ENDOSCOPIC TREATMENT OF OBESITY

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Endoscopy Therapy
Potential Roles

- Primary therapy of obesity
- Treat metabolic diseases such as diabetes in obese patients
- Bridge to surgical therapy
- Revision of failed surgical bariatric procedures
Main endoscopic possibilities in the treatment of obesity

- Balloons and prosthesis
- Injection of substances
- Systems of sutures
- Malabsorptive techniques
Balloons and prosthesis

- Orbera Intragastric Balloon
- Ullorex Intragastric Balloon (Swallowable balloons)
- Spatz Adjustable Intragastric Balloon
- Heliosphere Bag
- Semistationary Antral Balloon
- Reshape Duo™ Intragastric Balloon
- Endogast-ATIIP (Adjustable Totally Implantable Intragastric Prosthesis)
OTHER ORALLY AVAILABLE DEVICES IN DEVELOPMENT

**Gas-Fired Balloon Approaches**

- **Developer**: Tulip Medical Ltd.
- **Product**: TBD

*Orally-available, satiety-inducing device that inflates intra-gastrically using a gas-fired approach.*

- **Developer**: Obalon Therapeutics
- **Product**: TBD

*Orally-available, deflated balloon that inflates using gas emission.*

- **Developer**: Gelesis
- **Product**: Attiva™

*A non-caloric, orally-available polymer that expands into a food-like paste.*

- **Developer**: Zalak B
- **Product**: Electronic Dietary Foods

*10-15 CC pseudo-bezoars swallowed daily with degradation on order of hours.*

**Disadvantages**

- Increased product complexity, risk of inappropriate inflation
- Impervious membrane increases risk of obstruction
- Intra-gastric residence time uncontrolled

- Same disadvantages as Tulip Medical

- Brief Intra-gastric residence time
- Mechanism of action unvalidated
- Patient compliance suffers from frequent dosing requirement

- Elevated risk of pyloric obstruction/small bowel obstruction
- Variable degradation rate makes it impossible to determine in-place volume
- Transient residence time requires frequent dosing

Source: Company websites, USPTO
SEVERAL NON-INVASIVE APPROACHES TO GASTRIC VOLUME REDUCTION ARE ALSO IN DEVELOPMENT

<table>
<thead>
<tr>
<th>Device Type</th>
<th>Description</th>
<th>Developer</th>
<th>Source: Company websites, USPTO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas Filled Balloons</td>
<td>• Plastic balloon inflated with gas</td>
<td>Obalon Therapeutics, Inc.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ingested orally via natural swallowing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Inflated by timed chemical reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogel Filled Implants</td>
<td>• Open lumen, hydrogel-filled analog to the intragastric balloon</td>
<td>Allurion Technologies, Inc.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ingested orally via natural swallowing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Inflated by absorbing water in stomach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient Hydrogels</td>
<td>• Capsules of food-grade, highly expansive hydrogel</td>
<td>Gelesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Expands into a food-like paste</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dosing 30 minutes prior to meals</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ALLURION’S HYDROGEL-FILLED IMPLANT INCORPORATES SEVERAL PROMISING FEATURES

- Equal density to water keeps device in fundus
- Open central lumen increases effective size, reduces obstruction risk, may reduce nausea vs. others
- Easily titrated / removed / reversed
- Avoids cost, inconvenience, perceived risk of sedated endoscopic placement and removal

Space Occupying Balloon Analog | Administered as a capsule | Extended Gastric Residence | Natural Passage Following Degradation
Orbera™ Intragastric balloon

Heliosphere®

Spatz™ AIR

Orbera™ LIQUID

6 M

AIR

6 M

Spatz™ ADJUSTABLE

12 M
<table>
<thead>
<tr>
<th>Device</th>
<th>Duration</th>
<th>Absolute Weight Loss</th>
<th>% Excess Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heliosphere® Bag</td>
<td>24w</td>
<td>12.8±8Kg</td>
<td>27±16%</td>
</tr>
<tr>
<td>De Castro, 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIB® Alergan</td>
<td>24w</td>
<td>14.1± 8Kg</td>
<td>30.2±17%</td>
</tr>
<tr>
<td>De Castro, 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatz® Machytka</td>
<td>24w</td>
<td>15.6Kg</td>
<td>26.4%</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>52w</td>
<td>24.4Kg</td>
<td>48.8%</td>
</tr>
</tbody>
</table>

**NO SIGNIFICANT DIFFERENCE**
Evidence-based Review of the Intragastric Balloon for Weight Loss.

Patients who lost ≥ 10% of the initial weight

75%

Weight regain after 1 year

47%

Analysis Of The Safety And Effectiveness Of The Intragastric Balloon In Patients With Obesity: A Systematic Review and Meta-analysis

Pinto, MAF – 2007

- IGB (Intragastric balloon) vs. Diet:
  - Diet more effective (p<0.00001)

- IGB vs. No treatment:
  - IGB more effective (p<0.00001)

- IGB vs. IGB + Diet:
  - IGB + Diet more effective (p<0.00001)

- IGB + diet vs. Diet alone:
  - NS (p<0.83)
Intragastric Balloon

Combination?

Best period of effectiveness

Rigaud et al., 1995

GLP-1 like
Botulinum Toxin A

- Increased early satiety
- Increased gastric emptying time
- Decreased gastric maximum capacity
## Botulinum Toxin A

<table>
<thead>
<tr>
<th>Place</th>
<th>Number (U-TBA)</th>
<th>Duration</th>
<th>Side Effects</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foschi (2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=30</td>
<td>Antrum 120 U</td>
<td>2 m</td>
<td>No</td>
<td>-11.8Kg - 4.1BMI</td>
</tr>
<tr>
<td></td>
<td>Fundus 80 U</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topazian (2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=10</td>
<td>Antrum 100 U</td>
<td>4 m</td>
<td>No</td>
<td>- 4.9BMI</td>
</tr>
<tr>
<td></td>
<td>(EUS) vs. 300 U</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 m</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The injection of botulinum toxin, although secure, seems to offer a smaller and more transient efficacy.
Endoluminal Vertical Gastroplasty (EVG) and variants

Transoral Gastroplasty (TOGa)

Transoral Endoscopic Restrictive Implant System (TERIS)

Others
**Endoluminal Vertical Gastroplasty (EVG)**

**EndoCinch**

**Fogel R et al.**
GIE 2008;68(1):51-8

**Follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Excess Weight Loss (%EWL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1m</td>
<td>21.1 ± 6.2</td>
</tr>
<tr>
<td>3m</td>
<td>39.6 ± 11.3</td>
</tr>
<tr>
<td>12m</td>
<td>58.1 ± 19.9</td>
</tr>
</tbody>
</table>

Bard EndoCinch Sutting System (C.R.Bard, Inc., Murray Hill, New Jersey)
TRIM procedure
Restore Suturing System

Brethauer SA et al, 2012

12 months FU (18/14)  Number of plications: 6

Mean procedure time: 2.1h (range 1.5–2.8).

Decreases:
Mean weight (-11.0±10.0kg)  P=.0006
Mean BMI (-4.0±3.5kg/m2)  P=.0006
Mean waist circumference (-12.6±9.5cm)  P=.0004
Mean excess weight loss: (27.7%±21.9%)
ToGa - Transoral gastroplasty for morbid obesity: a multicenter trial with a 1-year outcome.

Familiari P et al. GIE 2011

Average percentage excess body mass index loss and percentage excess weight loss after the procedure.
The company developing TOGA closed down and sold its assets end of 2010.

Multicenter pivotal trial (300 pts) showed significant but modest effect vs Sham procedure and 2% severe complications.
Transoral Endoscopic Restrictive Implant System (TERIS)

- EWL at 3 months: 28%.
- BMI decreased from 42.1 to 37.9
- Gastric perforation (N=1); pneumoperitoneum (N=2)
- TERIS system is not being developed further due to unacceptable durability of lesser curvature anchor point and alternative implant design and plication patterns are being studied.
OTHERS SYSTEMS OF SUTURE

Eagle Claw – Eagle Claw VII (Olympus Corporation, Tokyo, Japan)
Hu B, 2005 & Kantsevoy SV, 2007

POSE
Primary Obesity Surgery Endoluminal

SafeStitch Device
(SafeStitch Medical Inc., Miami, Florida)

Medical Power System
(Power Medical Interventions, Inc., Langhorne, Pennsylvania)

Endoscopic Suturing Device
(Wilson-Cook Medical, Winston-Salem, North Carolina)

All are under clinical investigation
Early Resolution of Diabetes

“The authors propose that the improvement in the entero-insular system depends on the duodenal-jejunal exclusion... (Rubino F, Marescaux J, 2004)

“We think it is simply the product of more nutrients coming to distal bowel and enhancing GLP-1 production... (Patriti A et al., 2004)
GHRELIN AND GLP-1 EFFECT

- Anorectic Effect
- Delayed gastric emptying
- Delay in intestinal motility
- Increase in insulin secretion
- Trophic effect on beta cells
ValenTx
endoscopic and laparoscopic techniques

The device is attached by transmural anchors to the GEJ, and extends through the stomach and into the distal duodenum or proximal jejunum.

Prospective Trial = 12w

- 24p enrolled, mean BMI 41
- Device implanted in 22/24
- 12w completers (n=9): 39.7% EWL
- 7p with diabetes: normal glucose levels during trial, no anti-diabetic meds needed, improvement in HbA1c levels.

RCT = DJBL vs Sham

Weight Loss

RCT = randomized control trial

EndoBarrier™ (GI Dynamics Inc, Lexington, MA)

<table>
<thead>
<tr>
<th>Authors</th>
<th>DJBL</th>
<th>SHAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarnoff, 2009</td>
<td>22%</td>
<td>5%</td>
</tr>
<tr>
<td>3m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schouten, 2010</td>
<td>19%</td>
<td>7%</td>
</tr>
<tr>
<td>3m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gersin, 2010</td>
<td>8.7</td>
<td>2.1</td>
</tr>
<tr>
<td>12m</td>
<td>Kg</td>
<td>Kg</td>
</tr>
</tbody>
</table>
Weight Loss
Completers, n=13

HbA1c Decrease
Completers 52w, n=13/22

Diabetes Control
After 52w → 72.7%

Post-explant weight data, n=9
Post-explant HbA1c data, n=9

Escalona A - 2012
Improvement of Insulin Resistance and Reduction of Cardiovascular Risk Among Obese Patients with Type 2 Diabetes with the Duodenojejunal Bypass Liner.

Moura EGH et al. Obes Surg 2011;21(7):941-7

<table>
<thead>
<tr>
<th></th>
<th>Patients N</th>
<th>Initial average TG/HDL ratio</th>
<th>Final average TG/HDL ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled TG/HDL at</td>
<td>23</td>
<td>5.15</td>
<td>2.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>the end</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not controlled TG/HDL</td>
<td>31</td>
<td>6.2</td>
<td>5.47</td>
<td>0.1641</td>
</tr>
<tr>
<td>at the end</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>5.75</td>
<td>4.36</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Promotes sustained glucose homeostasis and weight loss for 1 year

Promotes significant improvement in cardiovascular risk factors

Sustained glucose homeostasis 6 months post-explant
CONCLUSION

- Preliminary results in humans testify to interesting progress in the development of minimally invasive bariatric procedures.

- Today, these procedures are at an early stage.

- However, with further technical improvements, they might evolve as attractive alternatives for selected obese patients.

- Randomized prospective studies are warranted.
Endoscopic aspects of obesity therapy

- Why do gastroenterologists do not think about (morbid) obesity as a real healthcare problem?
  - Weight loss is alarm symptom in GI-diseases
  - If the patient “complains” about gaining weight, he/she has no GI-problem

- Wake up: Obesity is a disease
- Wake up: Endoscopy may offer a solution
- Wake up: Endoscopy may cure Diabetes!

Deviere J, 2011