Temporary Controllable Pseudobezoars as a Non-Invasive Alternative to Surgical Gastric Volume Reduction for the Treatment of Obesity

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Abstract:

Introduction: Recently developed pseudobezoar concept provides an obesity treatment approach based on a non-invasive, dynamic, long term sustainable gastric volume reduction from inside the stomach. It combines successfully non-invasiveness with effectiveness, pretending to be a reliable alternative to bariatric surgery. This paper aims to investigate the impact of temporary controllable intragastric pseudobezoars on anti obesity therapy of a reasonable number of volunteers.

Methods: Dietary supplement pseudobezoar product (Zalak B, EDF Bulgaria Ltd., Sofia, Bulgaria) was tested. A total of 16 (3M, 13F, mean age 44.0 ± 12.0 years, mean body weight 93.8 ± 21.9 kg, BMI 33.3 ± 5.6 kg/m^2, mean waist 103.3 ±13.8 cm, mean hip 114.3 ±12.3 cm, mean waist-to-hip ratio 0.89 ± 0.10) healthy but overweight and obese subjects participated in a blind, placebo-controlled, cross-over chronic trial for a period of two months. Two groups of 8 participants were randomly formed, denoted as A- active (8 F) and B- placebo (3M, 5F). The administration pattern during the whole study period included a trans-oral intake of 2 pseudobezoar or placebo capsules 15 to 30 min before principal meals, 3 times a day. Group A started on pseudobezoar intake for the first 30 days, while group B was put on placebo. After the first month the groups were crossed-over for another month of study. In parallel, all subjects were given dietary recommendations. Body weight (BW), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), Haber's scale satiety scores and side effects were registered and assessed.

Results: One-month pseudobezoar treatment of all the participants induced an increased satiety (Haber's scores 4.2÷1.3 vs. 3.8÷1.1 in placebo, $p \leq 0.05$) and greater reductions in BW (3.5% vs. 2.6%), BMI (3.5% vs. 2.7%), WC (3.4% vs. 2.4%) and WHR (1.2% vs. 0.2%) compared to placebo ($p \leq 0.01$). After the first month group A produced greater reduction in BW (3.3% vs. 1.9%), BMI (3.3% vs. 2.0%), WC (2.6% vs. 1.7%), WHR (1.2% vs. 0.2%) and WHR (0,9% vs. 0,3%). After switching, the actual therapy month for group B resulted in BW, BMI, WC and WHR reductions of 3.7%, 3.5%, 4.2% and 1.3% respectively, while group A (switched to placebo) did not regain weight and continued its weight loss with an additional 3.3%. At the end of pseudobezoar therapy 56% of the volunteers gained more than 3% BMI-reduction and 25% registered more than 5% BMI-reduction. For both

groups, increased satiety was confirmed during their actual therapy months: 4.0÷1.2 in group A and 4.4÷1.4 in group B. 54% reduction of consumption between meals was reported during the therapy period for group A. Pseudobezoar therapy was generally well tolerated. The most common reported, but not notable side effects were heaviness in the stomach and bloating.

Conclusion: Intragastric temporary controllable pseudobezoars comprise the potential of a reliable noninvasive alternative to surgery gastric volume reduction for the treatment of obesity.

1. INTRODUCTION

1.1. The world-wide problem of obesity.

During the past 20 years there has been an epidemiological increase in obesity all over the world [1, 2]. Recent data for 2009 [3] indicated that only two states in the USA (Colorado and the District of Columbia) had a prevalence of obesity less than 20%. Thirty-three states had a prevalence equal to or greater than 25%, but nine of them had a prevalence of obesity equal to or greater than 30%. The International Association for the Study of Obesity reported that in most European countries the levels of overweight and obesity have reached more than 50% and 40%, respectively [4]. An extremely alarming trend was projected for the developed countries in the next two decades [5]: more than 22% of their populations will be obese and more than 36% will be overweight. Simultaneously, the prevalence of obesity rapidly affects the developing world and the initial age of obesity is getting younger [6]. The perception of obesity as one of the key factors which increase the risk of co-morbidities (diabetes mellitus, arthritis, cardiovascular diseases, dyslipidemias, and some types of cancer) and related mortality is widely discussed and outlined [7].

Overweight and obesity management is currently based on several different approaches. They could be classified in five groups, depending on the basic principle of their action: (1) diets and dietary regimens [8]; (2) pharmacological treatment [9]; (3) bariatric surgery [10]; (4) gastric electrical stimulation [11]; and (5) intragastric balloons [12]. Recently, a new method was proposed based on the newly formulated temporary controllable pseudo-bezoar concept [13].

1.2. State -of -the -Art

1.2.1. Diets and dietary regimens.

As the most popular weight-loss approach, diets and regimens exhibited an impressive growth in recent years [8]. Restricting dietary fat and added sugar [14] on one hand, and increasing the content of proteins [15] and food with low glicaemic index [16, 17] on the other, are the basic directions in contemporary dietetic recommendations and official guidelines [18]. This weight loss strategy is

strongly dependent on individual particularities, is efficient in the short term only, and its sustainable success in the long- term weight gain prevention has not been confirmed [8, 19, 20, 21].

Diets, combined with dietary supplements, are a hopeful trend which aims at improving the long-term sustainability of diets. The supplements are usually fiber-based substances or extracts of plant or animal origin [22, 23]. In particular, a special sub-group of dietary supplements consists of substances that expand in the stomach, thus invoking early satiety and pre-meal sensation of fullness [24].

Recently, a process of close binding of dietary regimens with individual programs for physical activity and behavior modification through counseling has been proposed [25]. The attempts for personalization of dietary plans have provoked a wide exploration of objective features which could reliably predict the weight loss outcome in individuals on specific dietary plans [26]. A significant number of studies has suggested energetic [27], biochemical [28], biological [29], psychological [30] and behavioral [27] predictors as prognostic markers. However, weak predictive power has been reported [29, 31] and the implementation of this approach in the general medical practice is still disputable [28, 31]. Up to date the predictive feature of waist-to-hip (WHR) ratio is widely explored. WHR was assumed to be a prognostic sign for a lot of physiological conditions, e.g. body "response" to a dietary supplement [32], risk of cardiometabolic diseases [33], longitudinal change in sex steroid hormones [34], etc.

1.2.2. Pharmacological treatment.

This stream of obesity treatment is based on the utilization of a limited number of specifically developed, clinically tested and governmentally-approved drugs. Most of these medications invoke appetite suppression by affecting the central nervous system, e.g. acting as adrenergic or serotonin agonists. Sibutramine (Meridia, Abbott Laboratories, Abbott Park, IL, USA) is the only drug that stimulates both types of neurotransmitters, claiming weight loss of 4—5 kg on the average [35]. In October 2010 the U.S. Food and Drug Administration (FDA) had requested Abbott Laboratories to voluntarily withdraw this drug from the United States market. Based on data from the Sibutramine Cardiovascular Outcomes (SCOUT) trial [36], the FDA has concluded that the 16% increase in the risk

for an adverse cardiovascular event in the population studied outweighed any benefit from the modest weight loss associated with the drug [37].

Rimonabant, the first of the endocannabinoid receptor antagonists, reduces weight by 4—5 kg on the average and improves waist circumference and concentrations of HDL cholesterol and triglyceride [38]. However, an increased incidence of mood-related disorders has been reported [38].

Today, Orlistat (Xenical, Roche Laboratories, Nutley, NJ, USA) is the only anti-obesity drug approved by the FDA [38]. It acts peripherally by inhibiting pancreatic and gastrointestinal lipases, thus blocking digestion and absorption of about a third of the ingested fat. Patients treated with Orlistat reported 5-10% weight reduction and decreased diabetes progression [40, 41]. However, side effects include potential liver damage [42] and common adverse gastrointestinal problems [39].

Additionally, a group of drugs has been identified [43], which have been designed to affect other disorders but influence also body weight reduction as an additional effect. Medications acting within the central melanocortin pathway could be promising antiobesity drugs, but they are still at the development stage [39].

Usually, many contraindicative conditions and side interactions with a number of other drugs are listed for each antiobesity drug. Therefore, pharmacological therapy is frequently accompanied with quite serious and even life-threatening side effects [44-47]. Clinical data have shown severe limitations in most of the antiobesity drug trials because of their high attrition rates and lack of long-term morbidity and mortality data [39].

1.2.3. Bariatric surgery.

Both pharmacological treatment and bariatric surgery objectively change the physiology and biochemistry of the human body, but it is the latter which modifies gastrointestinal anatomy, either permanently (Roux-en-Y bypass, biliopancreatic diversion, sleeve gastrectomy, etc [48, 49]) or temporarily (gastric banding [50]) through surgical interventions. It has been well established that bariatric surgery strongly influences gut hormone profiles as well [51-57]. To date, significant gastric volume reduction, through surgical anti-obesity modification of gastrointestinal anatomy, is considered

the most reliable avenue for sustainable weight reduction [58, 59]. Reported clinical data indicate that Roux-en-Y gastric bypass and biliopancreatic diversion are the most successful techniques in terms of weight reduction sustainability [56]. Compared to them, laparoscopic gastric banding offers more modest weight loss but with a significantly reduced mortality and morbidity at much lower price [60]. Nevertheless, Tanner and Allen [61] report a serious disadvantage of this group of invasive surgical techniques: more than 1% of risk-normalized mortality. Along with the high price [62], long recovery periods as well as serious and abrupt changes in lifestyle and eating habits [63] additionally reduce the applicability of this approach.

1.2.4. Gastric electrical stimulation.

Normal propulsive gastric peristalsis could be adversely affected by electrical signals directed to surgically microelectronic devices implanted in the stomach. This technique has been accepted as a possible alternative for morbid obesity, since it can delay gastric emptying and thus induce early satiety [64]. However, the element of invasiveness cannot be avoided, since the positioning of the stimulating electrodes and the implantation of the microelectronic implant are implemented surgically. Reliable data in terms of the long-term effect of this treatment, as well as its sustainability and safety are still lacking [11].

1.2.5. Intragastric balloons.

Another avenue to reduce gastric volume, this time from the inside of the stomach, has been proposed utilizing gastroscopically-positionable and inflatable silicone intragastric balloons [63]. Collected data from studies employing this technique throughout the last two decades report short-term mean weight loss of over 17 kg in about two-thirds of the patients [65]. Again, the long-term (over 2 years) sustainability of this technique is not supported by reliable data [12, 66]. The safety of this method has been jeopardized by serious adverse side effects. Cases of esophageal and gastric perforations, cardiac arrest, and even death have been associated with the method [65, 67].

1.2.6. Temporary controllable pseudobezoars.

The recently developed pseudo-bezoar concept [13] appears to be the first successful attempt to combine the advantages of both, invasive and noninvasive methods for gastric volume reduction, while overcoming their individual disadvantages. The concept aims at imitating the effect of two rare phenomena, phytobezoars [68] and trichobezoars [69], on weight loss. Based on this, the first artificial, non-nutritional, non-invasive, ingestible, temporary, permeable, controllable pseudobezoars for long-term sustainable gastric volume reduction have been designed, produced and tested in a pilot human study [13]. Each pseudobezoar consists of sac-like, permeable, biocompatible and biodegradable carrier and expandable, cellulose-based fibers. Swallowed with an abundant amount of water, the pseudobezoar expands rapidly in the stomach to dimensions that prevent its expulsion through the pylorus for a controlled time period. The regular intake of pseudobezoars increases the displaced non-nutritional volume in the stomach, thus invoking constant feeling of satiety. In a preliminary pilot study, two patients (2M, 78.9 kg/174 cm, girth 88.1 cm, and 89.7 kg/175, girth 95.2 cm) were treated with the pseudobezoar product for 30 days within three months (in a sequence of baseline, therapy and washout 30-days periods). Significant weight and girth reduction ($p < 0.05$) and substantially increased satiety levels were reported for both individuals during the therapy month. The retainment of the pseudobezoars in the stomach was sonographically confirmed, as well as their clearance at the end of the washout period. The volunteers reported no significant side effects throughout the therapy and the washout periods. However, blind, placebo-controlled, cross-over studies of this technique for dynamic, non-invasive gastric volume reduction from inside of the organ performed on a statistically-significant group of volunteers are still lacking.

1.3. Aim of the study

The aim of this research is, to test the pseudobezoar therapy approach for the treatment of obesity on 16 overweight human volunteers in a blind, placebo-controlled, cross-over study for a period of two months.

2. METHODS

2.1. Pseudobezoar design.

Acceptable pseudobezoar design was arrived at after several iterations, laboratory tests, and pilot animal and human studies [13, 70]. As a result, the pseudobezoars were registered as a biocompatible dietary supplement product with the Capital Inspectorate of the Bulgarian Food Safety Agency according to the European Union and Bulgarian legislation ("Zalak B", EDF Bulgaria, Ltd. Sofia, Bulgaria, www.zalakb.com).

In the commercially-available product the following important pseudobezoar features were embedded: (a) gastric retainment of the pseudobezoar for several days upon ingestion by rapidly achieving post-swelling dimensions higher than 1.5cm [71, 72] in all directions after loading it with forces of 1.5 N simulating the maximal range of dynamic gastric forces [71]; (b) reaching final expanded volume upon ingestion within 15 minutes for secure gastric retainment; (c) complete pH-based controllability for several days of gastric retainment in pH 1-3, but rapid disintegration within several hours in pH>5 for maximal safety in the small and large intestines, or for antacid-controlled disintegration in the stomach on demand; (d) heaviness upon swelling so that the expanded pseudobezoar sinks to the antral area of the stomach which is rich in gastric mechanoreceptors [73]; (e) structural permeability for liquids and gases for maximal safety; (f) disintegrability to safe natural fibers for a secondary beneficial effect in the intestines.

As a result, a safe biocompatible product was manufactured consisting of non-irritating, biocompatible, proprietary mixture of expandable polymer granules contained in an oxycellulose carrier which was inserted in a dark-colored ingestible hard gelatin capsule (DB–type, size AAA, Capsugel, Greenwood, SC, USA).

Three thousand capsules of this pseudobezoar product were manufactured in an ISO 9001 certified dietary supplement manufacturing facility (Arcadia Herba Ltd., Novi Han, Sofia, Bulgaria). The overall length of each capsule was 22.5 mm, with a diameter of 12 mm and dry volume before ingestion of 1.44 ml. After ingestion and upon swelling an approximate value of 15 ml per capsule was reached, or 90 ml non-nutritional expanded volume "ingested" per a day in a 6 capsules-per-day

schedule. Thus, in several days, the pseudobezoar accumulation delivered a substantial gastric volume reduction achievable without surgical or endoscopic intervention [13].

2.2. Study design

2.2.1 Subjects

The participants in the study have been chosen according to the following criteria:

(1) inclusion :

- men and women aged 18 years or older;
- overweight (25 kg/m^2 ≤ BMI ≤ 30 kg/m^2) or obese (30 kg/m^2 ≤ BMI ≤ 45 kg/m^2) but otherwise healthy;
- motivation for losing weight and ability to adhere to the study protocol for a period of two months;
- signed informed consent;

(2) exclusion:

- body weight fluctuation of more than 3 kg within the 3 months prior to the commencement of the study;
- being on a special weight-loss diet within the last 3 months or presently dieting;
- pharmacologically (slimming agents, laxatives, medications, etc.) or surgically-treated obesity in the last 3 months prior to the study;
- indications or history of alcohol and/or drug abuse;
- clinically significant gastrointestinal, endocrine or cardiovascular diseases in an acute phase;
- intolerance or allergy to any of the pseudobezoar ingredients [13];
- pregnancy or lactation;
- participation in a clinical study with new medications or dietary supplements in the last 6 months;

- systemic and long-term intake of prescribed medications that could influence body weight changes or appetite (steroids, antidepressants, lipid-lowering agents etc.)
- planned changes in physical activity and behavioral habits during the investigation period that could affect study results;

Initially 33 subjects met the selection criteria (9M, 24F), signed informed consent and agreed to participate in the study. Of them, 17 volunteers (6M, 11F) dropped out in the process of the study for various reasons. As a result, the study was completed by 16 subjects (3M, 13F) with mean initial characteristics presented in Table 1.

Table 1. Initially measured average values of the main study parameters from all participants

PARAMETER	**MEAN** ± SD	**RANGE**
Age [yrs]	44 ± 12	18 ÷ 62
Body height [m]	1,70 ± 0,10	1,56 ÷ 1,88
Body weight [kg]	93,8 ± 21,9	57,4 ÷ 149,3
BMI, [kg/m^2]	33,2 ± 5,8	22,4 ÷ 43,5
Waist circumference [cm]	103,3 ± 13,8	72,0 ÷ 118,0
Hip circumference [cm]	114,3 ± 12,3	97,0 ÷ 136,0
Waist-to-hip ratio	0,89 ± 0,10	0,77 ± 1,09

Subjects were recruited after information meetings, from word of mouth or by referrals from family doctors or endocrinologists. All study participants signed an informed consent after verbal and written instructions according to the BG/EU regulations. The subjects were asked not to change their daily routines and physical activity during the entire study period. The study was approved by the Ethical Committee of the Military Medical Academy, Sofia, Bulgaria.

2.2.2. Dietary recommendations and regimens.

All subjects recruited for the study were given the following dietary recommendations related to the specific nature of this novel pseudobezoar therapy: (1) for maximal expansion in the stomach the intake of salt and sodium-containing foods and liquids had to be reduced; (2) to achieve longer period of gastric retainment with preserved integrity of the carrier, drinks with pH >4 (other than water) were

excluded; (3) for rapid expansion in the stomach the capsules had to be ingested with 300-500 ml room temperature water; and (4) for better synchronization with gastric motility and for optimal retainment in the stomach, the capsules were ingested 15 to 30 minutes before meals. At the start of the study and at the end of each 14-day interval, subjects were provided with individual consultations regarding compliance with these recommendations.

In addition, four low-calorie dietary regimens (1200–1400 kcal/day, low fat, low sugar) were recommended to be used and changed every 2 weeks for the entire study period in a sequence individually chosen by the subjects. The regiments were designed as basic dietetic principles rather than strong daily eating schemes and included three principal meals (breakfast, lunch, dinner) and daily snacking at two times per day (usually between breakfast and lunch and between lunch and dinner). Table 2 lists the basic features of each of these regimens.

Table 2 Recommended dietary regimens

Meal [(1)]	Week	Diet. regimen	Type of food (1-10 days)									
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Breakfast	1, 2	I	P[(2)] *(milk)*	P*(milk)*	P*(milk)*	L[(3)]	C*(b)* [(4)]	C*(b)*	C*(b)*	L	Repeat day 1	Repeat day 2
	3, 4	II	L	C*(b)*	L	C*(b)*	L	C*(b)*	L	C*(b)*	Repeat day 3	Repeat day 4
	5, 6	III	P*(milk)*	P*(milk)*	L	P*(milk)*	P*(milk)*	L	P*(milk)*	P*(milk)*	L	Repeat day 1
	7, 8	IV	P*(milk)*	L	C*(b)*	P*(milk)*	C*(b)*	P*(milk)*	C*(b)*	P*(milk)*	L	Repeat day 3
Snack 10 a.m.	1 ÷ 8	I-IV	Tea + Fruit									
Lunch	1, 2	I	P	P	P	L	P	P	P	L	Repeat day 1	Repeat day 2
	3, 4	II	L	P	L	C[(5)]	L	P	L	P	Repeat day 3	Repeat day 4
	5, 6	III	P	P	L	P	P	L	C	C	L	Repeat day 1
	7, 8	IV	P	L	C	P	C	P	C	P	L	Repeat day 3
Snack 4 p.m.	1 ÷ 8	I-IV	Tea + Fruit									
Dinner	1, 2	I	P	P	P	L	C	C	C	L	Repeat day 1	Repeat day 2
	3, 4	II	L	P	L	C	L	P	L	P	Repeat day 3	Repeat day 4
	5, 6	III	P	P	L	P	P	L	C	C	L	Repeat day 1
	7, 8	IV	C	L	P	C	P	C	P	C	L	Repeat day 3

(1) *Basic principles:*
-intervals between meals: 2 – 4 hours; recommended time of the last meal for the day: 19.00 or 20.00 h;
-excluded: white bread, cookies, animal fat, fried food, alcohol; recommended substitutes: whole grain bread, polyunsaturated fatty acids instead of fat (flax oil, olive oil, grape seed oil, or pumpkin seeds oil, etc.);
- ½ hour before each main meal: fruit (before breakfast) or vegetable (before lunch or dinner) intake; during the meal – the same fruit or vegetable is consumed as well; within one day only one and the same combination of fruit /vegetable is consumed, as well as the same combination of fruits /vegetables;
- within one day only one and the same type of protein food is consumed (e.g. only chicken, only eggs, only cottage cheese);

(2) *Protein food; basic types: meat (without fat, non-fried), fish, eggs, milk products (cottage cheese, fresh milk or yogurt- no more than 400g; cheese - 50g; yellow cheese- 40g);*

(3) *Light dietary regimen: tea/water (30ml per each kilo of body weight, approx. 2 l daily) + fruits, 5 times per day; in case of strong hunger, tea or fruits can be replaced by fresh milk or yogurt;*

(4) *Carbohydrate food; C(b) –carbohydrate food for breakfast in two versions: i) vegetable (or 2-3 olives) + a slice of whole-bean bread and ii)fruit + oatmeal or muesli;*

(5) *Carbohydrate food; rice, potatoes, corn, oats, all leguminous vegetables (ripe or green beans, lentils, peas, buckwheat, chickpea, soybean). The products can be cooked as vegetable dishes, soup or salad.*

2.2.3. Placebo design.

Placebo capsules were manufactured in the same dietary supplement facility as the pseudobezoar capsules. The same dark-color DB–Capsugel capsules were utilized, but their content was 0.1g pure rose hip flour (Bilcocoop Ltd., Sofia, Bulgaria) instead of a pseudobezoar.

2.2.4. Trial design.

This two-month study was a blind, placebo-controlled, cross-over chronic trial. The volunteers were administered 2 pseudobezoars or placebo capsules 15 to 30 min before each principal meal, 3 times a day for 2 months.

The cross-over type of the study required the formation of two groups of participants, denoted as "A"- active (8 F) and "B"- placebo (3M, 5F). Each group consisted of 8 subjects. The participants have been randomly assigned to the groups. Group A started on pseudobezoar intake for the first 30 days, while group B was put on placebo. After the first month the groups were crossed-over for another month of study. Table 3 describes the cross-over scheme of the trial.

Table 3. Cross-over scheme of the trial.

GROUP	**PRODUCT INTAKE**	
	FIRST MONTH	SECOND MONTH
A (8F)	Pseudo-bezoar (***active product***)	**Placebo**

B (3M, 5F)	**Placebo**	Pseudo-bezoar (***active product***)

There were no significant differences between the two groups in terms of BMI and initial basic study parameters (*Table 4, Table 5*).

Table 4. BMI distribution of the subjects in both, "active"(A) and"placebo"(B) groups

BMI	**PARTICIPANTS**		
	Total	Group A (8F)	Group B (3M, 5F)
BMI = 25 kg/m^2	1	1	-
25 kg/m^2 < BMI < 30 kg/m^2 (overweight)	4	1	3
30 kg/m^2 < BMI < 35 kg/m^2 (obesity, grade I)	6	2	4
35 kg/m^2 < BMI < 40 kg/m^2 (obesity, grade II)	2	2	-
40 kg/m^2 < BMI < 45 kg/m^2 (obesity, grade III)	3	2	1

Table 5. Initial basic study parameters within each group of subjects.

PARAMETER	**MEAN ± SD**		**RANGE**
	Group A (8F) (starting with pseudo-bezoar)	Group B (5F, 3M) (starting with placebo)	
Age [yrs]	40,8 ± 8,9	47,4 ± 14,2	18 ÷ 62
Body height [m]	1,6 ± 0,1	1,7 ± 0,1	1,56 ÷ 1,88
Body weight [kg]	93,3 ± 17,9	94,3 ± 26,5	57,4 ÷ 149,3
BMI, [kg/m^2]	34,6 ± 6,9	31,9 ± 4,6	22,4 ÷ 43,5
Waist circumference, [cm]	100,1 ± 15,2	103,8 ± 17,2	72 ÷ 118
Hip circumference, [cm]	116,6 ± 14,5	112,0 ± 10,2	97 ÷ 136
Waist-to-hip ratio	0,86 ± 0,08	0.92 ± 0.11	0,77 ÷ 1,09

2.3. Data collection and assessment.

The study started with an initial visit which included an individual conversation to obtain data for the physiological and health status of the subjects and to measure their body weight (BW), height, waist

(WC) and hip circumferences (HC). Based on the WC and HC data, waist-to-hip ratio (WHR) as an additional anthropometric measure of obesity was calculated and evaluated. The WHR variance takes into account the reducing in subcutaneous fat on waist circumference and gluteofemoral muscle on hip circumference and is believed to be a reliable and independent predictor for a chronic or coronary heart disease risk [33, 74-76], as well as for body response to a dietary supplement intake [32].

All subjects received personal diary, which was checked at 14-day interval. The volunteers were asked to fill their personal diaries daily with updated values of their weight, waist and hip circumferences, as well as their sense of fullness and satiety.

Subjective appetite sensations were assessed according to the ten-level hunger/satiety scale of Haber [77]. In this scale each scale level was defined by a number and a sentence which described the feeling. Volunteers quantified their sense of satiety selecting the corresponding number four times daily, before and after three principal meals and one snack. For example, number 1 meant "famished, starving", number 4 meant "hungry - but could wait to eat", number 7 meant "feeling full, definitely no more food" etc [77]. In addition, all participants registered any notable discomfort, side effects, complaints or changes in their food and water intake patterns within the entire study period. These notes were classified by the type of complaint and were assessed by numbers from 1 to 5, according to the categories "rare", "some times", "often", "quite often", "very often" for the frequency of appearance, and/or according to the power of the sensation: "very weak", "weak", "strong", "quite strong" and "very strong". Attrition was monitored as well in order to evaluate how random customers would accept and use the product.

2.4. Statistical analysis.

The primary outcome parameter was weight loss. The other primary efficacy variables were changes of BMI, WC and HC after 30 days of treatment with pseudobezoars or placebo. The secondary outcome parameter was the sense of satiety before meals. Digital scores recorded daily by the subjects for each 30-days period were averaged separately for each principal meal and snacking. The results for the averaged parameters were given as means ± SD. The level of significance was examined using

Microsoft Excel-based two-tailed, paired Student's *t*-test, with $p \leq 0.01$ considered significant for the primary outcome parameters and $p \leq 0.05$ for the sense of satiety assessment. The parameters noted above were compared between the active product and the placebo groups at the end of each month for the two months duration of the study, and as a total result from the start to the end of the study.

3. Results

33 subjects, able to comply with the inclusion criteria (9M, 24F) signed informed consent and agreed to participate in the study. All subjects had the wish to loose weight. The study was completed by 16 subjects (3M, 13F). 17 volunteers (6M, 11F) dropped out in the process of the study for the reasons outlined in Table 6.

Table 6. Dropout reasons

	DISTRIBUTION OF THE SUBJECTS		
	TOTAL NUMBER	**MALE**	**FEMALE**
INITIALY INCLUDED	33 (100%)	9 (27.3%)	24 (72.7%)
COMPLETED STUDY	16 (48.5%)	3 (9.1%)	13 (39.4%)
ATTRITION	17 (51.5%)	6 (18.2%)	11 (33.3%)
DROPOUT REASON:			
1. Lost to follow-up	2 (6.1%)	-	2 (6.1%)
2. Not comply with the study protocol	3 (9.1%)	1 (3.0%)	2 (6.1%)
3. Discomfort in everyday life (Heaviness in the stomach)	3 (9.1%)	2 (6.1%)	1 (3.0%)
4. Unsatisfactory results	3 (9.1%)	1 (3.0%)	2 (6.1%)
5. Weight gain	2 (6.1%)	1 (3.0%)	1 (3.0%)
6. Gauze	2 (6.1%)	1 (3.0%)	1 (3.0%)
7. Capsule size	1 (3.0%)	-	1 (3.0%)
8. Others	1 (3.0%)	-	1 (3.0%)

18.2% (1M, 5F) of the initially included subjects dropped out the study because of reasons not connected with features of the product (lost to follow-up, not comply with the study protocol, others). The rest attrition cases (33% if the initially engaged, 5M, 6F) were caused by product features. 9.1% of the volunteers refused to proceed because of the big size of the capsules (impossible to be swallowed) and unusual content of the product (stress due to the carboxycellulose ingredient which looks like a gauze/textile). They cancelled their participation at the same beginning of the study. 9.1% of the subjects were unmotivated by unsatisfactory or lacking weigh loss. All of them were engaged in the initial placebo group B and stopped after the placebo month, at the beginning of the pseudobezoar therapy. Five of the dropped participants (15.2%) described reasons connected with the substantial action of pseudobezoars. Three of them (9.1%) reported excellent weight reduction during the pseufobezoar therapy. In spite of it subjects refuse to proceed because of uncomfortable feeling of

heaviness in the stomach and bloating (due to water amount), which have led to limitations in their daily round. The rest two participants (6.1%) gained their weight. One of them gained during the whole placebo period (1 ÷ 4 week of the study) and stopped during the first week of pseudobezoar therapy. The second one (female) dropped out at the end of her pseudobezoar treatment with a weight gain of 3kg.

3.1. Anthropometry

Anthropometric data for the whole study and all the 16 participants who completed study complying with its protocol are summarized in Table 7.

Table 7. Averaged anthropometric data- before and after two-month study period

PARAMETER	MEAN ± SD		P *	REDUCTION	
	INITIAL	FINAL		Absolute units	% **
BW, kg	93,8 ± 21,9	88,4 ÷ 22,1	<0,01	5,3 ÷ 2,5	6,0%↓
BMI, kg/m^2	33,2 ± 5,8	31,3 ÷ 5,9	<0,01	1,9 ÷ 0,9	6,1%↓
WC, cm	102,0 ± 15,8	96,5 ÷ 16,5	<0,01	5,5 ÷ 3,0	5,6%↓
HC, cm	114,3 ± 12,3	109,0 ÷ 12,2	<0,01	4,9 ÷ 3,0	4,3%↓
WHR	0,89 ± 0,10	0,88 ± 0,11	NS	0,01 ÷ 0,03	1,2%↓

***** *Student's T-test, two-tailed, paired, $p \leq 0.01$, n=16*
****** *based on initial value, %*

The subjects exhibited a total reduction of 6.0% and 6.1% for body weight and body mass index respectively. Additionally, a significant decrease of 5.6 % in waist and 4.3% in hip circumferences were achieved. The waist-to-hip result objectively corresponds to the weight loss [78] and describes an obvious trend although the total result is not statistically significant. The differentiation of the results by periods reveals an insight and explains the significance of waist-to-hip reduction. Table 8 includes the same type of data, separately given for both periods of the study: placebo and pseudobezoar therapy.

Table 8. Averaged anthropometric results at the end of placebo and active product (pseudobezoar) therapy

PARA-METER	PSEUDO-BEZOAR THERAPY					PLACEBO				
	INITIAL	FINAL	P *	REDUCTION		INITIAL	FINAL	P *	REDUCTION	
	Mean ± SD	Mean ± SD		Absolute units	% **	Mean ± SD	Mean ± SD		Absolute units	% **
BW, kg	92,9 ± 21,8	89,9 ± 22,1	<0.01	3,0 ± 1,7	3,5 ± 2,0	92,3 ± 22,1	90,0 ± 22,1	<0.01	2,3 ± 1,2	2,6 ± 1,4
BMI, kg/m^2	32,9±5,9	31,8±6,1	<0.01	1,1 ± 0,6	3,5 ± 2,0	32,7±5,9	31,8±5,8	<0.01	0,9 ± 0,4	2,7 ± 1,3
WC, cm	101,1±15,9	97,8±16,2	<0.01	3,3 ± 1,9	3,4 ± 2,0	100,7±16,1	98,6±16,6	<0.01	2,1 ± 1,6	2,4 ± 2,0
HC, cm	113,5±12,4	111,1±12,8	<0.01	2,4 ± 1,9	2,2 ± 1,8	113,4±12,3	111,0±11,9	<0.01	2,4 ± 2,1	2,2 ± 1,9
WHR	0.89±0.10	0.88±0.10	<0.01	0.01±0.01	1,2 ± 1,3	0.89±0.10	0.89±0.11	NS	0.00±0.02	0,2 ± 2,2

***** *Student's T-test, two-tailed, paired, $p \leq 0.01$, n=16*

****** *based on initial value, %*

Reduction in parameters was significant for both periods but obviously prevailing for the month with active product therapy. Results after the placebo therapy were partly influenced by the previously applied pseudobezoar therapy for the participants in group A. The WHR reduction was obviously outlined for the period of pseudobezoar therapy. Its minimal, but significant absolute value is assumed to be positively indicative for both: the potential of the pseudobezoars in healthy influencing of WHR after their long-term intake and the expected body response to the pseudobezoar therapy [32]. The lack of WHR reduction or its insignificance for the placebo period also assists such an expectation.

Data in the following Tables 9 and 10 illustrate the anthropometry dynamics separately, for each of two groups of volunteers. At the end of the first month, after the pseudobezoar therapy, the subjects in the initial active product group A reduced significantly their body weight, BMI and waist circumference by an average of 2.9 ± 2.0 kg, 1.0 ± 0.6 kg/m^2, and 2.5 ± 1.7 cm respectively. Insignificant reduction of 1.7 ± 1.5 cm in HC for group A was noted (*Table 9*). In contrast to this, after the initial 30- day placebo therapy the volunteers in group B also lost weight, but only by an average of 1.7 ± 0.6 kg of their initial weight. Reductions of BMI, WC and HC in the placebo group were insignificant: 0.6 ± 0.2 kg/m^2, 2.0 ± 1.6 cm and 1.9 ± 1.7 cm respectively (*Table 10*). Both groups exhibited WHR reduction after their pseudobezoar therapies, 0.9% and 1.3% for group A and B correspondingly.

Table 9. Anthropometric study results for group A (starting with pseudo-bezoar therapy)

PARA-METER	INITIAL MEAN± SD	PSEUDO-BEZOAR THERAPY (I-st month)			PLACEBO (II-nd month)			TOTAL RESULT	
		MEAN± SD	P *	REDUC-TION, % **	MEAN± SD	P *	REDUC-TION, % ***	REDUC-TION, % **	P *
BW, kg	93,3 ± 17,9	90,3 ± 18,3	<0.01	3,3%↓	87,5 ± 18,0	<0.01	3,3%↓	6,2%↓	<0.01
BMI, kg/m²	34,6 ± 6,9	33,5 ± 7,2	<0.01	3,3%↓	32,4 ± 7,1	<0.01	3,3%↓	6,4%↓	<0.01
WC, cm	100,1 ± 15,2	97,6 ± 15,3	<0.01	2,6%↓	95,1 ± 15,8	<0.01	2,8%↓	5,0%↓	<0.01
HC, cm	116,6 ± 14,5	114,9 ± 14,7	NS	1,5%↓	111,5 ± 14,4	<0.01	2,9%↓	4,4%↓	<0.01
WHR	0,86 ± 0,08	0,85 ± 0,09	NS	0,9%↓	0,85 ± 0,10	NS	0,0%	0,8%↓	NS

***** *Student's T-test, two-tailed, paired, p ≤ 0.01, n=8*
****** *based on initial value, %*
******* *based on average I-st month value*

Table 10. Anthropometric study results for group B (starting with placebo)

PARA-METER	INITIAL MEAN± SD	PLACEBO (I-st month)			PSEUDO-BEZOAR THERAPY (II-nd month)			TOTAL RESULT	
		MEAN± SD	P *	REDUC-TION, % **	MEAN± SD	P *	REDUC-TION, % ***	REDUC-TION, % **	P *
BW, kg	94,3 ± 26,5	92,5 ± 26,5	<0.01	1,9% ↓	89,4 ± 26,7	<0.01	3,7% ↓	5,6% ↓	<0.01
BMI, kg/m²	32,3 ± 4,6	31,2 ± 4,6	NS	2,0% ↓	30,1 ± 4,7	<0.01	3,5% ↓	5,7% ↓	<0.01
WC, cm	103,8 ± 17,2	102,0 ± 17,6	NS	1,7% ↓	97,9 ± 18,0	<0.01	4,2% ↓	5,7% ↓	<0.01
HC, cm	112,0 ± 10,2	110,4 ± 9,7	NS	1,4% ↓	107,3 ± 10,2	<0.01	2,8% ↓	4,2% ↓	<0.01
WHR	0,92 ± 0,11	0,92 ± 0,11	NS	0,3%↓	0,91 ± 0,11	<0.01	1,3% ↓	1,6%↓	NS

***** *Student's T-test, two-tailed, paired, p ≤ 0.01, n=8*
****** *based on initial value, %*
******* *based on average I-st month value*

3.1.1. Body weight.

After the first month group A (*Table 9*) produced greater reduction in BW (3.3% vs. 1.9%) and in WC (2,6% vs. 1,7%) compared to group B (*Table 10*). After switching, the actual pseudobezoar month for group B resulted in BW and WC reductions of 3.7% and 4.2% respectively, which is approximately twice the results for placebo month. While the initial active group A (switched to placebo) did not regain weight and continued its weight loss with an additional 3.3%. Table 11 clearly demonstrates pseudobezoar effectiveness in weight loss. Changes of BW, analyzed in parallel to the reduction of WC confirm the effect of pseudobezoar therapy on the central adiposity which is associated with a risk of cardiovascular and sex steroid hormonal disorders [33, 34]. The constant BW reduction in group A

during the two phases of the study also indicates the prolonged action of pseudobezoars in post-therapy period.

Table 11. Comparison of study results for "active" (A) and "placebo" (B) groups

GROUP	**REDUCTION, %**			
	I-st MONTH, active for Group A		**II-nd MONTH**, active for Group B	
	BW, kg	**WC**, cm	**BW**, kg	**WC**, cm
A	**3.3**	**2.6**	**3.3**	**2.8**
B	**1.9**	**1.7**	**3.7**	**4.2**

3.1.2. Body mass index.

Analysis of BMI data gives an additional confirmation for the pseudobezoar effectiveness. Compared to the initial status of the subjects (*Table 4)*, at the end of the study 25% of the participants reduced their BMI to an extent, which lowered their grade of obesity. 12,5% of the volunteers reduced their grade I of obesity to grade "overweight", 6,2% became obese I grade starting from II grade, while another 6,2% reduce the grade from III to II. Table 12 indicates the distribution of the volunteers by BMI at the end of the study.

Table 12. BMI distribution of the subjects in both, "active"(A) and"placebo"(B) groups at the end of the study

BMI	**PARTICIPANTS**		
	Total (13F, 3M)	Group A (8F)	Group B (5F, 3M)
BMI < 25 kg/m^2	1	1	-
25 kg/m^2 < BMI < 30 kg/m^2 (overweight)	6	1	5
30 kg/m^2 < BMI < 35 kg/m^2 (obesity, grade I)	5	3	2
35 kg/m^2 < BMI < 40 kg/m^2 (obesity, grade II)	2	2	-
40 kg/m^2 < BMI < 45 kg/m^2 (obesity, grade III)	2	1	1

A cross section of BMI data by groups and type of therapy (pseudobezoar or placebo) is illustrated in Table 13.

Table 13 Distribution of subjects depending on their BMI-reduction (%) during the study*

PARTICIPANTS		**PSEUDOBEZOAR THERAPY**			**PLACEBO**			**WHOLE STUDY**		
		< 3 %*	3 ÷ 5 %*	> 5%*	< 3 %	3 ÷ 5 %	> 5%	< 3 %	3 ÷ 5 %	> 5%
Group A	*Month of study*	*First*			*Second*			*Two months*		
(8F)	Subjects, % **	25.0	12.5	12.5	25.0	12.5	12.5	6.2	18.8	25.0
Group B	*Month of study*	*Second*			*First*			*Two months*		
(5F, 3M)	Subjects, %	18.8	18.8	12.5	43.8	6.2	_	12.5	6.2	31.3
Groups **A and B** (13F, 3M)	Subjects, %	**43.8**	**31.3**	**25.0**	**68.8**	**18.7**	**12.5**	18.7	25.0	51.3

***** *depending on their BMI-reduction, subjects were divided into three categories: BMI-reduction less than 3%, between 3 and 5%, and more than 5%;*
****** *based on total number of participants in the study.*

At the end of pseudobezoar therapy 56% of the volunteers gained more than 3% BMI-reduction and 25% registered more than 5% BMI-reduction. At the end of placebo period 3% BMI reduction was calculated for 31.2% of the subjects, while more than 5% BMI-reduction was achieved by 12.5% of the participants. It is important to note, that the last noted volunteers (12.5%) were included in group A and in fact during the placebo period reduced their BMI in more than 5% being influenced by the preceding pseudobezoar therapy.

3.1.3. Waist circumference, hip circumference, waist-to-hip ratio.

Being a widely explored as different types of predictors, changes of WHR influenced by a dietary treatment are reasonably to be analyzed. Table 14 compares group A and group B in terms of WHR reductions for each month of the study.

Table 14. Comparison of study results for "active" (A) and "placebo" (B) groups

GROUP	REDUCTION, %					
	I-st MONTH, active for Group A			**II-nd MONTH**, active for Group B		
	WC, cm	**HC**, cm	**WHR**	**WC**, cm	**HC**, cm	**WHR**
A	**2.6**	**1.5**	**0.9**	**2.8**	**2.9**	**0.0**
B	**1.7**	**1.4**	**0.3**	**4.2**	**2.8**	**0.3**

WHR-changes after pseudobezoar therapy were estimated for both groups: 0.9% in group A and 1.3% in group B. The result of the initial active product group A is statistically insignificant. Nevertheless, the order of its value tends to reach the significant result for group B rather than the insignificant and even missing WHR- reduction at the end of the placebo periods (0.0% and 0.3% for group A and B respectively). The difference in significance of post-pseudobezoar WHR-reductions can be closely connected with two aspects of the therapy: prolonged action and gender-specificity.

Comparable WC reductions in group A during the two separate months of the study (*Table 14*) can be illustrative for the prolonged action of pseudobezoars in post-therapy period.

Our initial active product group A does not include men in contrast to the initial placebo group B with three males (*Table 3*). Mean initial parameters for men significantly exceeded those for women e.g., BW: 120.2kg vs. 78.7kg, WC: 122.3cm vs. 92.6cm and HC: 117.9 vs. 108.4cm. After pseudobezoar therapy in group B the same parameters were significantly reduced irrespective of gender. A comparison of WC reductions for both groups after pseudobezoar therapies (2.6% for group A and 4.2% for group B) can be only an assisting and starting point/reason for further clearance of a possible gender-specificity of the therapy.

3.2. Satiety levels

Tables 15 and 16 include averaged satiety-scale scores for the initial active product (A) and the initial placebo (B) groups, calculated from the "before"-meal records in each separate study period. Mean values for each principal meal and one snack are given on separate rows. The last row gives scores for the entire one-month period of interest which were averaged for all meals per day. The scores in the two tables clearly outline an increase in the satiety levels during the pseudobezoar therapy. This trend

is clearly observed in the volunteers from group B (*Table 16)*. Although the volunteers from group A (*Table 15)* registered insignificant difference between averaged satiety scores for the placebo and the therapy periods, the results support the tendency pointed out in Table 16. Furthermore, the insignificant difference in satiety scores during the first (therapy) and the second (placebo) months in group A indicates an important pseudobezoar feature: the ability to be retained in the stomach for several days and therefore to keep the sense of fullness for a period of time after the discontinuation of the pseudobezoar therapy. Thus, Table 15 illustrates the prolonged effect of the pseudo-bezoar therapy in the post-therapy period. Participants in group A reported also 54% reduction of consumption between meals illustrated as missing records for snacking at 10.00 or at 16.00h.

Table15. Averaged satiety-scale scores for group A (initial pseudo-bezoar therapy)

MEAL TIME	**AVERAGED HABER'S SCALE SCORE** (before meals)		**P ***
	PSEUDOBEZOAR THERAPY (I-st month)	**PLACEBO** (II-nd month)	
Breakfast	3.9 ± 1.0	3.5 ± 0.8	NS
Lunch	4.1 ± 1.4	3.7 ± 0.4	NS
Dinner	4.1 ± 1.5	3.8 ± 0.8	NS
Snacking 10 /16 h	3.4 ± 1.1	3.2 ± 0.1	NS
Mean Haber's scale score for all 4 meals a day	**4.0 ± 1.2**	**3.6 ± 0.7**	NS

***** *Student's T-test, two-tailed, paired, $p \leq 0.05$, n=8*

Table 16. Averaged satiety-scale scores for group B (initial placebo)

MEAL TIME	**AVERAGED HABER'S SCALE SCORE** (before meals)		**P ***
	PLACEBO (I-st month)	**PSEUDOBEZOAR THERAPY** (II-nd month)	
Breakfast	4.2 ± 1.4	4.3 ± 1.4	< 0.05
Lunch	3.9 ± 1.4	4.3 ± 1.6	< 0.05
Dinner	3.9 ± 1.4	4.4 ± 1.7	< 0.05
Snacking 10 /16 h	4.2 ± 1.4	4.8 ± 0.9	NS
Mean Haber's scale score for all 4 meals a day	**4.0 ± 1.3**	**4.4 ± 1.4**	< 0.05

***** *Student's T-test, two-tailed, paired, $p \leq 0.05$, n=8*

Table 17 summarizes averaged satiety-scale scores based on the records of all the 16 participants. Data are separated for the two periods of the study and clearly demonstrate the effectiveness of pseudobezoar therapy in hunger overcoming and achieving a permanent and sustainable increase of the sense of fullness.

Table 17. Averaged satiety-scale scores results at the end of placebo and active product (pseudobezoar) therapy

MEAL TIME	**AVERAGED HABER'S SCALE SCORE** (before meals)		**P ***
	PLACEBO	**PSEUDOBEZOAR THERAPY**	
Breakfast	3.8 ± 1.2	4.1 ± 1.2	NS
Lunch	3.8 ± 1.0	4.2 ± 1.4	NS
Dinner	3.8 ± 1.1	4.2 ± 1.5	< 0.05
Snacking 10 /16 h	4.0 ± 1.3	4.3 ± 1.2	NS
Mean Haber's scale score for all 4 meals a day	**3.8 ± 1.1**	**4.2 ± 1.3**	< 0.05

***** *Student's T-test, two-tailed, paired, $p \leq 0.05$, n=16*

3.3. Side effects

Adverse side effects reported by the participants in the study are an indirect approach for assessing the safety of the pseudobezoar therapy. Table 18 summarizes the side effects recorded by the volunteers in both groups during the two months of the study. Seven of the 16 participants (44%) reported such effects. Half of them describe the occurrence of these events during the placebo periods of the study. These events are equally distributed between placebo periods for group A and for group B. Their origin cannot be connected and explained by the pseudobezoar retainment in the stomach after the discontinuation of the active product therapy. Three of the subjects reported more than one complaint, in most cases independently occurring. Half of the participants did not report any side effects.

The most frequently mentioned complaint was bloating - 4 entries for the pseudo-bezoar therapy month in group A. Only one of these entries was rated as "very often" and "very strong". All remaining entries for bloating described the complaint as "some times" occurring with "very weak" to "weak" power of the sensation. Burning and heaviness in the stomach were mentioned three times by

participants in group A and group B, respectively. Only one of the volunteers (from group A) described burning as "very strong" during the pseudobezoar therapy. Constipation is less frequently noted – once in each group, and during different periods of the study *(Table 18)*.

Except for one of the participants, in general nobody rated the complaints as serious and constant.

Table 18. Distribution of side effects records by groups and periods of the study

COMPLAINT	**PREVALENCE** (number of volunteers)				
	Group A		**Group B**		**Total**
	Pseudo-bezoar therapy (I-st month)	Placebo (II-nd month)	Placebo (I-st month)	Pseudo-bezoar therapy (II-nd month)	
Nausea	Not reported				
Vomiting	Not reported				
Heaviness in the stomach	-	1	2	1	3*
Burning (gastric acid indigestion)	2	1	1	-	3*
Gastric/abdominal pain	-	1	-	-	1
Bloating	4	1	-	-	4*
Regularity	Normal				
Constipation	1	-	1	-	2
Diarrhea	Not reported				
Disclaiming adverse events	2		6		8

**- one of the volunteers repeated the complaint's record during the whole two-month period.*

Although the complaints were not dramatic, group A (initially starting with the pseudobezoar therapy) registered more side effects than group B. Some of the participants probably changed their nutrition and eating habits in an untypical way. Rapid replacement of non-healthy food with a low- calorie, low–fat and rich in complex carbohydrates diet may cause trivial problems in the digestive system [31]. Most of the subjects reported difficulties in water intake – approximately 500 ml before each principal meal appears to be quite a lot. Four volunteers had problems with the intake of the capsule and recommended smaller size. Two of the subjects (group A) reported increased desire to consume sweets during the pseudobezoar period. One of them reported even stronger feeling of hunger.

Most of the participants confirmed an identifiable sense of fullness when the pseudobezoars were taken. They registered it clearly after the 5-th day of the pseudo-bezoar therapy. Four of them even

described it as disturbing and causing discomfort, although no nausea and vomiting were registered. Another group reported reduction in the sense of fullness after 10-15 days of pseudo-bezoar intake. The most motivated and experienced in dieting participants pointed out an important feature of the pseudo-bezoars: their ability to assist in the motivation for changing eating habits.

4. Discussion

The most popular and traditional approaches in overweight and obesity management [8, 9, 10, 11, 12] are projected to control the food intake by influencing both: gastric sensory/motor functions or volume reduction. The temporary controllable gastric pseudobezoars were shown to be a feasible noninvasive anti-obesity approach for gastric volume reduction inside the stomach [13]. Pilot chronic human trial with two patients clearly demonstrated that the administration of pseudobezoars is possible, safe and has weight loss effect. Current paper presents the results of the first blind, placebo-controlled, cross-over chronic study of the pseudobezoar impact in an anti-obesity treatment of a reasonable number of volunteers. The purpose of this study was to register the effect of prolonged pseudobezoar therapy on anthropometry, sense of satiety and complaints of the subjects. The study also aimed to give a further insight on the following aspects of pseudobezoar therapy: (i) is it a dietary option, a volume-reduction approach or a combination of both; (ii) effective dosage and administration pattern for the therapy, (iii) is the designed controllability reliable in terms of safety and (iv) large-scale acceptance of the method as an anti-obesity approach.

In this study of pseudobezoar therapy we tested sixteen volunteers. Their quite gratifying results unequivocally confirmed that pseudobezoar treatment is an alternative weight loss method. Initial parameters of all the participants were effectively influenced during one-month pseudobezoar treatment and gained significant reductions of 3.5% in BW and BMI, 3.4% in WC, 2.2% in HC and 1.2% in WHR. Both groups registered increased satiety during the actual therapy months and didn't report any notable side effects.

Temporary controllable gastric pseudobezoars, examined in a described administration pattern promoted weight loss (3.5% ÷ 2.0) in a prevailing range in terms of dieting. 34 randomized controlled trials assessed an effectiveness of low-calorie diets for lowering total body weight by an average of about 8% during a period of 3–12 months. [79]. The new therapy is free of restrictive limitations for the patients, as it has been reported for heavy diets and risky slimming drugs [19, 21, 80, 81]. Such an advantage provides wider accessibility of the pseudobezoar treatment in contrast to others. This was mediately confirmed by the significant number of gender- and age-diversified participants who were

engaged and completed the two-month trial as required by the protocol. In this trial pseudobezoar therapy promoted a mean weight loss significantly less than the reported 17 kg as a short-term result for the intragastric balloons [12]. Nevertheless it couldn't be defined as ineffective. It is worth to underline that the volunteers didn't reported discomfort due to dramatically change in lifestyle, eating habits or dietary regimens, typically appearing after surgical treatments. The pseudobezoar therapy has also incomparable advantages to the invasive approaches in terms of expenses. It also doesn't require recovery period and prevention of post-treatment morbidity [63].

Our study has several strengths. It is the first trial that has ever been carried out for wide application of pseudobezoar method in obesity treatment. A large number of motivated volunteers were attracted by its ideology to loose weight by gastric volume reduction in a noninvasive and controllable way. The study categorically confirmed previously formulated conclusion [13] that administration of temporary controllable pseudobezoars and their retainment in the stomach are entirely possible.

Designed as a placebo-controlled, this study clearly demonstrates the therapy effectiveness. The effect of the pseudobezoars on weight loss was reliably confirmed by different groups of results. The whole study results show an average of 6% reduction in BW and BMI, as well as 5.6%, 4.3% and 1.2% decreases in WC, HC and WHR respectively. Sheer pseudobezoar treatment of all the participants produced greater reduction in BW (3.5% vs. 2.6%), WC (3.4% vs. 2.4%) and WHR (1.2% vs. 0.2%) compared to placebo. Additionally, the cross-section of data by groups (*Tables 9 and 10*) repeated unequivocally the prevailing results for the pseudobezoar therapy.

Cross-over design of the study eliminates the confounding influence of imbalances in individuals and both groups e.g. the effect of applied dietary regimens in accordance to the study protocol. Reliable results in terms of two important pseudobezoar features were obtained by switching groups A and B: prolonged action of pseudobezoars in post-therapy period (due to the constant BW, BMI and WC reductions in group A during the two phases of the study (*Tables 9, 10 and 11*) and objective body response to the pseudobezoar treatment (revealed by WHR changes). The second supports our belief

that an optimal and individually scheduled administration pattern for pseudobezoar therapy can provide its long term sustainability.

The examined in this study pseudobezoar dosage was confirmed to be harmless. Subjects didn't record cases of need and usage of antacids to destroy the pseudobezoars in the stomach. Neither they reported disturbing adverse effects. The product is marketed with a recommended 3 to 12 capsules-per-day schedule. The volunteers in present study were daily administered six active product/placebo capsules. For the first wide application of the product, this administration scheme was chosen to guarantee the subjects' safety and to be confined to the dietary-regulations' discussion [32, 82-85]. Each pseudobezoar capsule is supposed to expand in the stomach to a volume of 12-14ml (max 10-fold of its original dry volume of 1.4 ml). By an optimal expanding, an approximate total non-nutritional volume of 70 ÷ 85 ml (approx. 70 ÷ 85 g weight, due to density of water 1 g/ml) per a day was ingested. It exceeds up to 2.4 times the recommended daily dosage (20-35 g) for health implication of dietary fiber in human menu [82]. Several trials showed that fiber supplements, ingested for a short or long term in the recommended or lower dosage do not induce weight loss [83, 84]. Our study clearly demonstrates that the scheduled amount of fiber pseudobezoars increases satiation with statistical significance (*Tables 15 and 16*) and induces a reduction of consumption between meals. This is in accordance to the assumption that doubling the recommended daily fiber amount may increase satiation [85]. Our results correlate positively also with the earlier reported that a total volume of 25 ml of ingested dietary fiber could hardly induce feelings of fullness and satiety for a mean maximal stomach volume of 1÷2 L [32]. In fact, based on the pilot trial results [13], we expected higher than resulted scores (mean 4.0 for pseudobezoar therapy vs. 3.6 for placebo) on the satiety scale of Haber. The difference could be explained by fiber amount. It is significantly lower in the commercial product compared to the pilot pseutobezoars. Additionally, a complex of factors can be also responsible: insufficient expansion of the pseudobezoars in gastric conditions; shorter retainment in the stomach; insufficient water amount for ingestion of the capsules; recommended low-calorie dietary regimen; inappropriate dosage or administration pattern etc.

The effectiveness of applied in the study dosage was estimated under condition of recommended dietary regimen. We were unable to evaluate objectively how the participants apply the recommendations. Nevertheless, at this stage we can conclude that pseudobezoar therapy as a volume reduction approach is effective in a combination with a diet. Further clinical study could optimize the administration pattern as well as clear the relation between dosage and type of pseudobezoar application: as a total stomach volume reductor, supporting dietary option or a combination of both .

Designed as a chronic, our study might have a possible weakness due to the fact that acute administration was not observed. Thus the effects of pseudobezoars on anthropometry and sense of satiety occur only after chronic administration and there are no data on their expression after acute single administration.

Although mediate confirmation of a proposed expanded-pseudobezoar volume (70 ÷ 85 ml per a day), objective evaluation of the total volume of the pseudobezoars collected in the stomach as well as their time of retention in it is still missing. Such an observation can give an insight on the mechanism of pseudobezoar action. This study was not aimed to prove the mechanism, namely whether it affects gastric sensory or motor functions. Based on the satiety-scale results for the pseudobezoar treatment, it could be proposed that the weight-lowering effect of the therapy depends on the increase in the feeling of satiety rather than the delayed gastric empting. Nevertheless, it is worth to explore also the effect of the new therapy on gastric motility, emptying and the Migrating Motor Complex (MMC) in the stomach during fasting [86].

In general, a separate assessment of the pseudobezoar effectiveness in women and men is needed. Such observations would answer if the pseudobezoar therapy repeats the gender-specific responsiveness to other weight loss approaches [87-89]. As it was pointed above (Table 14), the difference in significance of post-pseudobezoar WHR-reductions for groups A and B can be connected with a probable gender-specificity of the therapy. It is well known, that at comparable levels of weight loss, men had greater decreases in the waist, and smaller decreases in the hips than women, resulting in greater decreases in WHR [78]. Significant prevalence of group B (three males included) in WC

reductions after pseudobezoar therapies (2.6% for group A and 4.2% for group B) is not a sufficient argument to resume a gender specificity of the method. A large-scale gender-diversified study is needed to conclude this type of responsiveness for pseudobezoar approach.

Further clinical studies can compare the novel pseudobezoar approach with the bariatric surgeries in terms of gut hormonal changes demonstrated with the invasive techniques. [52-57, 90, 91]. Parallel and supplemental hormonal analysis for the female volunteers could give an additional clearance for the pseudobezoar therapy in terms of its gender-specificity. It was shown that women's weight and body composition is significantly influenced by the female sex-steroid hormones [89]. Therefore, two types of relationship between gut and female steroid hormonal changes during the pseudobezoar therapy are of interest: (1) across the menstrual cycle and (2) for different ages of women. The second one is also important for achieving an insight to the metabolic responsiveness to the therapy. Clinical study on a significant number of age –diversified patient will additionally clear the connection with the level of individual metabolism. It could also optimize dosage and pseudobezoar administration pattern for different metabolic types.

Further clinical studies with prolonged therapy and post-therapy periods can compare the novel pseudobezoar method with the bariatric surgeries in terms of effect of chronic intake, risk of weight regain and delayed side effects or co-morbidities.

The significant drop-out level (51.5% of initially engaged participants) might be considered a negative marketing sign. In fact, the impact of unacceptable features of pseudobezoars as a dropout reasons is significantly lower than the registered attrition (*Table 6*). Only 12,1% of the subjects were unmotivated by the feeling of heaviness in the stomach and bloating (2M, 1F) and because of weight gain (1F) during the pseudobezoar therapy. From the marketing point of view, it is worth to underline that 9,1% refuse to proceed the study because of the size and gauze-inclusion in the capsules.

5. Conclusions

This study unequivocally confirms pseudobezoar applicability in anti-obesity treatment. Ingestion of pseudobezoars in a combination with a low-fat and low-calorie diet influenced effectively the weight loss and reduced in significant level anthropometric body parameters. Several important pseudobezoar features were supported by results of a blind, placebo-controlled, crossover trial on reasonable number human subjects: (i) ability to increase satiety; (ii) prolonged action in post-therapy period; (iii) evokes body response to the therapy; (iv) tolerability; (v) safety and harmless and (vi) ability to assist in the motivation for changing eating habits. Depending on the administration pattern, pseudobezoars can be applied as a total stomach volume reductor, supporting dietary option or a combination of both.

Intragastric temporary controllable pseudobezoars have the potential of a reliable noninvasive alternative to surgery gastric volume reduction for the treatment of obesity.

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