Diabesity: Treatment Options for an Epidemic of Growing Proportions

Jennifer Poehls, MD
Clinical Assistant Professor
UW School of Medicine and Public Health
Section of Endocrinology, Diabetes, & Metabolism
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Disclosures

- Nothing to disclose financially
- I have no personal experience prescribing the new obesity medications presented
Objectives

- Prevalence of Obesity
- Prevalence of Diabetes
- Lifestyle modification trials for prevention of diabetes
- Dietary approaches to weight loss
- Anti-obesity agents, old and new
- Bariatric surgery
- Incretins and other GI hormone treatments on the horizon
Diabesity

- Ethan Sims first to describe strong link between T2DM and obesity in 1973, coining the term “diabesity”
- Large body of evidence supports relationship between being overweight/obese, esp abdominal fat, and increased risk of T2DM
- Both diabetes and obesity recognized as major public health problems, evolving into epidemics
- Prevalence increases despite decades of research

Colagiuri. 2010. Diabetes, Obesity, and Metabolism
Global Epidemic of Obesity

- In 2010, worldwide
  - 1.6 billion adults overweight (BMI>=25)
  - 400 million obese (BMI>=30)
- By 2015, worldwide
  - 2.3 billion adults will be overweight
  - >700 million will be obese

Colagiuri, 2010. Diabetes, Obesity, and Metabolism
OECD Obesity Update 2012
Obesity Trends* Among U.S. Adults
BRFSS, 1990, 2000, 2010
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)

1990

2000

2010

Source: Behavioral Risk Factor Surveillance System, CDC.
Causes of Obesity Epidemic

- Imbalance between energy intake and energy expenditure related to modern lifestyle
  - Consumption of high-calorie, high-fat foods/drinks
  - Insufficient physical activity
- Poor maternal/fetal nutrition
- Genetic predisposition
- Less common causes
  - Hypothyroidism
  - Cushing’s syndrome
  - Abnormalities in leptin action and regulation

Colagiuri. 2010. Diabetes, Obesity, and Metabolism
Obesity and Its Complications

- T2DM
- CAD/CVD
- HTN
- Dyslipidemia
- Cancer
- NAFLD
- Mobility problems from osteoarthritis
- OSA
- Depression

Increased risk of death compared to normal wt
- 20-40% in overweight individuals
- 2-3 fold in obese individuals

Farag et al 2011. Nephrol Dial Transplant
Association Between T2DM and Obesity

- Primary risk factor for T2DM is obesity
  - 90% of pts with T2DM are overweight or obese
- The Nurses Health Study
  - 84,941 women 1980-1996
  - Relative risk of DM increased 40 fold as BMI increased from <23 to >35kg/m2
- Lipotoxicity and resulting oxidative stress may be factor in the development of insulin resistance and decline in beta-cell mass

Global Epidemic of T2DM

- Globally diabetes prevalence increasing
  - ~284 million in 2010
    - 6.4% of world population
  - ~ 439 million by 2030

Farag et al 2011. Nephrol Dial Transplant
Global Epidemic of T2DM

- High economic burden
  - $376 billion in 2010
    - 12% of health expenditures per person worldwide
    - 14% US total health expenditure
  - $490 billion by 2030

• Farag et al 2011. Nephrol Dial Transplant
Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults Aged 18 years or older

**Obesity (BMI ≥30 kg/m²)**
- 1994
- 2000
- 2010

- No Data
- <14.0%
- 14.0% – 17.9%
- 18.0% – 21.9%
- 22.0% – 25.9%
- ≥26.0%

**Diabetes**
- 1994
- 2000
- 2010

- No Data
- <4.5%
- 4.5% – 5.9%
- 6.0% – 7.4%
- 7.5% – 8.9%
- ≥9.0%

T2DM and its Complications

- Elevated risk of life-threatening microvascular and macrovascular complications
- According to ADA, every day in the US
  - 66 people lose their eyesight
  - 112 people begin treatment for ESRD
  - 225 amputations are performed
  - 584 people die from diabetes, most often CAD or stroke

The Challenge

- With the exception of metformin, many antidiabetes medications are associated with weight gain
  - TZD, sulfonylurea, meglitinides, insulin
- Starts vicious cycle
  - ↑weight → ↑insulin resistance → ↑medication

Colagiuri. 2010. Diabetes, Obesity, and Metabolism
Lifestyle Modification Trials

- US Diabetes Prevention Program
- Look AHEAD trial
Diabetes Prevention Program

- Question: Does lifestyle intervention or metformin prevent or delay the onset of diabetes?
- Major multicenter trial of 3234 persons with preDM randomly assigned to placebo, metformin or lifestyle-modification program
- Characteristics:
  - Mean age 51 years
  - Mean BMI 34
  - 68% women
  - 45% minority groups

DPP Research Group. 2002. NEJM,
Diabetes Prevention Program

Interventions

- Standard lifestyle modifications + placebo bid
  - Written info and annual ~30 min session on healthy lifestyle

- Standard lifestyle modifications + metformin 850mg bid

- Intensive program of lifestyle intervention
  - Achieve and maintain wt loss of 7% thru healthy low-fat, low-calorie diet and 150 minutes of moderate physical activity per week
  - 16 lesson curriculum on diet, exercise, and behavior modification taught one-on-one by case manager over first 24 wks, followed by monthly group and individual sessions

- [Link](http://www.bsc.gwu.edu/dpp/lifestyle/dpp_part.html)
Figure 1. Changes in Body Weight (Panel A) and Leisure Physical Activity (Panel B) and Adherence to Medication Regimen (Panel C) According to Study Group.
Figure 3. Fasting Plasma Glucose Concentrations (Panel A) and Glycosylated Hemoglobin Values (Panel B) According to Study Group.
Diabetes Prevention Program

Figure 2. Cumulative Incidence of Diabetes According to Study Group.

DPP Research Group. 2002. NEJM
DPP Conclusions

- T2DM can be prevented or delayed in high risk patients
- Lifestyle interventions and metformin reduce incidence of T2DM, but risk reduction greatest for lifestyle intervention
Look AHEAD Trial

- Large multicenter, RCT, comparing effects of intensive lifestyle intervention (ILI) to diabetes support and education (DSE) on incidence of major CVD events in 5145 overweight or obese pts with T2DM
  - 59.5% female
  - Mean age 58.7 years

Wing et al. 2010. Arch Int Med
Look AHEAD Trial

- ILI: calorie restricted, low-fat diet with frequent behavioral therapy
  - Weekly x 6 months, 3 times/month x 6 months, then at least once monthly
- DSE: standard instruction on 3 occasions/year
- Wt loss significantly greater in ILI group
  - % initial wt -6.15 in ILI vs -0.88 in DSE
- ILI had greater improvement in fitness, A1C, BP, HDL, and TG

Wing et al. 2010. Arch Int Med
Dietary Approaches to Weight Loss

- Low-fat diets (20-35%)
- Very low-fat diets (20% or less)
- Moderate-fat diets (35-45%)
- High-protein diets (1.6g/kg/day)
  - Zone diet: 30% protein, 40% carb, 30% fat
- Low-carbohydrate diets (20-50g/day)
- Low-glycemic-index diets

Dietary Approaches

- Various diets can effectively reduce weight and improve health parameters.
- Poor long-term adherence and weight regain are common among all diets.
- Behavior therapy and ongoing support tend to produce longer lasting effects.
- Sustaining diet adherence may be more important than type of diet.

Dietary Approach Challenge

- Challenge adhering to lifestyle changes
  - Lack of pt readiness for change
  - Physical restrictions limiting activity
  - Labor intensive
  - Shortage of venues including multidisciplinary health care team
- Numerous large, well-controlled studies show once obesity established, no diet or exercise regimen can restore/sustain healthy weight for any prolonged period in more than tiny fraction of patients
Antiobesity Agents

- Until recently, only 2 anti-obesity agents available in US for BMI >30 OR BMI >27 + comorbidities

- Phentermine
  - Amphetamine analog (schedule IV) that suppresses appetite
  - Approved for short-term use only (up to 12 wks)
  - Contraindications: Pulm HTN, CAD, CVD, anorexia, depression, h/o drug abuse, pregnancy

- Orlistat
  - Gastrointestinal lipase inhibitor interfering with fat absorption
  - Reduces wt on average 3kg, improves CV risk factors, and decreases progression to DM
  - SE: fatty/oily stools, fecal urgency, oily spotting 15-30%

Colagiuri. 2010. Diabetes, Obesity, and Metabolism
Derosa. 2012. Expert Opinion on Drug
Orlistat

- Kelley et al. 2002. Diabetes Care

  - 1 year multicenter, randomized, double-blind, placebo controlled trial
  - Compared Orlistat (120mg tid) vs placebo, combined with reduced-calorie diet in overweight/obese pts with poorly controlled T2DM treated with insulin +/- oral agents
  - Orlistat group lost more wt (-3.9 vs -1.3 % of baseline body wt)
  - Orlistat group had greater decreases in A1C (-0.6 vs -0.3), FBG, total cholesterol and LDL
Antiobesity Agents

- Phentermine + topiramate
  - FDA approved 7/2012, available 9/2012
  - Topiramate
    - Side effect of wt-loss observed when used as Anticonvulsant (200-400mg/d) and Migraine prophylaxis (100mg/d)
    - Neuropsychiatric adverse events (memory and depression) hindered its development as monotherapy
  - Phentermine
    - Controlled release, low-dose (7.5 or 15mg vs 30mg)
  - Early 28 week randomized trial showed
    - 6.1% wt loss for phentermine alone,
    - 6.4% for topiramate alone, and
    - 9.2% for combination

Derosa. 2012. Expert Opinion on Drug
CONQUER Trial

- Effects of low-dose, controlled-release phentermine + topiramate on weight and associated comorbidities
  - 56 week, randomized, placebo-controlled, phase 3 trial
  - 2487 obese/overweight pts with 2 or more comorbidities (HTN, dyslipidemia, DM, preDM, abdominal obesity)
    - 70% women, mean age 51, BMI 36.6
  - Placebo, low dose (7.5/46mg), high dose (15/92mg) (2:1:2)
  - Primary endpoints: % change in body wt and proportion of pts achieving at least 5% wt loss

Gadde et al. 2011. The Lancet
CONQUER Results

- Change in body weight:
  - -1.4kg placebo, -8.1kg 7.5/46mg, and -10.2kg 15/92kg

- Achieving at least 5% wt loss:
  - 21% placebo, 62% 7.5/46mg, 70% 15/92mg

- >10% wt loss:
  - 7% placebo, 37% 7.5/46mg, 48% 15/92mg
CONQUER Results

- Significant improvements were noted in BP, waist circumference, lipids, glycemia, and inflammatory markers with phen+tpm
- Improvements in risk factors most pronounced in pts with pre-existing comorbidities
  - greater reduction in BP, with more antihypertensive drugs withdrawn
  - greater improvement in TG and HDL
  - greater reduction in A1C, FBG, fewer progression to T2DM
  - greater improvement in QOL
CONQUER trial

- Most frequent adverse events, dose-related trends
  - Dry mouth
  - Parasthesias
  - Constipation
  - Insomnia
  - Dizziness
  - Alteration in taste

- Rates of serious AE similar across treatment groups

- Depression/anxiety occurred mainly during early phase of treatment, resolved on drug d/c, higher frequency at higher dosing

Gadde et al. 2011. The Lancet
CONQUER Trial

- **Strengths**
  - Assess effects of wt loss on comorbidities
  - Inclusion of susceptible pts

- **Limitations**
  - Endpoint assessment not available for 31%
  - Restriction of upper BMI limit to 45
  - Lack of ethnic diversity
  - Few men
  - Pts with diabetes only on metformin included
SEQUEL Trial

- Extension of CONQUER trial
- Assess long term efficacy and safety by extending trial another 52 weeks
- 1542 pts completed CONQUER, 676 pts enrolled in SEQUEL
- Primary endpoints: mean % wt loss and % achieving \geq 5% wt loss
- Secondary endpoints: waist circumference, BP, lipids, glycemic measures, and progression to diabetes

Garvey, 2012 Am J Clin Nutr
SEQUEL Trial

- Both treatment arms showed greater percentage of wt loss, which was sustained during 108 wk
  - % change in body wt from baseline greater in treatment arms (-1.8, -9.3, -10.5%)
  - 10% wt loss was achieved by >50% of the phen/tpm treated subjects compared to <12% of placebo
  - Higher dose appeared more effective in pts with class III obesity
- In pts with T2DM at baseline, phen/tpm cr pts showed greater weight loss compared to placebo (2% vs 9%)

Garvey, 2012 Am J Clin Nutr
SEQUEL Trial

- Comorbidities were improved in treatment arms and there was decreased need for associated medications
  - SBP and DBP decreased and there was net decrease in number of antihypertensive medications
  - Progressively greater reductions in TG and greater increases in HDL. Placebo arm required increase in lipid lowering medications.
  - In pts with T2DM, A1C did not change in placebo, -0.4% in 7.5/46mg, and -0.2% in 15/92mg, without any net increase in anti-diabetes medications
  - In pts without T2DM, there was decrease in progression to T2DM

Garvey, 2012 Am J Clin Nutr
SEQUEL trial

- Most frequent adverse effects
  - URI/sinusitis
  - Constipation
  - Parasthesias
  - Dry mouth
- AE Incidence lower in 2nd year
- Reduction in serum bicarbonate in first 3 months returned to normal by 2 years
- Incidence and % subjects discontinuing due to AE similar across treatment groups
  - 3.1% placebo, 4.5% 7.5/46mg, 4.4% 15/92mg

Garvey, 2012 Am J Clin Nutr
Antiobesity Agents

- Activation of serotonin (5-HT) receptor decreases food intake thru proopiomelanocortin system
- Fenfluramine
  - Non-selective serotonin receptor agonist
  - Effective at wt loss, but increased risk of serotonin-associated valvulopathy (5-HT 2B receptors expressed on cardiac valvular interstitial cells)
- Lorcaserin
  - Selective serotonin (5HT) 2C receptor agonist
  - 12 week clinical trial, lorcaserin associated with dose-dependent wt loss without effect on heart valves
  - FDA approved 6/2012, available early 2013

Smith et al. 2010. NEJM
BLOOM Trial

- Behavioral Modification and Lorcaserin for Overweight and Obesity Management
  - 2 year, multicenter, randomized, placebo-controlled, double blind clinical trial
  - 3182 obese/overweight pts randomized to receive lorcaserin 10mg or placebo BID x 52 wks
  - At week 52, lorcaserin group randomly assigned to placebo or lorcaserin
  - Primary outcomes: wt loss at 1 year, maintenance of wt loss at 2 years
  - Serial echo used to identify valvulopathy

Smith et al. 2010. NEJM
Figure 1. Effects of the Study Drug on Body Weight, According to Study Group.

The proportions of patients who lost 5% or more or 10% or more of their baseline body weight at 1 year are shown (Panel A). For the intention-to-treat population (with last-observation-carried-forward imputation), the mean body weight at each study visit is shown, according to study group, during year 1 among all patients (Panel B) and during years 1 and 2 among only those patients who continued the study past year 1 (Panel C). Error bars indicate standard errors.
BLOOM Trial

- Most frequent adverse events
  - Headache
  - URI/Nasopharyngitis
  - Dizziness
  - Nausea
- Rate of cardiac valvulopathy was not increased with use of lorcaserin (2.7% vs 2.3%)
- Rates of depression and serious adverse events similar in placebo and lorcaserin groups
BLOOM Trial

Limitations

- 50% discontinuation rate at 1 year (similar to rates of other large, long-term trials of obesity).
- Applicability to broader populations (BMI>45, pts with DM were excluded)
- Trial slightly underpowered regarding primary echo safety endpoint
  - Actual incidence of FDA-defined valvulopathy was below pretrial estimates of 5%
Potential Risks

- Phentermine+Topiramate
  - Increased resting heart rate-->avoid in pt with recent or unstable CAD
  - Teratogenicity (orofacial cleft)--->contraception recommended
  - FDA approval required risk evaluation and mitigation strategy (REMS)
    - Medication guide and pt brochure
    - **Formal training program for prescribers recommended**
      - stressing need for contraception in women
      - www.qsymiarems.com
    - Only dispensed by specially certified mail-order pharmacies

Coleman et al. 2012. NEJM
Potential Risks

- **Lorcaserin**
  - Initial animal studies showed increased incidence of multiple tumors, including mammary, but these concerns were diminished after independent pathology review
  - BLOOM study underpowered regarding valvulopathy
  - Not studied in patients on SSRIs

- Because of the potential for serious and yet unknown risks, it is important their use be limited to ONLY those patients for whom they are indicated
  - BMI $\geq 30$ OR BMI $\geq 27$ + comorbidities

Coleman et al. 2012. NEJM
Antiobesity Agents

- Taken off the market
  - Fenfluramine/Dexfenfluramine 1997
  - Ephedra 2004
  - Rimonabant 2006
  - Sibutramine (Meridia) 2010

- Healthy skepticism is important, especially when decades of research have failed to achieve needed breakthrough
Bariatric Surgery

From 1990 to 2000, the national annual rate of bariatric surgery increased nearly six fold, from 2.4 to 14.1 per 100,000 adults.

- Annual rates plateaued in 2004 at ~110-120k/yr

Weight and T2DM after Bariatric Surgery

  - Wt loss overall 38.5kg or 55.9% excess body wt
  - 78.1% T2DM completely resolved
  - 86.6% T2DM improved
  - Wt loss and DM resolution greater in biliopancreatic diversion/duodenal switch than gastric bypass than banding
Bariatric Surgery

- **Shortcomings**
  - Requirement for specialist surgeons and facilities, restricting access and increasing cost
  - Perioperative mortality 0.1-1.1%
    - May be higher for BMI >70
  - Perioperative complications
    - VTE, anastomotic leaks, infection, bleeding, hernia, splenectomy, SBO
  - Relative irreversibility
  - Post-operative complications
    - Dumping syndrome, nausea/vomiting, vitamin/mineral deficiencies

DeMaria. 2007. NEJM*
Bariatric Surgery

Observations

- Multiple studies demonstrate improvement or resolution of diabetes after bariatric procedures.
- Reduction in hyperglycemia occurs within days, before meaningful wt loss and persists >10 years.
- Learning mechanism underlying these improvements is active area of research, leading to possible pharmacologic targets.

Bariatric Surgery

- Foregut hypothesis
  - Overstimulation of foregut (stomach, duodenum, jejunum) important causative factor in T2DM

- Hindgut hypothesis
  - Increased stimulation of distal small bowel leads to alterations in secretion of GI tract hormones, leading to improvement in carbohydrate metabolism
    - Higher glucagon-like peptide-1 (GLP-1)

GLP-1

- Secreted from L-cells of small intestine in response to nutrients
- Main effect is stimulating glucose-dependent insulin release from pancreatic islet
- Other effects
  - Slow gastric emptying
  - Inhibit post-meal glucagon release
  - Reduce food intake
  - In animal models, stimulate beta-cell proliferation and differentiation
GLP-1 Receptor Agonists

- Exenatide (BID dosing)
  - First approved GLP-1
  - 3 double-blind placebo-controlled, 30 week trials in poorly controlled T2DM on metformin and/or sulfonylurea
    - A1C -0.8%
    - Body weight -2.1kg, progressing to -4.7kg after 2 years
  - Side effects: Nausea
    - 30 cases of pancreatitis reported
    - T2DM risk of pancreatitis 3x normal population
  - Contraindications: Severe renal insufficiency or ESRD

-Buse et al 2007 Clin Ther
GLP-1 Receptor Agonists

- Liraglutide (QD dosing)
  - Decreases A1C and body weight relative to placebo and glimepiride Garber et al 2009 Lancet
    - 1.2mg decreased wt 2.1kg and A1C 0.8%
    - 1.8mg decreased wt 2.5kg and A1C 1.1%
    - Glimepiride increased wt 1.1kg and decreased A1c 0.5%
  - Liraglutide shows slightly greater wt reduction (-2.8 to -4.1kg) than exenatide (-2.7 to -3.1kg) and greater A1C reduction (-1.1 vs 0.8%)
  - Side effects: nausea, usually transient

Colagiuri. 2010. Diabetes, Obesity, and Metabolism
New Developments in GLP-1

- Exenatide LAR once weekly injection
  - DURATION-1--similar reductions in A1C compared to exenatide BID
  - DURATION-2--significant improvement in A1C compared to pioglitazone or sitagliptin when added to metformin
  - DURATION-3--significant reduction in wt compared to insulin, no significant improvement in A1C

- Other once weekly GLP-1 receptor agonists under development
  - Taspoglutide
  - Albiglutide
  - Semaglutide

Other Promising GI Hormones

- Oxyntomodulin (OXM)
  - Combines effects of GLP-1 and glucagon to suppress food intake and increase energy expenditure

- Peptide YY
  - Reduces appetite by negative feedback

- Gastric Inhibitory Protein (GIP)
  - Direct anabolic effects on adipose tissue

- Grehlin
  - Increases food intake

No Silver Bullet

- Multiple peptides/proteins have emerged as drug candidates, but no silver bullet has emerged despite promising early results.
- GI hormone therapies often have dose-limiting side effect of nausea.
- Bariatric surgery effects secretion of multiple GI hormones secretion without nausea.
  - Combination therapies being explored:
    - GLP-1 + glucagon
    - GLP-1 + GIP
    - GLP-1 + PYY
    - PYY + OXM


- Small study of 11 pts s/p gastric bypass compared to 14 matched patients put on very low calorie diet (500 calories/day) x 21 days to see if magnitude of change due to surgery or caloric restriction
- Both groups lost equivalent amount of wt (8.1% v 7.2%)
- Insulin secretion, C-peptide levels, HOMA-IR, and acute C-peptide response were similar
- GLP-1 and adiponectin higher in gastric bypass group.

Conclusion: both surgery and very low calorie diet improve insulin sensitivity and beta-cell function in the short term
Conclusions

- Curbing the global diabetes and obesity epidemic requires a population-based, multi-disciplinary, and culturally relevant approach.
- Effective interventions for weight management should start ideally BEFORE diagnosis of preDM and/or T2DM.
  - Caloric restriction with increased activity.
  - Consider anti-obesity agents when intermediate amount of weight loss required (5-15% of body weight) and/or surgery too risky.
    - Combination therapy likely better than monotherapy.
    - Exercise caution when selecting patients.
  - Consider bariatric surgery when large amount of weight loss required (>15% of body weight).
  - If T2DM present, choose anti-diabetic therapy with favorable effect on body weight (i.e., GLP-1 agonists, SGLT inhibitors) when possible.
References

DPP Research Group. Reduction in the incidence of Type 2 diabetes with lifestyle intervention or metformin. NEJM. 2002; 346:393-403.
Arroyo K et al. Surgical therapy for diabesity. Mount Sinai Jour Med. 2010; 77:418-430.