The World Wide Epidemic of Obesity

- 400 million are obese, 700 million projected by 2015
- In USA, 32% men, 35.5% women

<table>
<thead>
<tr>
<th>Class</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal*</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>30.0-34.9</td>
</tr>
<tr>
<td>Class II</td>
<td>35.0-39.9</td>
</tr>
<tr>
<td>Class III*</td>
<td>≥40</td>
</tr>
</tbody>
</table>

BMI = [Weight in pounds/ (Height in inches)^2] x 703
*increased weight circumference can be present in persons with normal weight,
**Extreme obesity

-↑in mortality overweight & obesity
-Obese individuals have a 50-100% ↑ risk all cause premature death compared to normal BMI
-Estimated 300,000 deaths a year attributable to obesity

Predicted that obesity over the next 20 years will be the number one health problem worldwide
# Health Risks Associated with Obesity

Obesity is associated with an increased risk of:

1. Premature death
2. DM
3. Heart disease
4. Stroke
5. Hypertension
6. Gallbladder disease
7. Osteoarthritis
8. Sleep apnea
9. Asthma
10. Hypoventilation syndromes
11. Cancer (endometrial, colon, kidney, gallbladder, and breast)
12. Venous stasis ulcers
13. Hyperlipidemia
14. Complications of pregnancy
15. Menstrual irregularities
16. Hirsutism
17. Stress incontinence
18. Increased surgical risk
19. Psychological disorders
20. Psychological difficulties due to social stigmatization
21. NASH
22. GERD
23. Pulmonary HTN

# Health Risks Associated with Obesity in Children

- Early puberty
- Orthopedic problems
- Type 2 diabetes mellitus
- Obstructive sleep apnea (6X more likely)
- Hypertension (9X more likely)
- Hepatic steatosis (38%)
- PCOS
- Lipid abnormalities (12-17%)
- CVD
Biological Function of Adipose Tissue - Homeostasis

- Energy expenditure
- Appetite regulation
- Glucose regulation
- Thyroid function
- Immune responses
- Bone health
- Fertility
- Blood clotting

BIOLOGICAL FUNCTION OF ADIPOCYTE

Inert Storage Depot
- Fed: Fatty acids, Glucose
- Fasted: Fatty acids, Glycerol

Secretory/Endocrine Gland
- Brain
- Leptin, Fatty acids, TNFα, Cytokines, Adipsin, PAI-1, Other

Growth, fertility, immunity
Etiology of Obesity

Results from a long-term imbalance between energy intake and energy expenditure

- Expansion of lipid storage favoring adipogenesis or an ↑ in the number of fat cells.
- Numerous biological and behavioral factors can affect energy balance
- Environmental and lifestyle factors
Once Obese, Weight Loss Feedback Control System Kicks In

- Declines in energy expenditure (can last 3-5 years)
- Decreased circulating $T_3$ and $T_4$
- Increased parasympathetic tone, decreased sympathetic tone
- Increased appetite, metabolic changes that promote weight gain
- Weight loss/stabilization is a lifelong commitment

1) nucleus of the tractus solitarius, 2) arcuate nucleus 3) paraventricular nucleus (PVN) 4) ventromedial hypothalamus 5) lateral hypothalamus
Hormone Signaling from GI Tract

- Incretins – modulate food processing
  - Appetite regulation
  - GI motility
  - Satiety
  - Glucose regulation
- Ghrelin (foregut) - ↑ before meals ↓ after meals
- PYY, GLP-1, neurotensin (hindgut) – GI motility

Complex interaction that control fuel modulation

Consequences of Increasing Fat Mass

- Changes in body fat distribution
  - Visceral vs. subcutaneous fat deposition
  - Ectopic fat accumulation
- Defects in lipid metabolism
- Increased inflammatory markers
- Insulin resistance

Consequences of Adipocyte Dysfunction

- Cardiac Hypertrophy
- Endothelial Dysfunction
- Beta Cell Apoptosis
- Adipokines, FFA
- NASH


Insulin Resistance in Obesity – Early Pathological Finding

Concentrations of glucose, insulin and c-peptide and insulin secretion in normal weight and obese subjects during hyperglycemic clamp

Inflammation and Obesity Co-Morbidities in Adults

- OSA – ↑inflammatory CRP, IL-6, hypoxia triggers inflammatory cascade
- HTN – sympathetic tone, renin, endothelin 1 related to obesity, IR, DM
- Hepatic steatosis correlated to DM, obesity, IR, lipids, associated to hepatic IR
- Lipids - ↑LDL oxidation, setting of FFA, visceral adipocytes, hyperinsulinemia
- Type 2 diabetes - Chronic inflammation provoke IR and beta cell dysfunction, ↑CRP, IL-6, MCP-1, IL-8, PAI-1

Current Surgeries Performed
Operations Performed on Adolescents

Lars Sjöström, et al. NEJM 2007; 357:741-752
Effects of Bariatric Surgery on Mortality in Swedish Obese Subjects

Medical - 129 deaths
Surgical- 101 deaths

Figure 1. Unadjusted Cumulative Mortality.
The hazard ratio for subjects who underwent bariatric surgery, as compared with control subjects, was 0.76 (95% confidence interval, 0.59 to 0.99; P=0.04), with 129 deaths in the control group and 101 in the surgery group.

Lars Sjöström, et al. NEJM 2007; 357:741-752

Adolescent RYGBP

33 - 63% EWL at 5 to 14 years

Sugarman, J Gastrointest Surg 2003; 7:102
# Morbidity of Bariatric Surgery at academic centers (2002-06)

<table>
<thead>
<tr>
<th>Procedure related (%)</th>
<th>Adults</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>Reopening wound</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Perforation/laceration</td>
<td>1.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Bleeding/hematoma</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>GI hemorrhage/ulcer</td>
<td>1.0</td>
<td>0.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-procedure related (%)</th>
<th>Adults</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1.1</td>
<td>0</td>
</tr>
</tbody>
</table>

Varela et al. Surg Obes Relat Dis. 2007 3:537

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## T2DM & THE METABOLIC EFFECTS OF BARIATRIC SURGERY

### Bariatric Surgery Efficacy

<table>
<thead>
<tr>
<th>Author</th>
<th>Procedure</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pories et al 1995</td>
<td>Gastric Bypass</td>
<td>89%</td>
</tr>
<tr>
<td>Torquati et al 2005</td>
<td>Gastric Bypass</td>
<td>74%</td>
</tr>
<tr>
<td>Schauer et al 2003</td>
<td>Gastric Bypass</td>
<td>82%</td>
</tr>
<tr>
<td>Sugerman et al 2003</td>
<td>Gastric Bypass</td>
<td>86%</td>
</tr>
<tr>
<td>Dixon et al 2003</td>
<td>Lap Band</td>
<td>64%</td>
</tr>
<tr>
<td>Gagner (unpublished)</td>
<td>Sleeve Gastrectomy</td>
<td>65%</td>
</tr>
</tbody>
</table>
Reversal of Type 2 Diabetes

- 11 teens > 1 year after Roux-en-Y bypass
- Mean BMI 50 ± 5.9 kg/m²
- 50% metabolic syndrome
- Post-op
  - BMI fell by 34% to 33 ± 7 kg/m²
  - Improvement of fasting glucose, insulin, HOMA-IR, Hb A1C, AST, ALT, LDL, triglycerides, total cholesterol, BP
  - Remission of diabetes in 10 of 11 cases
  - Removal of oral hypoglycemics in 10 cases

Inge et al, Pediatrics 2009; 123:214-222

Changes in Hormone Signaling with Bypassing the Small Bowel


Ghrelin ↓ after bypass
PYY, neurotensin ↑
RNYGB Plays a Role in Resolution of DM

- Changes in gut hormone responses directly and indirectly affect fuel metabolism and play a role in regulation of insulin and glucagon secretion
- Changes in $S_I$ and resolution or improvement in hyperglycemia after RNYGB are commonly seen
- Hormones that appear to be important in this process include Ghrelin, GLP-1, and PYY.
- Reductions in Ghrelin may have an anti-diabetic effect by decreasing levels of GH, cortisol, and epinephrine and improving peripheral glucose utilization.
- The increase in GLP-1 levels often seen after RNYGB has a positive effect on insulin secretion, beta cell function, and possibly $S_I$.

Resolution of Co-Morbidities: Hypertension

- All forms of weight loss results in reduction in BP
  - *Resolution 62% with significant improvement 78.8%
  - **In DM subset, 69% resolution at 1yr., 66% at 7yr.
  - Gastric bypass is more effective than vertical banding in resolution of HTN

Resolution of Co-Morbidities: Dyslipidemia

- Significant improvement in lipids in 70%
  - Gastric by-pass better than vertical bands
  - HDL improve significantly with vertical bands
- Swedish Obesity Study
  - 2 & 10 yrs, improvement in HDL & triglycerides
  - Total cholesterol was not changed

Resolution of Other Co-Morbidities
OSA, NASH, Pseudotumor Cerebri

- NASH – decrease in severity
- OSA - 85.7-93% resolution
- Pseudotumor Cerebri – success rates are higher than results of shunt placement

No long term studies examining recurrence
Resolution of Obesity-Related Co-morbidities 20 wks after Pediatric RYGB

Psychological Disorders After Weight Loss Surgery

• Does mental health improve?
  – Balsiger, et.al. 2000 93% followed for 3yrs. reported improvement
  – Maddi, et.al. 2001 improvement in MMPI-2
  – Waters, et.al. 1991 found improvement in psychological fx, but lack of difference by 3 yrs.

No standards exist
Quality of Life Measures (PedsQL 4.0)
6 months post – Bariatric Surgery

<table>
<thead>
<tr>
<th></th>
<th>Healthy Mean (SD)</th>
<th>Pre-Op Mean (SD)</th>
<th>6 month Post-Op Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Score</td>
<td>83.8 (12.6)</td>
<td>55.7 (15.4)</td>
<td>77.3 (12.3)</td>
</tr>
<tr>
<td>Physical Score</td>
<td>87.5 (13.5)</td>
<td>54.2 (18.5)</td>
<td>78.0 (14.0)</td>
</tr>
<tr>
<td>Psychosocial Function</td>
<td>81.8 (14.1)</td>
<td>56.6 (16.6)</td>
<td>77.0 (14.0)</td>
</tr>
<tr>
<td>Emotional</td>
<td>79.3 (18.1)</td>
<td>57.2 (21.0)</td>
<td>80.8 (19.3)</td>
</tr>
<tr>
<td>Social</td>
<td>85.1 (16.8)</td>
<td>56.6 (23.7)</td>
<td>80.0 (18.3)</td>
</tr>
<tr>
<td>School</td>
<td>81.1 (16.5)</td>
<td>55.1 (18.2)</td>
<td>69.5 (21.3)</td>
</tr>
</tbody>
</table>

Michalsky et al. unpublished data

Obesity Surgery and Reduction in Long-Term Mortality

- Christou, et.al. *Advances in surgery* vol. 39, (2005): 165-79. Reported mortality rate of 0.67% vs. 6.17% in surg vs. nonsurg
- MacLean, Lloyd D MacDonald, et.al. *J Gastrointest Surg* 1:213-220, 1997. The 6-9yr mortality 1% vs. 4.5% in surg vs. nonsurg
- Sjostrom, et.al. *NEJM* 357(8):741-52, 2007. Gastric bypass reduced all cause mortality by 40%
Toward the Rational and Equitable Use of Bariatric Surgery
Flum, David R. MD, MPH; Khan, Tipu V. BA, BS; Dellinger, E. Patchen MD
JAMA 298(12), 26 September 2007, p 1442–1444

1. More than 5% of the USA population qualify for bariatric surgery but only small fraction is considered for it.
2. Demographics of individuals having bariatric surgery do not equate to the demographics of the morbidly obese population
   – 84% female (rates of morbid obesity 2.8M vs. 6.9%F)
   – >90% Caucasian
   – Most have higher income levels
3. Etiology unclear
   – Predictive scoring of obesity risk vs. surgical risk
   – Social and attitudinal behaviors
   – Lack of understanding of causes of obesity

Years of Obesity and Metabolic Impact

- The age at which the association between obesity & obesity-related co-morbidities begin is unclear
- With the rising rates of obesity in youth, the question of whether there is a relationship between years of obesity & severity of associated medical conditions will need to be answered.
- Studies have demonstrated higher rates of mortality and mortality from CVD, stroke, colorectal cancer in the adults with a history of adolescent-onset obesity vs. those who were not obese as adolescents

On December 3, an FDA advisory panel recommended the expansion of the use of Allergan’s Lap-Band™ system for weight reduction in patients with a BMI of at least 35 kg/m² or a BMI of at least 30 kg/m² with one or more comorbid conditions.

November 18, 2010

Margaret McCabe Janicki
Food and Drug Administration
Center for Devices and Radiological Health
10903 New Hampshire Ave., Bldg. 66, rm. 1535
Silver Spring, MD 20993–0002

Dear Ms. McCabe Janicki:
I am writing to indicate the support of the American Society for Metabolic and Bariatric Surgery (ASMBS) for the application to extend clinical indications for use of the Lap Band® among patients with BMI 30-35 kg/m² and serious comorbidity as well as patients above BMI 35 with or without identified specific comorbidity. The Executive Council of the ASMBS has reviewed the proposal by Allergan and has unanimously endorsed this proposal. I therefore represent the Executive Council and the membership of the ASMBS in this matter.
Case Study

- 53yo WF with type 2 diabetes (>20y), HTN, hyperlipidemia, GERD, depression and fibromyalgia – taking medication for each of these medical problems.
- Weight 242lb, BMI 35.4, BP 126/73, HbA1c 6.5%
- Diabetes medications
  - Glargine 86 units qhs
  - Lispro 18units qac
  - Metformin 1000 Bid
Follow-up Data

Weights 2 hour postprandial BG
- 1 month 229 168
- 2 months 208 155
- 3 months 201 137
- 4 months 185 154
- 5 months 180 139
- 6 months 180 118

At 6 months – Weight down 61lbs, Diabetes medications include: meformin 1000 bid, glargine 24units (86) qhs, off all meal coverage, Hba1c 6.4%

New Treatment modalities:

<table>
<thead>
<tr>
<th>Restrictive</th>
<th>Toga (transoral gastroplasty)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malabsorptive</td>
<td>Endo-barrier</td>
</tr>
<tr>
<td>Neuro-modulation</td>
<td>V-Block</td>
</tr>
</tbody>
</table>
Transoral Gastroplasty (TOGA)

Restrictor inserted to reduce size of outflow tract
Bariatric Surgery: Now and in the Future

**EndoBarrier™ - GI Dynamics**
- Endoscopically delivered and retrievable sleeve
- 60 cm - anchored in the duodenum
- Creates a duodenal-jejunal bypass

*Intragastric balloon Implant*
Why is the obese population different?

- Physiology
- Anatomy
- Psychological
- Co-morbidities

Understanding the role of the adipose tissue will be the key to developing treatment and prevention strategies to reduce the rising incidence of obesity.
Conclusions

• Development of obesity is a pathophysiologic ↑ in fat in which multiple metabolic pathways are deranged
• With ↑ prevalence of obesity there is an ↑ risk of obesity-related co-morbidities in adults & children
• IR and inflammation may play a role in the development of obesity-related comorbidities
• Given the negative short and long term impact of obesity on children, careful attention should be paid to the unique health issues of this “at risk” population with both prevention and aggressive early intervention strategies