

### Pilot Studies of Temporary Controllable Gastric Pseudobezoars (Pseudofood) as an Alternative to Bariatric Surgery for the Treatment of Obesity

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**BACKGROUND:** Recent NIH statistics indicates that more than 40% of Americans are obese, with more than 20% of these individuals being morbidly obese. Invasive surgical procedures have been considered the most effective and reliable avenue for sustainable long-term weight reduction. However, non-invasive techniques for dynamically achieving volume reduction from inside the stomach are lacking. **AIM:** The aim of this study was to design temporary, permeable, controllable pseudobezoars for non-invasive but long-term sustainable gastric volume reduction and to test them in pilot chronic animal and human experiments. **METHODS:** Permeable sac-like carriers made from biocompatible and biodegradable material were filled with expandable absorbent fiber and polymer granules, and the designed implements were packed into standard 000 gelatin capsules. The material of the carrier and the mixture of fiber and polymer granules were optimized for maximal volume expansion in simulated gastric acid environment, for swelling speed and for dimensional hardness to prevent the expulsion of the pseudobezoars through the pylorus. The implements were administered chronically and transorally to 2 dogs (1M, 25.1 kg, 1F, 30.25 kg) and two human volunteers (1M, 78.9 kg/174 cm, BMI 26.06 kg/m<sup>2</sup>, girth 88.1 cm, and 1M, 89.7 kg/175 cm, BMI 29.29 kg/m<sup>2</sup>, girth 95.2 cm) according to a pre-designed administration schedule. Food intake, body weight and girth dynamics, stools, regularity and notable side effects were monitored in three distinct periods, baseline, therapy, and washout, lasting one month each. **RESULTS:** The presence of the pseudobezoars in the stomach was confirmed endoscopically in the dogs and sonographically in the humans. Both dogs exhibited a significant reduction of food intake (2-tailed Student t-test,  $p < 0.05$ ), which did not materialize in significant weight reduction probably due to the relatively short therapy period. Significantly increased water intake was noted, and very few side effects were recorded. After an extensive implement optimization for improved controllability and safety, a more vigorous pseudobezoar therapy was administered to the volunteers resulting in significant weight loss and girth reduction during the therapy period, and high satiety scores on the satiety scale of Haber. These effects diminished gradually during the washout period. The subjects did not report any notable discomfort or side effects. **CONCLUSION:** Controllable temporary pseudobezoars have been designed, optimized and tested in pilot chronic animal and human studies. The results clearly demonstrated the feasibility of this novel alternative approach in obesity management.

## W1860

### T-Cell Responses to Gut Antigens in Visceral Adipose Tissue of Mice Contribute to Glucose Intolerance in Obesity

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**BACKGROUND:** Obesity often results in inflammation of visceral adipose tissues, which involves T-lymphocytes. It is unknown why T-cells infiltrate adipose tissue in obesity. **AIM:** To test whether immune responses to antigens absorbed from the gut can contribute to adipose tissue inflammation. **METHODS:** BALB/c mice were sensitized with ovalbumin (OVA) or vehicle before receiving OVA-enriched low- or high (10 or 60% Kcal) fat diets for up to ten weeks. Adipose tissue OVA and CD3 were measured by immunohistochemistry. Inflammation was assessed by real-time PCR and was related to bodyweight, adiposity, and glucose tolerance. **RESULTS:** Antigenic, dietary OVA was clearly detectable in mesenteric adipose tissues. OVA-sensitized, but not naive mice showed substantial accumulation of CD3+ cells in mesenteric adipose depots. Expression of interferon gamma and osteopontin were increased in mesenteric adipose depots of OVA-sensitized mice. The difference in expression between naive and sensitized mice increased over time and was significantly more pronounced with high-fat diets. In contrast to mesenteric adipose tissue, gene expression was not significantly altered in subcutaneous fat. Adipose tissue responses to OVA did not affect obesity, bodyweight, and macrophage accumulation even after 10 weeks high-fat dieting, perhaps because of increased regulatory T-cell activity as reflected by significantly increased FOXP3 mRNA levels. However, responses to OVA impaired glucose tolerance at 10 weeks. **CONCLUSION:** The intestinal microflora and the diet are a likely source of antigens causing T-cell responses in visceral adipose depots. High fat diets may exacerbate such responses, perhaps by increasing antigen absorption. The resulting inflammation in visceral fat may accelerate metabolic syndrome.

## W1861

### Fibroblast Growth Factor 19 as a Possible Cause and a Treatment Target for Obesity

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**Background:** Bile acids have been implicated to have a metabolic role. Fibroblast Growth Factor 19 (FGF19) is expressed in the ileum in response to bile acid absorption and regulates hepatic bile acid synthesis. Furthermore FGF19 influences metabolic parameters and energy expenditure. We hypothesise that serum FGF19 differs between obese and non-obese individuals. Furthermore we propose that FGF19 is involved in the enhanced gut hormone profile, facilitating appetite control and weight loss following Roux-en-Y gastric bypass. **Methods:** We prospectively studied patients undergoing either gastric bypass (n=12) or gastric banding (n=6). We also studied a group of non-obese individuals as a control group (n=19). Patients were studied pre-operatively and at four and forty two days post-operatively. An ELISA method was utilised for measuring serum FGF19 levels. Results: FGF19 was significantly lower in obese compared to non-obese individuals (122.6 versus 231.5 ng/L;  $p < 0.01$ ). Following gastric bypass FGF19 levels were significantly higher on days 4 and 42 compared to preoperatively (232.5 ng/L versus 122.6 ng/L,  $p < 0.01$ , and 199.4 ng/L versus 122.6 ng/L,  $p < 0.05$  respectively). There was no change in FGF19 following gastric banding.

**Conclusion:** Obese individuals have reduced fasting serum FGF19. Gastric bypass surgery is associated with an increase in fasting serum FGF19. This increase can be attributed to the altered anatomy postoperatively as this effect is not present in patients undergoing gastric banding. We propose that accelerated bile delivery to the terminal ileum following gastric bypass causes increased bile acid absorption as evidenced by the increased FGF19. This phenomenon may lead to increased gut hormone production.

## W1862

### The Effect of Diet, Genetic Background and Age on the Energy Harvesting Capacity of the Gut Microbiota in OB/OB and Diet-Induced Obese (Dio) Mice

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**Introduction:** Recent work from Gordon et al., has suggested a role for increased efficiency of energy harvest, due to alterations in the gut microbiota, in the development of obesity in mice. However, while genetic background, age and diet play vital roles in the propensity of mice to gain weight, the roles of these variables in determining the efficiency of energy harvest are not clear. **Aim:** To examine the effects of genetic background, age, and diet on the efficiency of energy harvest, using the energy content of feces and cecal/fecal short chain fatty acid (SCFA) levels as markers of the energy harvesting capacity of the gut microbiota. **Methods:** Seven week old male *ob/ob* and wild-type mice fed either a low-fat diet or a high-fat diet (DIO) were housed individually for 8 weeks (n=8/group). Body weights, fecal/cecal SCFA levels and fecal energy content were measured at 7, 11 and 15 weeks of age. **Results:** Both *ob/ob* and DIO mice gained significantly more body weight than controls ( $p < 0.05$ ) over 8 weeks. At 7 weeks, the fecal energy content was significantly lower (13.12±0.39 kJ/g vs. 13.52±0.36 kJ/g;  $p < 0.05$ ) for *ob/ob* mice compared to controls. However, this relationship did not persist at ages 11 and 15 weeks. In contrast, fecal energy content increased from age 7 to 11 weeks in response to a high-fat diet in DIO mice (13.59±0.29 kJ/g vs. 14.62±0.78 kJ/g;  $p < 0.05$ ) but no further increase was observed from age 11 to 15 weeks. Cecal propionate decreased from age 7 to 15 weeks in both the *ob/ob* (9.17±1.57 vs. 0.98±1.95 nmol/g;  $p < 0.01$ ) and the DIO mouse model (6.63±1.58 vs. 0 nmol/g;  $p < 0.01$ ) while cecal acetate decreased significantly in *ob/ob* alone (68.13±5.41 vs. 40.78±13.01 nmol/g;  $p < 0.05$ ). Fecal acetate levels decreased from age 7 to 15 weeks in both the *ob/ob* (36.9±20.58 vs. 14.40±3.78 nmol/g;  $p < 0.01$ ) and DIO mouse model (11.85±3.08 vs. 4.10±2.72 nmol/g;  $p < 0.001$ ). **Conclusions:** The energy content and/or composition of the diet influences the efficiency of energy harvest in DIO mice. While the energy harvesting capacity of the gut microbiota increased in *ob/ob* mice, as measured by decreased fecal energy content and increased cecal SCFA production, this phenomenon was transient and did not persist with increasing age. SCFA levels in both the *ob/ob* and DIO mice may reflect changes in the gut microbiota in response to increasing obesity or increased efficiency of energy absorption.

## W1863

### Functional Characteristics of Calcium and Potassium Channels in Diet Induced Obese (Dio) Rats

Shiyang Li, Jiande Chen

**Background and aims:** Gastrointestinal motility not only regulates the rate at which nutrients are being processed but also participates in the control of appetite and satiety. Alteration in gastric motor functions in obesity could be a potential factor in the maintenance of weight or the development of obesity. The aim of the present study was to explore possible alterations in smooth muscle functions in obese rats by investigating differences in electrical properties of calcium and potassium channels of antrum smooth muscle cells (SMC) between DIO-Prone (DIO-P) and DIO-Resistant (DIO-R) rats. **Materials and Methods:** Thirty rats at 10 weeks were fed with high fat diet for 8 weeks. The top third and bottom third weight gainers were then identified as DIO-P and DIO-R rats, respectively. The whole-cell patch clamp technique was used to measure calcium and potassium currents in single isolated antral circular SMC. Current-voltage curve was studied from a holding potential of -80mV (L-type calcium current, I<sub>CaL</sub> and transient outward potassium current, I<sub>Kto</sub>) or -40mV (Calcium activated potassium current, I<sub>KCa</sub>). Steady state inactivation kinetics or recovery kinetics from channel inactivation was also studied. **Results:** 1) After 8-week exposure to the high-fat diet, DIO-P (n=9) rats were about 21% heavier than DIO-R (n=9) rats. The body weight at the day of sacrifice were 730±41g and 639±33g in DIO-P and DIO-R rats, respectively ( $P < 0.001$ ). 2) The resting membrane potential in DIO-P (-48.0±2.7mV) was not different from DIO-R rats (-47.0±2.8mV); 3) In both DIO-P and DIO-R rat antral myocytes, depolarizing pulses activated I<sub>CaL</sub> which were activated at around -30mV, peaked around 10mV and reversed at around 60mV. The peak amplitude of I<sub>CaL</sub> at 10mV in DIO-P myocytes (-23.2±2.3pA/pF) was greater than that in DIO-R rats (-14.9±2.7pA/pF,  $P = 0.03$ ) without alternation of steady state inactivation kinetics. 4) No difference was found in the current density, steady activation/inactivation kinetics or recovery kinetics of I<sub>Kto</sub> between the two groups of rats; 5) The mean current density of I<sub>KCa</sub> at 50mV in DIO-P SMC (70.0±19.3pA/pF, n=10) was not significantly different from that in DIO-R rat myocytes (60.1±12.5pA/pF, n=9,  $P = 0.40$ ). **Conclusions:** Biophysical properties of the potassium channel are not altered in DIO rats. However, a higher density of L-type calcium channels was noted in DIO-P rats and this may allow more Ca<sup>2+</sup> influx during action potentials, possibly leading to enhanced antrum contractions and provide a cellular basis for accelerated gastric emptying previously reported in DIO rats.

## W1864

### Ghrelin Alleviates Social Isolation-Associated Anorexia in Mice

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**Background/Aim:** Social isolation triggers excessive stress reactions in both rodents and humans, and chronic isolation is known to exacerbate aggressiveness and cause loss of weight. Decrease in food intake, the most typical feature of the stress response, is a very

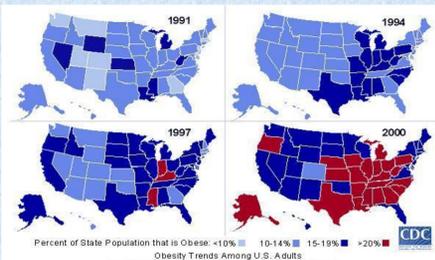
# Pilot Study of Temporary Controllable Gastric Pseudo-bezoars (Pseudofood) for Dynamic Non-Invasive Gastric Volume Reduction

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## BACKGROUND

- Recent statistics (106 countries, 88% of the world population): > 22% overweight; > 9% obese [1, 2];



- Five major treatment streams in obesity research: (A) diets, dietary regimens and supplements[3]; (B) pharmacological [4]; (C) gastric electrical stimulation [5]; (D) intragastric balloons [6]; and (E) bariatric surgery, including gastric banding [7]. **Only the latter long-term successful.**

## AIMS

- To propose a design of temporary, permeable, controllable pseudo-bezoars for non-invasive but long-term sustainable gastric volume reduction;
- To test this design in pilot human experiments.

## METHODS: DESIGN CRITERIA FOR THE PSEUDOBEZOARS

- Safety:**
  - Biocompatible carrier and expandable polymers;
  - Nonirritating components;
  - Biodegradable carrier;
  - Expandable polymer granules in the stomach;
  - Optimal and pH-dependent chemical and mechanical strength of the carrier;
  - fluid (liquids and gases) permeable carrier-material;
  - stable but sufficiently soft not to injure gastric mucosa;
- Dimensions:**
  - Pseudo-bezoar expulsion through the pylorus impossible;
  - Dimensions should exceed 1.5cm in all directions even if forces higher than 1.5N are applied on the pseudo-bezoar from any side.
- Timing:**
  - Optimal blend and quantity of expandable polymers to ensure immediate swelling of the pseudo-bezoar in gastric liquid upon swallowing;

- Gastric retention for several days;

## III. Dietary compatibility:

- Non nutritional components;
- Heavy upon swelling to sink in the antrum.

## IV. Ease of administration: tablet form

### METHODS: MATERIALS

- Carrier: Carboxycellulose gauze with micropores;
- Suture: Carboxycellulose thread, 12 tex;
- Polymer Blend: PolyGlycopleX (PGX) (Natural Factors, Vancouver, BC, Canada) and Polyacrylic Acid Sodium Salt (Carbomer) (Waco Pure Chemical Industries, Tokyo, Japan) granules in a proprietary ratio.
- Carrier sutured into a pillow-like sac, filled with the polymer blend and packed in a standard 000 gelatin capsule (Capsugel, Peapack, NJ, USA).



### METHODS: LABORATORY TESTING

- Optimization of polymer blend for maximal (15 cc) and rapid (10 min) swelling in pH 1-7, steps of 1;
- Optimization of design for retaining dimensions when force of 1.5N applied from all directions



### METHODS: REGISTRATION AND MANUFACTURING

- 720 capsules manufactured in an ISO-certified dietary supplement facility in Sofia, Bulgaria
- Implement registered with the Regional Directorate for Public Health Protection in Sofia, Bulgaria for sales as a dietary supplement as per EU regulations.



### METHODS: PILOT HUMAN TESTING

- Two overweight healthy male adults (Subject 1: 78.9 kg/174 cm, BMI 26.06 kg/m<sup>2</sup>, girth 88.1 cm; Subject 2: 89.7 kg/175 cm, BMI 29.29 kg/m<sup>2</sup>, girth 95.2 cm);
- Baseline period; Therapy period; Washout period, 1 month each;
- Therapy period: 2 capsules, 3 times/day, 1/2 hour before meals with 300 to 500 ml of water;
- Baseline and Washout periods: Water intake only 1/2 hour before meals, no capsules.
- Daily routines, eating habits and diets not changed; weight and girth recorded daily; Satiety Scale of Haber [8] filled daily;
- At the end of Therapy and Washout months: 3D abdominal ultrasound tests (GE Voluson E8, Fairfield, CT, USA)
- Student's two-tailed test to compare weight and girth dynamics between the Baseline, Therapy and Washout months, p < 0.05.

### RESULTS: PILOT HUMAN TESTING

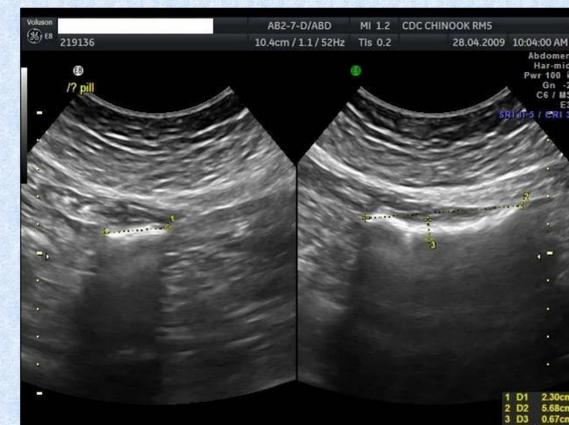
	Volunteer 1 (M)	Volunteer 2 (M)
<b>Haber Satiety Scale (Baseline)</b>	6.4+/-0.7	6.3+/-0.9
<b>Haber Satiety Scale (Therapy)</b>	8.8+/-1.1 *B ↑	9.0+/-0.8 *B ↑
<b>Haber Satiety Scale (Washout)</b>	6.7+/-0.7, *T ↓	6.2+/-1.1, *T ↓
<b>Girth (Baseline)</b>	88.0+/-0.3 cm	95.2 +/- 0.14 cm
<b>Girth (Therapy)</b>	85.5+/-1.3 cm *B↓	91.8 +/- 2.1 cm*B↓
<b>Girth (Washout)</b>	85.7+/-0.6cm *B↓	90.9 +/- 1.7 cm*B↓
<b>Weight (Baseline)</b>	78.7+/-0.4 kg	89.2 +/- 0.15 kg
<b>Weight (Therapy)</b>	76.0+/-1.7 kg, *B↓	85.8 +/- 2.2 kg *B↓
<b>Weight (Washout)</b>	75.5+/-0.4 kg, *B↓	83.9 +/- 1.4 kg *B↓

## RESULTS: ULTRASOUND

### End of Therapy Month: Volunteer 1



### End of Therapy Month: Volunteer 2



### End of Washout Month: Volunteer 1



### End of Washout Month: Volunteer 2



## CONCLUSIONS

- New Avenue for Dynamic Non-Invasive Gastric Volume Reduction from Inside of the Organ
- The integrity of the Temporary Controllable Gastric Pseudo-bezoars is pH-dependent and they can disintegrate in a couple of hours in pH>5-6; long-term integrity in pH 1-3 pivotal for effectiveness
- In these pilot studies the two volunteers exhibited more than 5% weight reduction in 1 month of therapy

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