

Diker D, Vishne T, Maayan R, Weizman A, Vardi P, Dreznik Z, Seror D and Ram E 2006 Impact of gastric banding on plasma adiponectin levels *Obes. Surg.* **16** 1057–61

Dubnov-Raz G and Berry E M 2008 The dietary treatment of obesity *Endocrinol. Metab. Clin. North Am.* **37** 873–86

Dumonceau J M 2008 Evidence-based review of the bioenterics intragastric balloon for weight loss *Obes. Surg.* **18** 1611–7

Eastwood M A 1992 The physiological effect of dietary fiber: an update *Annu. Rev. Nutr.* **12** 19–35

Encinosa W E, Bernard D M, Du D and Steiner C A 2009 Recent improvements in bariatric surgery outcomes *Med. Care* **47** 531–5

Ernst B, Thurnheer M, Wilms B and Schultes B 2009 Differential changes in dietary habits after gastric bypass versus gastric banding operations *Obes. Surg.* **19** 274–380

Fernstrom J D and Choi S J 2008 The development of tolerance to drugs that suppress food intake *Pharmacol. Ther.* **117** 105–22

Florentin E N, Liberopoulos and Elisaf M S 2007 Sibutramine-associated adverse effects: a practical guide for its safe use *Obes. Rev.* **9** 378–87

Genco A, Balducci S, Bacci V, Materia A, Cipriano M, Baglio G, Ribaudo M C, Maselli R, Lorenzo M and Basso N 2008 Intragastric balloon or diet alone? A retrospective evaluation *Obes. Surg.* **18** 989–92

Guh D P, Zhang W, Bansback N, Amarsi Z, Birmingham L B and Anis A H 2009 The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis *BMC Public Health* **9** 88–107

Gupta S 2007 Diet-pill dilemma *Time (New York)* **170** 76

Haber G B, Heaton K W, Murphy D and Burroughs L F 1977 Depletion and disruption of dietary fibre: effects on satiety, plasma glucose and serum-insulin *Lancet* **310** 679–82

Haselbach J, Hey S and Berner T 2000a Short-term oral toxicity study of FAVOR PAC in rats *Regul. Toxicol. Pharm.*. **32** 310–6

Haselbach J, Hey S, Diener B and Mehta N 2000b Mutagenicity studies of FAVOR PAC *Regul. Toxicol. Pharm.* **32** 317–25

Haselbach J, Hey S and Jones C 2000c Disposition of radiolabeled FAVOR PAC in rats *Regul. Toxicol. Pharm.* **32** 326–31

Hasler W L 2009 Methods of gastric electrical stimulation and pacing: a review of their benefits and mechanisms of action in gastroparesis and obesity *Neurogastroenterol. Motil.* **21** 229–43

James W P T 2008 The epidemiology of obesity: the size of the problem *J. Intern. Med.* **263** 336–52

Karamanakos S N, Vagenas K, Kalfarentzos F and Alexandrides T 2008 Weight loss, appetite suppression, and change in fasting and postprandial ghrelin and peptide-YY levels after roux-en-Y gastric bypass and sleeve gastrectomy *Ann. Surg.* **247** 401–6

Katz D L 2005 Competing dietary claims for weight loss: finding the forest through truculent trees *Annu. Rev. Public Health* **26** 61–88

Kelly T, Yang W, Chen C-S, Reynolds K and He J 2008 Global burden of obesity in 2005 and projections to 2030 *Int. J. Obes.* **32** 1431–7

Kolanowski J A 1999 Risk-benefit assessment of anti-obesity drugs *Drug Saf.* **20** 119–31

Kong F and Singh R P 2008 A model stomach system to investigate disintegration kinetics of solid foods during gastric digestion *J. Food Sci.* **73** E202–10

Koutelidakis I, Dragoumis D, Papaziogas B, Patsas A, Katsougianopoulos A, Atmatzidis S and Atmatzidis K 2009 Gastric perforation and death after the insertion of an intragastric balloon *Obes. Surg.* **19** 393–6

Lyly M, Liukkonen K, Salmenkallio-Marttila M, Karhunen L, Poutanen K and Lahteenmaki L 2009 Fibre in beverages can enhance perceived satiety *Eur. J. Nutr.* **48** 251–8

le Roux C W, Aylwin J B, Batterham R L, Borg C M, Coyle F, Prasad V, Shurey S, Ghatei M A, Patel A G and Bloom S R 2006 Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters *Ann. Surg.* **243** 108–14

le Roux C W and Bloom S R 2005 Editorial: why do patients lose weight after roux-en-Y gastric bypass? *J. Clin. Endocrinol. Metab.* **90** 591–2

le Roux C W, Welbourn R, Werling M, Osborne A, Kokkinos A, Laurenius A, Lonroth H and Olbers T 2007 Gut hormones as mediators of appetite and weight loss after roux-en-Y gastric bypass *Ann. Surg.* **246** 780–5

Lancaster R T and Hutter M M 2008 Bands and bypasses: 30-day morbidity and mortality of bariatric surgical procedures as assessed by prospective, multi-center, risk-adjusted ACS-NSQIP data *Surg. Endosc.* **22** 2554–63

Lenz A and Diamond F B 2008 Obesity: the hormonal milieu *Curr. Opin. Endocrinol., Diabetes Obes.* **15** 9–20

Malagelada J R 1990 Where do we stand on gastric motility? *Scand. J. Gastroenterol. Suppl* **175** 42–51

Malhotra A, Jones L and Drugas G 2008 Simultaneous gastric and small intestinal trichobezoars *Pediatr. Emerg. Care* **24** 774–6

Malik V S and Hu F B 2007 Popular weight-loss diets: from evidence to practice *Nat. Clin. Prac. Cardiovasc. Med.* **4** 34–41

Matulka R A, Lyon M R, Wood S, Marone P A, Merkel D J and Burdock G A 2009 The safety of PolyGlycopleX (PGX) as shown in a 90-day rodent feeding study *Nutr. J.* **8** 1–11

McGehee F T and Buchanan R 1980 Trichophagia and trichobezoar: etiologic role of iron deficiency *J. Pediatr.* **97** 946–8

Miller K and Hell E 2003 Laparoscopic surgical concepts of morbid obesity *Langenbecks Arch. Surg.* **388** 375–84

Mintchev M P and Yadid-Pecht O 2009 Controlled degradation of expandable polymers in gastric volume reduction treatment *US Patent* Application No 20090035367

Newman B and Girdany B R 1990 Gastric trichobezoars—sonographic and computed tomographic appearance *Pediatr. Radiol.* **20** 526–7

Perez-Torres B G and El Hafidi M 2008 Medicinal agents in the metabolic syndrome *Cardiovasc. Hematol. Agents Med. Chem.* **6** 237–52

Powers P S and Bruty H 2008 Pharmacotherapy for eating disorders and obesity *Child. Adolesc. Psychiatr. Clin. N Am.* **18** 175–87

Rubino F, Gagner M, Gentileschi P, Kini S, Fukuyama S, Feng J and Diamond E 2004 The early effect of the roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism *Ann. Surg.* **240** 236–42

Ruiz D, Vranas K, Robinson D A, Salvatore L, Turner J W and Addasi T 2009 Esophageal perforation after gastric balloon extraction *Obes. Surg.* **19** 257–60

Shak J R *et al* 2008 The effect of laparoscopic gastric banding surgery on plasma levels of appetite-control, insulinotropic, and digestive hormones *Obes. Surg.* **18** 1089–96

Smith B R, Schauer P and Nguyen N T 2008 Surgical approaches to the treatment of obesity: bariatric surgery *Endocrinol. Metab. Clin. North Am.* **37** 943–64

Snow V, Barry P, Fitterman N, Qaseem A and Weiss K 2005 Pharmacologic and surgical management of obesity in primary care: a clinical practice guideline from the American college of physicians *Clin. Guidelines* **142** 525–31

Tanner B D and Allen J W 2008 Complications of bariatric surgery: implications for the covering physician *Am. Surg.* **75** 103–12

te Riele W W, Vogten J M, Boerma D, Wiezer M J and van Ramshorst B 2008 Comparison of weight loss and morbidity after gastric bypass and gastric banding. A single center European experience *Obes. Surg* **18** 11–6

Tsai A G and Wadden T A 2005 Systematic review: an evaluation of major commercial weight loss programs in the United States *Am. Coll. Phys.* **142** 56–66

Umemura T, Ichijo T, Matsumoto A and Kiyosawa K 2005 Severe hepatic injury caused by orlistat *Am. J. Med.* **119** E7–7

Varela J E, Hinojosa M W and Nguyen N T 2008 Bariatric surgery outcomes in morbidly obese with the metabolic syndrome at US academic centers *Obes. Surg.* **18** 1273–7

Vincent R P and le Roux C W 2007 New agents in development for the management of obesity *Int. J. Clin. Pract.* **61** 2103–12

Wang G J, Yang J, Volkow N D, Telang F, Ma Y, Zhu W, Wong C T, Tomasi D, Thanos P K and Fowler J S 2006 Gastric stimulation in obese subjects activates the hippocampus and other regions involved in brain reward circuitry *Proc. Natl Acad. Sci.* **103** 15641–5

Wang Y and Beydoun M A 2007 The obesity epidemic in the United States-gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis *Epidemiol. Rev.* **29** 6–28

Wang Y and Liu J 2009 Plasma ghrelin modulation in gastric band operation and sleeve gastrectomy *Obes. Surg.* **19** 357–62

Willman H R, Ley F and Pruckner S 2002 Significant weight reduction by stimulation of satiation sensors *Der Algemeinarzt* **24** 1464–8

Zhu L, Kumar V and Banker G S 2001 Examination of oxidized cellulose as a macromolecular prodrug carrier: preparation and characterization of an oxidized cellulose-phenylpropanolamine conjugate *Int. J. Pharm.* **223** 35–47

Zissin R, Osadchy A, Gutman V, Rathaus V, Shapiro-Feinberg M and Gayer G 2004 CT finding in patients with small bowel obstruction due to phytobezoar *Emerg. Radiol.* **10** 197–200