Obesity: Management of the Burgeoning Waistline

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Director, Obesity Clinical Program
Joslin Diabetes Center
Harvard Medical School
Boston, MA
Evolution of our concepts of the value of body fat
Obesity on track as No. 1 killer

Inactivity, poor diet may overtake tobacco

Pill in the works to cut cravings
Drug has helped obese people and smokers, 6D

For more parents, kids are a charm

Joslin Diabetes Center
E-selectin
VCAM-1
ICAM-1
CD14
Monocytes CD14 Exp
TNF-α
TNF-R
IL-1β
IL-1ra
IL-6

Obesity
Smoking
Stress
Natural History of Diabetes

- Obesity → Prediabetes
- Controllable Hyperglycemia
- Uncontrolled Hyperglycemia
- Controllable Hyperglycemia or Diabetes Remission
- Insulin Resistance
- Diabetes Remission
- \( \beta \)-cell function

Years of Diabetes

Yrs before Diabetes

Relative Function (%)

-10 -5 0 5 10 15 20 25 30
Donna at her Why WAIT start in April 2009

63 yo with type 2 diabetes for 17 years
On 2 oral medications and >100 units of insulin
A1C 7.3%

Donna at her last visit in November 2014

Maintained 36 lbs of weight loss
A1C 6%
0 medications
Diabetes remission for 6 years
What is the core of the obesity problem?
Obesity is Brain Dysfunction
Brain Puzzle

Protein

Carbohydrates

Open Buffet
LECTURES
ON THE
DISEASES OF WOMEN AND CHILDREN.
EXHIBITED AT GUY'S HOSPITAL BY
DR. BLUNDELL.
LECTURE XXXI.
Menorrhagia.

It sometimes happens, that women are affected with a discharge of blood from the genitals, independent of any organic disease, and this it is which constitutes menorrhagia, as it is called, of which there are two varieties, the one the active and the other the passive. The active menorrhagia is, perhaps, more apt to occur in women who are robust and puerile, and still more frequently in women who have had their nerves agitated by some domestic calamity, as the death of a near relative for example. In this disease, you will find occasionally eruptions of blood from the uterus, more or less or more copious, tending occasionally to obstruct the menstruating period, but not always, the discharge being more especially proceeded, at the first, by an unusual heaviness of the surface, a whiteness of the tongue, and a certain degree of hardness and frequency of the pulse, which rises, perhaps, to 100 or 110 in the minute, a slight degree of fever is being produced. When menorrhagia is in this manner occurring in women who possess a moderate share of strength, and have a degree of febrile excitement lurking about the system, one of the first steps to be taken, in the puerile or more especially in the case of blood from the arm to the amount of eight or ten ounces; or if the attacks be less considerable, by means of leeches, which seem the rather to be indicated in these cases, because there is increased action of the aminas vessels. These leeches may be applied either to the orifices of the vagina, or above the symphysis pubis, to the number of ten or twelve, three large positions being applied afterwards, (each remaining there two hours,) for the purpose of keeping the leech orifices pervious and bleeding. If the discharge from the genitals is copious and rather alarming to the friends, (though I believe it is rarely dangerous,) cold may be applied in front and behind, just in the same manner as you would apply it in the case of miscarriage; but this is not, perhaps, usually required. Refrigerating purgatives, as nitre, for example, or salut of magnesium, or salut of soda, may be of use to diminish the hemorrhagic effort of the habit; and if there is an obsesst tendency to the increased vascular action of the system, you may then give your patient digitalis in operative quantities. Now, there are three indications by which you may know that digitalis is in action, one is a sickness of the stomach, and perhaps some action of the bowels, another a change of the pulse, which becomes intermittent or irregular, and a third increase in the quantity of the urine; and whenever you find any one of these symptoms, you must watch the digitalis with care, for it is in action on the system; and we must not forget, that the remedy, though valuable, is not without its danger, and that the digitalis may accumulate, suddenly operate, and destroy. Again, in cases of this kind, I should recommend you to give diaphoretics, so as to keep up the action of the circulation. Stimulants, as general remedies, seem decidedly improper, wine more especially; and I mention this the rather, because patients are apt to have recourse to this stimulant, red wine more especially, either because they have a relish on its astringent properties, or because they have a great dislike to its flavour. In active menorrhagia, if the preceding remedies fail you, and the disease shows no disposition to yield spontaneously, there is yet another remedy, which may be worth a trial, and that is, a gentle mercurial action; for five or six weeks together, let the grains be kept as lightly as, and by its action on the capillaries, the mercury may sometimes destroy the

No. 209.
To the Editor of The Lancet.

Sir,—In a late communication, I ventured to point out that Mercurial Purgatives were an useful remedy in purpura hemorrhagica, and supported my opinion by cases and references to authorities, to which any one may have access. I shall now endeavor to show, by the following case which occurred to Mr. William, of this town, that colonists may be advantageous when it exercises its specific action on the system. A girl, aged 9 years, was observed by her friends to be unusually dull and listless, when interrogated, she said that she had been complaining of these symptoms for some time. When on the 2nd of October, 1828, she was visited with violent epistaxis, the trunk and extremities were covered with numerous small dark petechiae, and on one arm were two extensive extravasations very sensibly elevated, the gums were exceedingly pale, and the tongue, spotted and bleeding, she vomited a great deal of a thick, frothy, frothy froth, and had a purgative of colonic and jalap; on the 3rd the symptoms continued the same, she was referred to a surgeon, and was prescribed with 3 grains of calomel every fourth hour and to continue the fluid: in the course of that day blood from the nose ceased, but the extravasations continued the same; on the 5th, the girl became slightly afflamed, when the blood disappeared from the stools, on the following day, the gums were absorbed, the epistaxis ceased, and the patient appeared to be improving, the pyrexia also gradually subsided.

Thence I have brought my remarks on purpuric condition, and beg permission to add a few words to Mr. Moore.

Mr. Moore should attempt to express his feelings without surprise or vexation, as they should have disturbed the natural serenity of his temper, caused more serious offense. I shall endeavor to express it in a words, although it may appear, perhaps, unprofitably, having been written to him. Mr. Moore should not have done so, but to a practical illustration of the usefulness of the following case:

"In his reply" by way of encouraging...
Peripheral signals

GLP-1 = glucagon-like peptide 1
PYY3–36 = peptide YY residues 3–36
OXM = oxyntomodulin
CCK = cholecystokinin

CB1 = cannabinoid-1
GABA = γ-aminobutyric acid
NA = nucleus accumbens
VTA = ventral tegmental area

VTA

CB1 Antagonists

Glutamate

Topiramate
Acamprosate

Varenicline

Acetylcholine

Dopamine

SS
RI

Serotonin

Opioid

GABA

Topiramate
Acamprosate

CB1 Antagonists

Aripiprazole
Quetiapine

Odansetron

CB1 = cannabinoid-1
GABA = γ-aminobutyric acid
NA = nucleus accumbens
VTA = ventral tegmental area
Fate of centrally acting anti-obesity Medications

1. Fenfluramine
2. Dexfenfuramine
3. Sibutramine
4. Rimonabant
5. Taranabant
# Newly FDA-Approved Weigh Loss Medications

<table>
<thead>
<tr>
<th>Agents</th>
<th>Action</th>
<th>Approval, Dose</th>
</tr>
</thead>
</table>
| 1. Lorcaserin                 | • 5-HT$_{2c}$ serotonin agonist
  • Little affinity for other serotonergic receptors                                               | • Approved in 2012
  • 10 mg twice daily                                                           |
| 2. Phentermine/Topiramate ER  | • Sympathomimetic
  • Anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism) | • Approved in 2012
  • 3.75/23, 7.5/46, 11.25/69, 15/92 once                                             |
| 3. Naltrexone HCl/bupropion HCl| • Opioid antagonist
  • Neuronal reuptake inhibitor of dopamine and norepinephrine                             | • Approved, September 2014
  • Escalating dose from 8/90 mg to 32/360 mg over 4 weeks                                |
| 4. Liraglutide                | • GLP-1 analog
  • Central suppression of appetite                                                       | • Excepted approval, winter 2014
  • 3 mg SC once                                                                    |
# Summary of efficacy and safety of new antiobesity drugs

<table>
<thead>
<tr>
<th></th>
<th>Locaserin</th>
<th>Phentermine/Topiramate ER</th>
<th>Naltrexone SR/Bupropion SR</th>
<th>Liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>10 mg bid</td>
<td>15/92 mg qd</td>
<td>32/360 mg qd</td>
<td>3 mg SC qd</td>
</tr>
<tr>
<td>&gt;5% at 1 year</td>
<td>47.5%</td>
<td>70%</td>
<td>48%</td>
<td>63%</td>
</tr>
<tr>
<td>&gt;10% at 1 year</td>
<td>22.6%</td>
<td>48%</td>
<td>25%</td>
<td>33%</td>
</tr>
<tr>
<td>Major SE</td>
<td>Headache, dizziness, fatigue, nausea, constipation, dry mouth</td>
<td>Paresthesia, dry mouth, constipation, headache dysgeusia, insomnia, Nasopharyngitis</td>
<td>Nausea, constipation, headache, vomiting, dizziness, insomnia</td>
<td>Nausea, diarrhea, and constipation</td>
</tr>
<tr>
<td>Contraindication/ warning</td>
<td>Co-administration with other serotonergic or antidopaminergic agents Valvular disease</td>
<td>Pregnancy, Glaucoma, Hyperthyroidism, MAO inhibitors</td>
<td>Risk of suicidal thoughts and behaviors associated with antidepressant drugs</td>
<td>Acute Pancreatitis, thyroid medullary carcinoma, gall bladder disorder</td>
</tr>
</tbody>
</table>

*Hamdy O, 2014 Joslin Diabetes Center*
The Impact of Diet on Diabetes: Known Before the Era of Diabetes Medications

1869-1962
Joslin Clinic
Boston, MA

1879–1964
Physiatric Institute
Morristown, NJ
### Joslin Diabetes Diet, 1923

<table>
<thead>
<tr>
<th>Food</th>
<th>Calories (%)</th>
<th>Calories (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>75 g</td>
<td>300 (17%)</td>
</tr>
<tr>
<td>Fat</td>
<td>150 g</td>
<td>1350 (75%)</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>10 g</td>
<td>40 (2%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>15 g</td>
<td>105 (6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1795</td>
</tr>
</tbody>
</table>
Advancing Carbs to Treat Fatty
Bread and Butter Effect

Glucose → Insulin

Insulin → Lipogenesis

O. Hamdy, 2014
Historically Food Myths, Fad Diets and Dietary Trends Have Always Been Popular

- The Allen Diet (a starvation diet)
- The Diabetes Diet (40% fat, 40% carbs, 20% protein)
- Oat Diet
- Grapefruit Diet
- Milk Diet
- Potato Therapy
The Roots of Dietary Problems
Eisenhower had a left anterior MI in September 1955, while on vacation at his in-laws' house in Denver. He was treated with heparin.

Eisenhower broke with precedent and released detailed information about his illness to the public.

Eisenhower's long term treatment included coumadin, a low fat diet, and maintenance of weight at 175 lbs.
1- Increase carbohydrates consumption to account for 55-60 percent of energy (caloric) intake

2- Reduce overall fat consumption from approximately 40 to 30 percent energy intake

3- Reduce saturated fat consumption to account for about 10% of total energy intake; and balance that with poly-unsaturated and mono-unsaturated fats, which should account for about 10 percent of energy intake each

4- Reduce cholesterol consumption to about 300 mg a day

5- Reduce sugar consumption by about 40 percent to account for 15 percent of total energy intake

6- Reduce salt consumption by about 50 to 85 percent to approximately 3 grams a day
Historically Food Myths, Fad Diets and Dietary Trends Have Always Been Popular

1900 - 1915
- Oat Diet
- Grapefruit Diet
- Milk Diet
- Potato Therapy

1922 - 1910
- The Allen Diet (a starvation diet)

1970 - 1977
- The Diabetes Diet (40% fat, 40% carbs, 20% protein)
- High Carbs Diet (30% Fat, 50-55% Carbs, 15-20% protein)
- The Atkins Diet
Changing Course from 1977

- 29% decrease in meat intake
- 8% decrease in added fat and oil
- 21% decrease in eggs
- 8,853% increase in high-fructose corn syrup
- 198% increase in fruit
- 3% increase in potatoes
- 67% increase in added fat and oil
Change in Dietary Composition in Relation to Obesity Prevalence (1971-2010)

The Carbohydrates Cycle & CVD

O. Hamdy, 2014

Glucose

Insulin Resistance

Insulin

Cardiometabolic Syndrome

CVD

TG

HDL

BP

Lipogenesis

Reactive Hypoglycemia

Glycogen

Hepatocytes

Insulin Resistance

O. Hamdy, 2014

Joslin Diabetes Center
## Strategies for optimal weight loss

- **Aim for 5-10% weight loss and a maintenance of ~7% for long-term**

### Proper Medical Nutrition Therapy (MNT)
- Caloric level & Dietary Composition
- Meal Replacer

### Proper Exercise
- Type
- Duration
- Frequency

### Behavioral Modification
- SMART Goals
- Cognitive support

### Medications
- Diabetes Medications
- Weight loss medications

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**Patient adherence and compliance for long-term success**
Multidisciplinary Intervention

- Effective intervention program should include diet, physical activity, and behavior therapy

- Medical nutrition therapy (MNT) for weight loss should last at least 6 months or until weight loss goals are achieved

- Weight maintenance program should follow initial weight loss

- Addition of weight loss medications and adjustment of other medication that affect body weight are important
1- Structured dietary intervention & modified macronutrient composition

- Relatively higher protein, LGI & higher fibers
- Provide structure menus
- Calorie replacements

- Calorie intake (~500 less)
  Carbs to 40-45%

- Glycemic index

- Protein intake to 30%
  Fiber
  MUFA

- Saturated fat and sodium
Strong Correlation Between Calorie Replacement and Weight Loss (Look AHEAD Study)

Number in the bar is mean number of MRs used in that quartile

Reduction in Initial Weight in ill participants (%)

1st: -5.9%
2nd: -7.2%
3rd: -9.4%
4th: -11.2%

MRs = meal replacements

Reproduced with permission from Wadden TA et al. Obesity 2009; 17:713-722
Diets with High or Low Protein Content and Glycemic Index for Weight-Loss Maintenance (26 weeks)

N = 773
Initial weight loss ≥8%
13% protein (LGI/HGI) versus 25% protein (LGI/HGI)

“I did a 30 minute workout today: 10 minutes looking for my sneakers, 15 minutes looking for sweatpants, and 5 minutes on the treadmill.”
Exercise
Exercise at any Age

IT’S NEVER TOO LATE!

SOFT SHOULDER
BLIND CURVES
STEEP GRADE
BIG TRUCKS
GOOD LUCK!
2- Gradual, balanced and individualized physical activity

- Duration of exercise
- Type of exercise
- Short versus long-bouts of exercise
- Exercise records/exercise monitor

Visceral Fat
BP & lipids
Metabolic Control
Physical Fitness & QOL
Maintenance of Weight Loss
Vascular Resistance
Balanced Exercise Model

Strength exercise is particularly important during weight reduction.

- **Flexibility**: Stretching, Yoga
- **Aerobic**: Walking, Swimming, Biking, Dancing
- **Strength**: Resistance tubing, Weight lifting, Yoga

 Joslin Diabetes Center
Effect of Long vs Short Bouts of Exercise on Adherence and Weight Loss

<table>
<thead>
<tr>
<th>Activity (min/wk)</th>
<th>Long Bouts</th>
<th>Short Bouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Long bout = one 40-min session; short bout = four 10-min sessions.

Structure of Look AHEAD Versus Why WAIT

**Look AHEAD Study**

- **Dietary Intake:**
  - 1200–1500 kcal/day < 250 lb
  - 1500–1800 kcal/day > 250 lb

- **Calorie Replacements:**
  - (2 liquid meal + one snack bar)
  - Transition at week 20
  - Menu plans provided

- **Physical Activity:**
  - Gradual increases
  - Goal of 175 min/wk
  - 10,000 steps

- **Medication Changes:** PCP

**Why WAIT Program**

- **Dietary Intake:**
  - 1500 kcal/day for **women**
  - 1800 kcal/day for **men**

- **Calorie Replacements:**
  - (2 liquid meal + 2 snacks food)
  - Transition at week 10
  - Menu plans provided

- **Physical Activity:**
  - Gradual increases
  - Goal of 300 min/wk average
  - Balanced exercise (more resistance exercises)

- **Medication Change:** Endocrinologist

Percentage Weight Reduction in Patients with Diabetes in the Real-World Clinical Practice over 5 years (Joslin Why WAIT Program)

- **14% Remission**
- **21% Stopped insulin**
- **50-60% Reduction in Medications**

- Total Group n=129
  - Group 1 n=61 (Participants maintained <7% weight loss at 1 year)
  - Group 2 n=68 (Participants maintained ≥ 7% weight loss at 1 year)
Changes in % Body Fat, Fat Mass, and Lean/Fat Ratio After 12 Weeks of the Why WAIT? Program

$\text{Fat mass (lbs)}$

$\text{Body fat (%)}$

$\text{Lean/fat}$

$n = 85$

*$p<0.05$  **$p<0.01$  ***$p<0.001$

**Percentage Changes in Lipid Profile after Why WAIT? Program**

<table>
<thead>
<tr>
<th>Lipid Profile</th>
<th>TC</th>
<th>Triglycerides</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Change</td>
<td>-12.2</td>
<td>-21.8</td>
<td>-11.4</td>
<td>-3</td>
</tr>
</tbody>
</table>

- **n = 62**
- *p < 0.05 **p < 0.01 ***p < 0.001

---

**Percentage of Patients Achieved Target A1c after 12-Week of Why WAIT? Program**

- **Percentage HbA1c**
  - <7%: 59.7%
  - <6.5%: 69%

- **n = 115**
- *p < 0.05 **p < 0.01 ***p < 0.001 versus baseline

---

**Changes in Urinary Albumin/ Creatinine Ratio after 12-Week and One Year of the Why WAIT? Program**

<table>
<thead>
<tr>
<th>Time</th>
<th>Urinary Albumin/creatinine Ratio mcg/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>29.4</td>
</tr>
<tr>
<td>12 Weeks</td>
<td>20.16 ***</td>
</tr>
<tr>
<td>1 Year</td>
<td>25 ***</td>
</tr>
</tbody>
</table>

- **n = 115**
- *p < 0.01 **p < 0.001 versus baseline

---

**Percentage of Patients Achieved Target A1c after 12-Week of Why WAIT? Program**

- <7%: 7.5%
- <6.5%: 6.6%

- **n = 115**
- *Hamdy O et al, ADA 2009

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**Change in A1c after Why WAIT program**

- **Hamdy O et al, 2009**

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**Percentage HbA1c**

- **n = 115**
- *Hamdy O et al, ADA 2009**
Economic Impact of Non-Surgical Weight Loss in One Year in Patients With Diabetes

Cost Saving (1% wt loss)
- $256 (-3.6%)
- $131 (-5.8%)

Estimated Saving with (7% wt loss)
- $996 (-44%)
- $1,946 (-27%)

1. p<0.05    2. p<0.001

YU AP et al. Curr Med Res Opin. 2007;23(9):2157-69

Health Care Cost  Diabetes Related Cost
Impact of Bariatric Surgery on Healthcare Utilization & Costs in Patients with DM over 6 Years

7,806 patients with diabetes who received bariatric surgery

**Conclusion**

In the six years following bariatric surgery, individuals with type 2 diabetes did not have lower healthcare costs than before surgery.

Harvard Health Publications

Osama Hamdy, M.D., Ph.D.
and Sheri R. Colberg, Ph.D.

THE DIABETES BREAKTHROUGH

BETTER HEALTH IN JUST 12 WEEKS

BASED ON A SCIENTIFICALLY PROVEN PLAN TO LOSE WEIGHT AND CUT MEDICATIONS

http://www.TheDiabetesBreakthrough.com
In Conclusion

1. Long-term weight reduction can be achieved through non-surgical and surgical weight management.

2. Exercise type and duration significantly impact long-term weight maintenance.

3. Changing macronutrient compositions, providing structured meal plan plus adding calorie replacements are effective dietary intervention.

4. Adjusting medications is important for patients with diabetes and addition of weight loss medications is effective for long-term weight reduction.

5. Long-term weight reduction is cost-effective.
Thank You