Prevention of Type 2 Diabetes

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Swedish Health Care Systems
In compliance with accrediting board policies, the American Diabetes Association requires the following disclosure to participants:

Fran Broyles:

Speaker’s Bureau: AstraZeneca
“Type 2 diabetes is part of a worldwide health crisis of noncommunicable disease that is replacing pandemics and infectious diseases as the greatest threat to public health”
50%

UNITED STATES HAS PRE DIABETES OR DIABETES

JAMA SEPT 8, 2015.VOL314,NUMBER10
Prevalence of Diabetes 12 to 14% (29 million, of those 8.1 million undiagnosed, 36%)
Prevalence of Pre diabetes 38% (86 million)
NHANES Between 1988-1994 and 2011-2012, Prevalence of DM increased:
  Among overall population
  Among each age group (20-44, 45-64, >65)
  Both sexes
  Every Racial / Ethnic Group
  Every Education level
  Every income level

Highest Prevalence was seen in Non-Hispanic black, Non-Hispanic Asian, and Hispanic
Total cost in 2012 of diagnosed DM $245 billion
DM pts cost 2.3 x more than pts without DM
Toddler May Be Youngest Ever Diagnosed With Type 2 Diabetes

The case report was session at the European Association for the Study of Diabetes (EASD) 2015 Meeting by Michael Yafi, MD, director of pediatric endocrinology at the University of Texas Health Science Center at Houston, presented September 16 in a poster discussion.

The child, a 3-year-old Hispanic girl weighing 35 kg (77 pounds; > 95th percentile for age) presented at Dr. Yafi's pediatric endocrinology clinic for evaluation of obesity. She didn't seem ill, she had polyuria and polydipsia, so he screened her and found she had a fasting plasma glucose of 230 mg/dL, and an HbA1c of 7.2%. Her C-peptide was positive, Anti GAD and islet cell antibodies were negative.
Pediatric and Adolescent Type 2 DM

Type 1 DM is still the most common
Type 2 in Children in the US is 12/100,000 with majority in AA, Hispanics, Asian/Pacific Islanders, and American Indians with Pima Indians 22/100,000 9 to 14 yo

The prevalence although still lower has tripled in the last decade and closely mimics increase obesity in children

Majority were Obese
Usually diagnosed in middle to late puberty
1/3 diagnosed on UA during PE
5 to 25 % present in DKA

Differentiation from Type 1 DM (85 to 98 % + Beta cell antibodies and low C peptide) and MODY
OBESITY

THE INCREASE IN DIABETES MAY BE DUE TO THE INCREASE IN OBESITY, THE MOST IMPORTANT RISK FACTOR FOR TYPE 2 DM, AFFECTING 30 TO 35% OF AMERICANS, WITH ANOTHER 35% BEING OVERWEIGHT, FOR A TOTAL OF 70% ADULT AMERICANS OVERWEIGHT OR OBESE, AND 17% OF CHILDREN
T2DM along with Obesity, may yet be the greatest chronic disease epidemic in the history of human existence. The basis for this claim is the meteoric rise of the global estimate, a greater than 2 fold increase, from 151 million people with DM in 2000 to the current estimate of 415 million, to the 2040 prediction of 642 million.
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**

Obesity at Swedish

Total patients meeting criteria*: 107,772
Patients without HbA1c Measured: 76,622

*All SMG active patients aged 40-70 with BMI > 25

29%

HbA1c testing in overweight and obese patients

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade (What's This?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults aged 40 to 70 years who are overweight or obese</td>
<td>The USPSTF recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese. Clinicians should offer or refer patients with abnormal blood glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity.</td>
<td>B</td>
</tr>
</tbody>
</table>
Paradigm Shift/When to Intervene

PREVENT TYPE 2 DIABETES/AGGRESSIVE TREATMENT PRE DM /OVERWEIGHT AND OBESITY
## Categories of Increased Risk for Type 2 Diabetes (Prediabetes)

<table>
<thead>
<tr>
<th></th>
<th>FPG</th>
<th>2-hr PG*</th>
<th>A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100-125 mg/dL</td>
<td>140-199 mg/dL</td>
<td>5.7-6.4%</td>
</tr>
<tr>
<td></td>
<td>5.6-6.9 mmol/L</td>
<td>7.8-11.0 mmol/L</td>
<td>39-46 mmol/mol</td>
</tr>
<tr>
<td>Impaired fasting glucose (IFG)</td>
<td>Impaired glucose tolerance (IGT)</td>
<td></td>
<td></td>
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</tbody>
</table>

Risk is continuous, extending below lower limit of range and becoming disproportionately greater at higher ends of range.

*In 75-g OGTT

FPG=fasting plasma glucose; OGTT=oral glucose tolerance test; PG=plasma glucose

Progression of Pre DM to DM

- DPPPT 11% conversion annually
- ADA expert panel 70% of pts with pre DM will get DM
- In the Chinese DM prevention trial it was 90%
- Gestational DM 20 to 60% of women had DM within 5 to 10 years
- Multifactorial DM risk scores are promising future tools
- RF include gestational DM, first degree relative, metabolic syndrome, BMI, ethnicity, age, physical activity, Waist circumference
Pathophysiology of Pre Diabetes (British Whitehall II)

- 2-hour postload glucose (mmol/L)
- Fasting glucose (mmol/L)
- Insulin sensitivity (HOMA2-%S)
- Beta-cell function (HOMA2-%B)

Graph showing changes in glucose, insulin sensitivity, and beta-cell function over time (years) until diagnosis of diabetes (year 0).
MULTISTAGE MODEL

- **Stage I** - long compensatory period when IR is present and accompanied by increased insulin secretion and beta cell mass
- **Stage II** – stable adaptation, B cells no longer fully compensating for increased IR, FPG and/or post glucose load BS not completely maintained, initially BS are normal
- **Stage III** – Unstable decompensation period glucose levels begin to rise with Beta Cell inability to compensate for IR and glucose levels rise rapidly
**β-Cell Function Declines Over Time**

*Dashed line shows extrapolation backward from year 0 and forward from year 6 from diagnosis based on Homeostasis Model Assessment (HOMA) data from UKPDS. †IGT = impaired glucose tolerance. ‡The data points for the time of diagnosis (0) and the subsequent 6 years are taken from the obese subset of the UKPDS population and were determined by the HOMA model. Adapted with permission from Lebovitz HE. Diabetes Rev. 1999;7:139-153. ©1999 American Diabetes Association.*
Beta cell function

• Beta cell dysfunction already present in the Pre DM stage
• Studies using different measures of beta cell function have reported severely abnormal (up to 80% decreased) insulin secretion in pre DM people
• Autopsy data report a 50% decrease in beta cell volume in pts with IFG
Why treat Pre DM

Decrease or prevent progression to DM

DM complications:
- Kidney – albuminuria, and decreased GFR
- Neuropathies – autonomic, sensorimotor
- DR
- Macrovascular DECODE Trial Increased Coronary death and total CV death related to IFG and IGT
FBG, A1c and post load Glucose are all robust predictors of vascular mortality independent of other vascular RFs (data from prospective trials) 5.6 =100

History of diabetes at baseline: Yes  No

Vascular Death
(50 studies; 16,211 deaths)

Mean Fasting Glucose (mmol/liter)
Complications-Centric Model for Care of the Overweight/Obese Patient

**Step 1: Evaluation for Complications and Staging**

**Cardiometabolic Disease**
- **No Complications**
  - BMI 25–26.9, or BMI ≥ 27

**Biomechanical Complications**
- **BMI ≥ 27 with Complications**
  - Stage Severity of Complications:
    - Low
    - Medium
    - High

**Step 2: Select**
- Therapeutic targets for improvement in complications
- Treatment modality
- Treatment intensity for weight loss based on staging

- **Lifestyle Modification:**
  - MD/RD counseling; web/remote program; structured multidisciplinary program

- **Medical Therapy:**
  - phentermine; orlistat; lorcaserin; phentermine/topiramate ER; naltrexone/bupropion; liraglutide

- **Surgical Therapy (BMI ≥ 35):**
  - Lap band; gastric sleeve; gastric bypass

**Step 3**
- If therapeutic targets for improvements in complications not met, intensify lifestyle and/or medical and/or surgical treatment modalities for greater weight loss
Diabetes Prevention Program Trial (NEJM 2/2002)

3234 pts x 3 years to 3 arms, Standard lifestyle recommendations with placebo bid,
Standard lifestyle recommendations with Metformin 850 mg bid, and intensive lifestyle

Standard lifestyle - written instructions and a 30 min annual visit that emphasized healthy lifestyle, follow the Food pyramid and NCEP Step 1 Diet, and to increase activity

Intensive lifestyle – goal to achieve and maintain 7% wt loss through low calorie, low fat diet and moderate intensity exercise such as walking for 150 min per week, 16 wk of diet, exercise and behavior modification 1:1 visit, followed by monthly 1:1 and grp sessions to reinforce behavior

Incidence of T2DM was reduced by 58% in the Intensive lifestyle grp, by 31% in Metformin grp versus placebo

1 kg of weight loss decreased conversion by 16%

Findings consistent with the Finnish DM Prevention Study with lifestyle intervention 58% reduction in DM
Changes in Body Weight (Panel A) and Leisure Physical Activity (Panel B) and Adherence to Medication Regimen (Panel C) According to Study Group.
Cumulative Incidence of Diabetes According to Study Group.
DPP Outcomes study

- Reversion of pre DM to normoglycaemia during the randomized phase of the study even if transient, was associated with a 56% reduced future risk of DM, independent of whether the reversion happened spontaneously, with lifestyle or Metformin during 5.7 years of follow up.
- Those who remained pre DM despite intensive lifestyle had an even higher risk of developing DM than those on metformin or placebo.
Q2. How is prediabetes managed?

Medical and Surgical Interventions Shown to Delay or Prevent T2D

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Follow-up Period</th>
<th>Reduction in Risk of T2D (P value vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihyperglycemic agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin¹</td>
<td>2.8 years</td>
<td>31% (P&lt;0.001)</td>
</tr>
<tr>
<td>Acarbose²</td>
<td>3.3 years</td>
<td>25% (P=0.0015)</td>
</tr>
<tr>
<td>Pioglitazone³</td>
<td>2.4 years</td>
<td>72% (P&lt;0.001)</td>
</tr>
<tr>
<td>Rosiglitazone⁴</td>
<td>3.0 years</td>
<td>60% (P&lt;0.0001)</td>
</tr>
<tr>
<td>Weight loss interventions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orlistat⁵</td>
<td>4 years</td>
<td>37% (P=0.0032)</td>
</tr>
<tr>
<td>Phentermine/topiramate⁶</td>
<td>2 years</td>
<td>79% (P&lt;0.05)</td>
</tr>
<tr>
<td>Bariatric surgery⁷</td>
<td>10 years</td>
<td>75% (P&lt;0.001)</td>
</tr>
</tbody>
</table>

Lifestyle modification should be used with all pharmacologic or surgical interventions.

T2D, type 2 diabetes.

Multidisciplinary group of 48 international clinicians/scholars (75% non surgeons) including representatives of leading DM organizations, reviewed data from January 2005 to September of 2015.

Given its role in metabolic regulation, the GI tract constitutes a meaningful target to manage T2DM. Numerous clinical trials, albeit mostly short term/midterm, demonstrate that metabolic surgery achieves excellent glycemic control, and reduces CV RFs. Although additional studies are needed to further demonstrate long-term benefits, there is sufficient clinical and mechanistic evidence to support metabolic surgery among anti diabetes interventions for people with T2DM and obesity. Available data, based predominantly on modeling studies, suggest that bariatric/metabolic surgery is also cost effective, especially in patients with T2DM.
BMI $\geq 40$ (Class III) Bariatric Surgery **Recommended regardless of glycemic control** (Asian 37.5)

- BMI 35-39.9 (Class II) & inadequate glycemic control Bariatric Surgery **Recommended** (Asian 32.5 – 37.5)

- BMI 30-34.9 (Class I) & inadequate glycemic control Bariatric Surgery **Considered** (Asian 27.5 to 32.5)

- For pts of Asian descent subtract 2.5 kg/m² from above BMI recommendations

- Surgery should be performed in only high volume centers with multidisciplinary teams, who understand and are experienced in DM and GI surgeries with capability for long term follow up (mortality 0.1 to 0.5% and major complx 2 to 6%)

- Diabetes Care June 2016
Type 2 Diabetes Treatment Algorithm

Obese with type 2 diabetes
BMI ≥40 (Asian ≥37.5)

- Class III
  BMI ≥40
  (Asian ≥37.5)
  Rapid assessment for metabolic surgery
  - Poor glycemic control
    - Recommend metabolic surgery
  - Good glycemic control
    - Consider metabolic surgery

Not obese with type 2 diabetes
BMI <30† (Asian <27.5)

- Class I
  BMI 30-34.9
  (Asian 27.5-32.4)
  Lifestyle and medical therapy
  - Poor glycemic control
    - Nonsurgical treatment
  - Good glycemic control

- Class II
  BMI 35-39
  (Asian 32.5-37.4)
  Lifestyle and medical therapy
  - Poor glycemic control
  - Good glycemic control

*Including injectable medications and insulin

Patient Selection for Metabolic Surgery for the Treatment of Type 2 Diabetes

Contraindications for metabolic surgery:
- Type 1 diabetes diagnosis*
- Current drug or alcohol abuse
- Uncontrolled psychiatric illness
- Lack of comprehension of the risks/benefits, expected outcomes, alternatives
- Lack of commitment to nutritional supplementation, long-term follow-up
- In adolescent patients, GI surgery is inappropriate

Metabolic surgery is recommended as a treatment option in patients with:
- Class III obesity (BMI ≥40 kg/m²)† regardless of the level of glycemic control or complexity of glucose-lowering regimens
- Class II obesity (BMI 35.0-39.9)† with poor glycemic control despite lifestyle and optimal medical therapy

Metabolic surgery may be considered as a treatment option in patients with:
- Class I obesity (BMI 30.0-34.9)† with poor glycemic control despite optimal medical treatment by oral or injectable medications

*Unless surgery is otherwise indicated, such as for severe obesity
†BMI thresholds should be reconsidered depending on ancestry; reduce by 2.5 for Asian patients
GI=gastrointestinal

RCT data showing consistent superior efficacy of Surgery over med/lifestyle interventions for up to 5 years

<table>
<thead>
<tr>
<th>Study (Operation) [Follow-up; HbA1c, end point]</th>
<th>Surgery</th>
<th>Medical/Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parikh 2014 (RYGB/LAGB/SG) [6 mo; ≤6.5% off meds] (18)</td>
<td>13/20</td>
<td>0/24</td>
</tr>
<tr>
<td>Courcoulas 2014 (RYGB/LAGB) [12 mo; ≤6.5% off meds] (14)</td>
<td>18/41</td>
<td>0/17</td>
</tr>
<tr>
<td>Ding 2015 (LAGB) [12 mo; ≤6.5%] (22)</td>
<td>6/18</td>
<td>5/22</td>
</tr>
<tr>
<td>Halperin 2014 (RYGB) [12 mo; ≤6.5% off meds] (15)</td>
<td>11/19</td>
<td>3/19</td>
</tr>
<tr>
<td>Ikramuddin 2013 (RYGB) [12 mo; ≤7.0%] (13)</td>
<td>28/57</td>
<td>11/57</td>
</tr>
<tr>
<td>Liang 2013 (RYGB) [12 mo; ≤7.0% off meds] (16)</td>
<td>28/31</td>
<td>0/70</td>
</tr>
<tr>
<td>Schauer 2012 (RYGB/SG) [12 mo; ≤6.0%] (12)</td>
<td>34/99</td>
<td>0/41</td>
</tr>
<tr>
<td>Cummings 2016 (RYGB) [12 mo; ≤6.5% off meds] (23)</td>
<td>9/15</td>
<td>1/17</td>
</tr>
<tr>
<td>Dixon 2008 (LAGB) [24 mo; ≤6.2% off meds] (10)</td>
<td>22/29</td>
<td>4/26</td>
</tr>
<tr>
<td>Ikramuddin 2015 (RYGB) [24 mo; ≤7.0%] (21)</td>
<td>26/60</td>
<td>8/59</td>
</tr>
<tr>
<td>Mingrone 2012 (RYGB/BPD) [24 mo; ≤6.5% off meds] (11)</td>
<td>34/40</td>
<td>0/20</td>
</tr>
<tr>
<td>Wentworth 2014 (LAGB) [24 mo; ≤7.0%] (17)</td>
<td>12/23</td>
<td>2/25</td>
</tr>
<tr>
<td>Courcoulas 2015 (RYGB/LAGB) [36 mo; ≤6.5% off meds] (24)</td>
<td>14/37</td>
<td>0/14</td>
</tr>
<tr>
<td>Schauer 2014 (RYGB/SG) [36 mo; ≤6.0%] (19)</td>
<td>27/97</td>
<td>0/40</td>
</tr>
<tr>
<td>Mingrone 2015 (RYGB/BPD) [60 mo; ≤6.5% off meds] (20)</td>
<td>19/38</td>
<td>0/15</td>
</tr>
</tbody>
</table>

Fixed-Effects Model

| | | | 624 | 466 | 100.0% | 8.45 [6.44, 11.10] |

Heterogeneity: $\chi^2 = 45.43$, df = 14 ($p < 0.0001$); $I^2 = 69$

Test for overall effect: $Z = 15.36$ ($p < 0.00001$)
11 RCTs/ Median A1c drop of 2 % for surgery vs 0.5% medical/ Final A1c in surgical groups was near 6%
11 RCTs Change from baseline A1c

B

Mean baseline BMI ≤35 kg/m²
Mean baseline BMI >35 kg/m²

Change in HbA₁c

Surgery

Medical/Lifestyle

Wentworth 2014
Liang 2013
Parikh 2013
Ikrumuddin 2013
Courcoulas 2014
Courcoulas 2014
Halpern 2014
Ding 2015
Dixon 2008
Schauer 2012
Schauer 2012
Cummings 2016
Mingrone 2012
Mingrone 2012
# Types of Metabolic Surgery Procedures for Treating Type 2 Diabetes

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>RYGB (gastric bypass)</td>
<td>More favorable risk-benefit profile vs other options in most patients with type 2 diabetes</td>
</tr>
<tr>
<td>Vertical sleeve gastrectomy (VSG)</td>
<td>Effective weight loss</td>
</tr>
<tr>
<td></td>
<td>Major improvement of type 2 diabetes in short to medium term (1-3 years – longer-term studies required)</td>
</tr>
<tr>
<td></td>
<td>Valuable option for patients concerned about risk of operations with bowel diversion</td>
</tr>
<tr>
<td>Laparoscopic adjustable gastric banding (LAGB)</td>
<td>Effective in improving glycemia in patients with obesity and type 2 diabetes primarily by causing weight loss</td>
</tr>
<tr>
<td></td>
<td>Greater risk for reoperation/revision due to failure, complications</td>
</tr>
<tr>
<td>Biliopancreatic diversion (BPD)</td>
<td>Most complex surgery – most effective for glycemic control/weight loss but risk-benefit profile is less favorable</td>
</tr>
<tr>
<td></td>
<td>Significant risk of nutritional deficiencies</td>
</tr>
<tr>
<td></td>
<td>Highest perioperative morbidity/mortality</td>
</tr>
<tr>
<td></td>
<td>Should be considered only in patients with BMI &gt;60</td>
</tr>
</tbody>
</table>

*RYGB = Roux en-Y gastric bypass*
Adjustable Gastric Band  
Roux-en-Y Gastric Bypass  
Vertical Sleeve Gastrectomy
Baseline vs final A1c following surgery

![Baseline vs final A1c following surgery](image)

- LAGB Baseline
- VSG Baseline
- RYGB Baseline
- BPD Baseline
- Surgery Outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wentworth</td>
<td>2014</td>
</tr>
<tr>
<td>Courcoulas</td>
<td>2014</td>
</tr>
<tr>
<td>Ding</td>
<td>2015</td>
</tr>
<tr>
<td>Dixon</td>
<td>2008</td>
</tr>
<tr>
<td>Schauer</td>
<td>2012</td>
</tr>
<tr>
<td>Liang</td>
<td>2013</td>
</tr>
<tr>
<td>Parikh</td>
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<td>Mingrone</td>
<td>2012</td>
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<td>2012</td>
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</tbody>
</table>
How much weight loss?

- 5-10% achieved with lifestyle reduces CVD RFs, prevents or delays DM, and improves other health outcomes of obesity
- Clinically meaningful is $\geq 5\%$
- Long term weight maintenance of loss is difficult
- There are now multiple medications approved by the FDA to treat weight
- FDA indications considering meds if BMI $\geq 27$ with complications of wt, and if $\geq 30$
Why Do Obese Patients Get Worse Care? Many Doctors Don’t See Past the Fat
By GINA KOLATA
SEPT. 25, 2016
FDA approved medications for weight loss

- Xenical (Orlistat) – longterm
- Diethylpropion (Tenuate)
- Lorcaserin (Belviq) - longterm
- Wellbutrin/Naltrexone (Contrave) –longterm
- Phentermine (adipex P, Fastin)
- Phentermine/Topamax (Qysmia) – longterm
- Liraglutide (Saxenda) - longterm

- Combine with lifestyle changes, with FUV monthly x first 3 months then every 3 months
Assessing Efficacy and Safety of Weight Loss Medications

**Effective**
- Weight loss ≥5% body weight at 3 months and safe

**Ineffective**
- Weight loss <5% at 3 months
- Safety or tolerability issue

- Continue medication
- Discontinue medication
  - Seek alternate medication or refer for alternative therapy

Treating Patients With Type 2 Diabetes Who Are Overweight or Obese

- Use antihyperglycemic medications that promote weight loss or weight neutrality
  - GLP-1 receptor agonists
  - SGLT2 inhibitors
  - Metformin
- DPP-4 inhibitors (weight neutral)
- Pramlintide

- Type 2 patients who require insulin:
  - Add metformin, pramlintide, or GLP-1 RA to mitigate insulin-associated weight gain
  - First-line insulin: basal (consider prior to premixed or combination insulin therapy)

- Type 2 diabetes & hypertension:
  - ACEIs, ARBs, calcium channel blockers preferred over beta-adrenergic blockers

*Liraglutide is the only GLP-1 receptor agonist approved by the FDA for weight loss in the United States
*SGLT2 inhibitors are not approved by the FDA for weight loss in the United States
*Metformin is not approved by the FDA for weight loss in the United States
*Pramlintide is not approved by the FDA for weight loss in the United States

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

doi: 10.1210/jc.2014-3415
Breaking the cycle of Obesity and Diabetes

- Genetic and Epigenetics Obesity/Gestational DM/Increased Obesity and DM in offspring
- Public Health Policy
- School Interventions
- Food Industry
SUGAR IS THE OLD CRACK
Big Sugar's Sweet Little Lies
How the industry kept scientists from asking: Does sugar kill?

GARY TAUBES AND CRISTIN KEARNS

COUZENS NOVEMBER/DECEMBER 2012 ISSUE
2016 US Dietary Guidelines

- Average American gets 25 teaspoons of added sugar per day, 100% more than recommended, = 500 calories per day = 3500 calories per week = 1 pound of weight per week
- Goal is not more than 12 tsp per day in men
- Not more than 10 tsp per day in women
- Not more than 6 tsp per day in children
- One can of Coke is 10 teaspoons
- Kids fruit juice < 6mos none, 1 to 6 yo 4 to 6 oz, 7 to 18 yo 8 to 12 oz (high fructose corn syrup linked to fatty liver, obesity and insulin resistance)
2016 American Dietary Habits

- 70% above the added sugar recommendations
- 71% above the saturated fat intake
- 89% above the sodium intake
- 87% below the vegetable goal intake
- 75% below the fruit goal intake
THANK YOU!
# Preoperative Workup for Metabolic Surgery for the Treatment of Type 2 Diabetes

**Patient evaluation**

*Grade U*

- Include assessment of endocrine, metabolic, physical, nutritional, and psychological health

**Evaluation**

*Grade A*

- Include routine clinical tests and diabetes-specific metrics
- Recommended tests:
  - Standard preoperative tests used for GI surgery at individual providers’ institution
  - Tests to characterize current diabetes status – eg, A1C, FPG, lipid panel
  - Tests to distinguish type 1 from type 2 – eg, fasting C-peptide, anti-GAD antibodies

**Pre-surgery**

*Grade A*

- Improve glycemic control!
- Reduces risk for postoperative infection due to hyperglycemia

<table>
<thead>
<tr>
<th>Study (Operation) [Follow-up; HbA\text{1c} end point]</th>
<th>Glyc. Endp. N</th>
<th>Glyc. Endp. N</th>
<th>Weight</th>
<th>Peto, Fixed, 95% CI</th>
<th>Peto Odds Ratios</th>
</tr>
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<tbody>
<tr>
<td>Wentworth 2014 (LAGB) [24 mo; ≤7.0%] (17)</td>
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<td>4.9%</td>
<td>8.11 [2.37, 27.84]</td>
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<td>31</td>
<td>8.4%</td>
<td>86.76 [33.89, 222.08]</td>
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<td>20</td>
<td>4.5%</td>
<td>21.15 [5.85, 76.51]</td>
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<td>28</td>
<td>57</td>
<td>12.5%</td>
<td>3.72 [1.72, 8.04]</td>
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</tr>
<tr>
<td>Ikramuddin 2015 (RYGB) [24 mo; ≤7.0%] (21)</td>
<td>26</td>
<td>60</td>
<td>11.8%</td>
<td>4.25 [1.92, 9.38]</td>
<td></td>
</tr>
<tr>
<td>Courcoulas 2014 (RYGB/LAGB) [12 mo; ≤6.5% off meds] (14)</td>
<td>18</td>
<td>41</td>
<td>5.1%</td>
<td>7.51 [2.24, 25.21]</td>
<td></td>
</tr>
<tr>
<td>Courcoulas 2015 (RYGB/LAGB) [36 mo; ≤6.5% off meds] (24)</td>
<td>14</td>
<td>37</td>
<td>4.0%</td>
<td>6.44 [1.65, 25.21]</td>
<td></td>
</tr>
<tr>
<td>Halperin 2014 (RYGB) [12 mo; ≤6.5% off meds] (15)</td>
<td>11</td>
<td>19</td>
<td>4.4%</td>
<td>5.82 [1.59, 21.39]</td>
<td></td>
</tr>
<tr>
<td>Ding 2015 (LAGB) [12 mo; ≤6.5%] (22)</td>
<td>6</td>
<td>18</td>
<td>3.9%</td>
<td>1.68 [0.42, 6.66]</td>
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</tr>
<tr>
<td>Dixon 2008 (LAGB) [24 mo; ≤6.2% off meds] (10)</td>
<td>22</td>
<td>29</td>
<td>6.7%</td>
<td>10.83 [3.79, 30.96]</td>
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</tr>
<tr>
<td>Schauer 2012 (RYGB/SG) [12 mo; ≤6.0%] (12)</td>
<td>34</td>
<td>99</td>
<td>10.4%</td>
<td>6.39 [2.74, 14.88]</td>
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<tr>
<td>Schauer 2014 (RYGB/SG) [36 mo; ≤6.0%] (19)</td>
<td>27</td>
<td>97</td>
<td>8.7%</td>
<td>5.73 [2.28, 14.42]</td>
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</tr>
<tr>
<td>Cummings 2016 (RYGB) [12 mo; ≤6.5% off meds] (23)</td>
<td>9</td>
<td>15</td>
<td>3.4%</td>
<td>11.48 [2.63, 50.13]</td>
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<tr>
<td>Mingrone 2012 (RYGB/BPD) [24 mo; ≤6.5% off meds] (11)</td>
<td>34</td>
<td>40</td>
<td>6.4%</td>
<td>30.08 [10.28, 88.06]</td>
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<tr>
<td>Mingrone 2015 (RYGB/BPD) [60 mo; ≤6.5% off meds] (20)</td>
<td>19</td>
<td>38</td>
<td>4.9%</td>
<td>8.44 [2.46, 29.01]</td>
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</tbody>
</table>

**Fixed-Effects Model**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>624</td>
<td>466</td>
<td>100.0%</td>
<td>8.45 [6.44, 11.10]</td>
</tr>
</tbody>
</table>

**Heterogeneity:** Chi² = 45.43, df = 14 (P < 0.0001); I² = 69%

**Test for overall effect:** Z = 15.36 (P < 0.00001)
<table>
<thead>
<tr>
<th>Study (Operation) [Follow-up; HbA&lt;sub&gt;1c&lt;/sub&gt; end point]</th>
<th>Surgery</th>
<th>Medical/Lifestyle</th>
<th>Mean Differences in HbA&lt;sub&gt;1c&lt;/sub&gt; Mean Differences in HbA&lt;sub&gt;1c&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parikh 2014 (RYGB/LAGB/SG) [6 mo; ≤6.5% off meds] (18)</td>
<td>6.2 0.9 20</td>
<td>7.8 1.7 24</td>
<td>6.1% -1.60 [-2.39, -0.81]</td>
</tr>
<tr>
<td>Courcoulas 2014 (RYGB/LAGB) [12 mo; ≤6.5% off meds] (14)</td>
<td>6.6 0.8 41</td>
<td>7 0.9 17</td>
<td>6.9% -0.40 [-0.89, 0.09]</td>
</tr>
<tr>
<td>Ding 2015 (LAGB) [12 mo; ≤6.5%] (22)</td>
<td>7.17 0.3 18</td>
<td>7.15 0.28 22</td>
<td>7.5% 0.02 [-0.16, 0.20]</td>
</tr>
<tr>
<td>Halperin 2014 (RYGB) [12 mo; ≤6.5% off meds] (15)</td>
<td>6.2 1.4 19</td>
<td>8.8 1 19</td>
<td>6.1% -2.60 [-3.37, -1.83]</td>
</tr>
<tr>
<td>Ikramuddin 2013 (RYGB) [12 mo; ≤7.0%] (13)</td>
<td>6.3 0.9 57</td>
<td>7.8 1.5 57</td>
<td>7.0% -1.50 [-1.95, -1.05]</td>
</tr>
<tr>
<td>Liang 2013 (RYGB) [12 mo; ≤7.0% off meds] (16)</td>
<td>6 0.3 31</td>
<td>7.6 1.4 70</td>
<td>7.3% -1.60 [-1.94, -1.26]</td>
</tr>
<tr>
<td>Schauer 2012 (RYGB/SG) [12 mo; ≤6.0%] (12)</td>
<td>6.5 0.95 99</td>
<td>7.5 1.8 41</td>
<td>6.7% -1.00 [-1.58, -0.42]</td>
</tr>
<tr>
<td>Cummings 2016 (RYGB) [12 mo; ≤6.5% off meds] (23)</td>
<td>6.4 1.6 15</td>
<td>6.9 1.3 17</td>
<td>5.3% -0.50 [-1.52, 0.52]</td>
</tr>
<tr>
<td>Dixon 2008 (LAGB) [24 mo; ≤6.2% off meds] (10)</td>
<td>6 0.8 30</td>
<td>7.2 1.4 30</td>
<td>6.7% -1.20 [-1.78, -0.62]</td>
</tr>
<tr>
<td>Ikramuddin 2015 (RYGB) [24 mo; ≤7.0%] (21)</td>
<td>6.5 1.6 56</td>
<td>8.4 2.9 54</td>
<td>5.8% -1.90 [-2.78, -1.02]</td>
</tr>
<tr>
<td>Mingrone 2012 (RYGB/BPD) [24 mo; ≤6.5% off meds] (11)</td>
<td>5.65 0.95 20</td>
<td>7.69 0.57 20</td>
<td>7.0% -2.04 [-2.53, -1.55]</td>
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<tr>
<td>Wentworth 2014 (LAGB) [24 mo; ≤7.0%] (17)</td>
<td>6.1 0.8 23</td>
<td>7.3 1.4 25</td>
<td>6.5% -1.20 [-1.84, -0.56]</td>
</tr>
<tr>
<td>Courcoulas 2015 (RYGB/LAGB) [36 mo; ≤6.5% off meds] (24)</td>
<td>7.1 0.4 38</td>
<td>7.2 0.4 14</td>
<td>7.5% -0.10 [-0.35, 0.15]</td>
</tr>
<tr>
<td>Schauer 2014 (RYGB/SG) [36 mo; ≤6.0%] (19)</td>
<td>6.85 1.3 97</td>
<td>8.4 2.2 40</td>
<td>6.3% -1.55 [-2.28, -0.82]</td>
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<tr>
<td>Mingrone 2015 (RYGB/BPD) [60 mo; ≤6.5% off meds] (20)</td>
<td>6.55 0.5 38</td>
<td>6.9 0.6 15</td>
<td>7.3% -0.35 [-0.69, -0.01]</td>
</tr>
</tbody>
</table>

Random-Effects Model

Heterogeneity: $\tau^2 = 0.63; \chi^2 = 200.88, df = 14 \; (P < 0.00001); I^2 = 93\%$

Test for overall effect: $Z = 5.20 \; (P < 0.00001)$
BMI < 35 T2DM remission

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgery Remission</th>
<th>Surgery N</th>
<th>Control Remission</th>
<th>Control N</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%–CI</th>
<th>W(fixed)</th>
<th>W(random)</th>
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<tbody>
<tr>
<td>Observational</td>
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<tr>
<td>Scopinaro 2011 (BPD)</td>
<td>9</td>
<td>30</td>
<td>0</td>
<td>38</td>
<td>13.12</td>
<td>9.0%</td>
<td>[3.23; 53.31]</td>
<td>11.7%</td>
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<tr>
<td>Abbatini 2012 (SG)</td>
<td>8</td>
<td>9</td>
<td>0</td>
<td>9</td>
<td>29.96</td>
<td>5.4%</td>
<td>[4.92; 182.55]</td>
<td>9.2%</td>
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</tr>
<tr>
<td>Scopinaro 2014 (RYGB)</td>
<td>5</td>
<td>20</td>
<td>0</td>
<td>27</td>
<td>13.12</td>
<td>5.1%</td>
<td>[2.05; 83.86]</td>
<td>8.9%</td>
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<tr>
<td>Fixed effect model</td>
<td>59</td>
<td>74</td>
<td></td>
<td></td>
<td>16.49</td>
<td>19.5%</td>
<td>[6.37; 42.69]</td>
<td></td>
<td>29.8%</td>
</tr>
<tr>
<td>Random effects model</td>
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<td></td>
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<tr>
<td>Dixon 2008 (AGB)</td>
<td>22</td>
<td>29</td>
<td>4</td>
<td>26</td>
<td>10.83</td>
<td>16.0%</td>
<td>[3.79; 30.96]</td>
<td>14.2%</td>
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</tr>
<tr>
<td>Liang 2013 (RYGB)</td>
<td>28</td>
<td>31</td>
<td>0</td>
<td>70</td>
<td>86.76</td>
<td>20.0%</td>
<td>[33.89; 222.08]</td>
<td>15.0%</td>
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<tr>
<td>Courcoulas 2014 (RYGB/AGB)</td>
<td>18</td>
<td>41</td>
<td>0</td>
<td>17</td>
<td>7.51</td>
<td>12.0%</td>
<td>[2.24; 25.21]</td>
<td>13.0%</td>
<td></td>
</tr>
<tr>
<td>Schauer 2014 (RYGB/SG)</td>
<td>27</td>
<td>97</td>
<td>0</td>
<td>40</td>
<td>5.73</td>
<td>20.8%</td>
<td>[2.28; 14.42]</td>
<td>15.2%</td>
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<tr>
<td>Wentworth 2014 (AGB)</td>
<td>12</td>
<td>23</td>
<td>2</td>
<td>25</td>
<td>8.11</td>
<td>11.6%</td>
<td>[2.37; 27.84]</td>
<td>12.8%</td>
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<tr>
<td>Fixed effect model</td>
<td>221</td>
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<td>14.00</td>
<td>80.5%</td>
<td>[8.76; 22.37]</td>
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<td>Random effects model</td>
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<tr>
<td>Fixed effect model</td>
<td>280</td>
<td>252</td>
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<td>14.45</td>
<td>100%</td>
<td>[9.49; 22.01]</td>
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<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2$-squared=0%, $tau^2$-squared=0, $p=0.7481$

Heterogeneity: $I^2$-squared=80.1%, $tau^2$-squared=1.165, $p=0.0005$

Heterogeneity: $I^2$-squared=66.2%, $tau^2$-squared=0.7439, $p=0.0042$
Choosing Nutritional Therapy for Obesity

- Nutritional approaches for weight loss typically focus on the manipulation of the three macronutrients: protein, fat, or carbohydrate

- Very low-calorie diets contain less than 800 kcal/day and require close medical supervision for safety reasons

- Low calorie diets range from 1200-1800 kcal/day (1200-1500 for women, 1500-1800 for men).

- Restricting dietary fat leads to a greater reduction in total and LDL cholesterol, whereas restricting dietary carbohydrate leads to a greater reduction in serum triglycerides and an increase in HDL-cholesterol

- Reduction of carbohydrates can lead to a greater reduction in serum glucose and hemoglobin A1C

Reference/s: [8] [55] [91] [93]
Recommendations for Preventing or Delaying Type 2 Diabetes

Individuals with prediabetes: IGT, IFG, or A1C 5.7%-6.4%
Refer to intensive diet & physical activity behavior counseling program targeting
- Weight loss (7% of body weight)
- Increased physical activity (≥150 min/week moderate activity)

Consider metformin therapy for type 2 diabetes prevention in individuals with prediabetes
Especially in presence of
- BMI >35 kg/m²
- Age <60 years
- Women with prior GDM

At least annual monitoring of individuals with prediabetes
Screen for and treat modifiable CVD risk factors: obesity, hypertension, dyslipidemia

DSME & DSMS appropriate for prediabetes to receive education and support for diabetes prevention or delay

Metformin is not FDA approved in the United States for type 2 diabetes prevention
CVD=cardiovascular disease; GDM=gestational diabetes mellitus; IFG=impaired fasting glucose; IGT=impaired glucose tolerance

Screening for Type 2 Diabetes & Prediabetes in Asymptomatic Individuals

- Type 2 diabetes testing
  - Adults of any age who are overweight or obese* and who have ≥1 diabetes risk factor
  - Begin testing at age 45
  - Normal test? Repeat at ≥3-year intervals
- Prediabetes testing
  - A1C, FPG, or 2-h PG after 75-g OGTT
  - Identify & treat other CVD risk factors
  - Consider testing in children and adolescents who are overweight or obese and have ≥2 diabetes risk factors

*BMI ≥25 kg/m² or ≥23 kg/m² for Asian Americans
†African-American, Latino, Native American, Asian American, Pacific Islander
‡Severe obesity, acanthosis nigricans, polycystic ovarian syndrome

Postoperative Follow-Up for Metabolic Surgery for Treating Type 2 Diabetes

After surgery, patients should be managed by multidisciplinary teams.

Evaluations

- At least every 6 months during the first 2 postoperative years
- At least annually thereafter

Monitor glycemic control to avoid potential hyperglycemia relapse

Stable nondiabetic glycemic for < 5yrs

- Monitor for complications
- 5-yr remission: reduce monitoring frequency
- Persistent normoglycemia & no complications: cease screening for complications

In first 6 months, evaluate for glycemic control and tapering of diabetes medications

- After 6 months, further diabetes treatment should be dosed accordingly
- Discontinue meds only after stable normoglycemia for at least two 3-month A1C cycles

If glucose levels quickly reach normoglycemic range early post-surgery:

- Adjust therapy to prevent hypoglycemia

Ongoing and long-term monitoring of micronutrient status, nutritional supplementation, patient support

---

*Metformin, TZDs, GLP-1 receptor agonists, DPP-4 inhibitors, alpha-glucosidase inhibitors, and SGLT2 inhibitors are suitable for early postoperative diabetes care*

Metabolic surgery is recommended to treat:
- Type 2 diabetes in patients with Class II and Class III obesity when glycemia is inadequately controlled by lifestyle and optimal medical therapy.

Metabolic surgery should be considered to treat:
- Type 2 diabetes in patients with Class I obesity if glycemic control is poor despite optimal treatment with oral or injectable medications.

Surgery should be performed in high-volume centers with multidisciplinary teams that understand and are experienced in the management of diabetes and GI surgery.

Mortality rates with bariatric/metabolic operations are typically 0.1%-0.5%.

Major complications rates are 2%-6%, with minor complications in up to 15%.

Postoperative follow-up: Ongoing and long-term monitoring of micronutrient status, nutritional supplementation, and support.

Short/mid-term RCTs have shown that metabolic surgery achieves excellent glycemic control and reduces CV risk factors. Surgical value is more related to improved glucose homeostasis than weight loss. Additional studies are needed to demonstrate long-term benefits.

GI=gastrointestinal

Strategies for Long-Term Weight Loss

Use approved weight loss medications to:
- Ameliorate comorbidities
- Increase adherence to lifestyle
- Improve physical functioning

Individuals with:
- BMI ≥30
- BMI ≥27 with ≥1 weight-related comorbidity

Combined use of weight loss medication with lifestyle changes can produce greater weight loss and cardiometabolic improvements vs lifestyle alone.

Assess efficacy and safety of pharmacotherapy at least monthly for first 3 months, then at least every 3 months.

Weight loss medications available in the United States:
- Phentermine†‡
- Phentermine/topiramate
- Diethylpropion
- Lorcaserin
- Orlistat
- Naltrexon/bupropion
- Liraglutide

*Hypertension, dyslipidemia, type 2 diabetes, obstructive sleep apnea
†Use of phentermine and diethylpropion not recommended in patients with uncontrolled hypertension, history of CVD, history of cardiac arrhythmia, or seizures
‡Phentermine is not FDA approved for long-term use in the United States

Cumulative Incidence of Type 2 Diabetes.
Identify and Manage Concomitant Pharmacotherapy That Might Alter Body Weight

**Cardiovascular Medications**

May increase body weight:
- Some beta-blockers
  - Propranolol
  - Atenolol
  - Metoprolol
- Dihydropyridine ("dipine") calcium channel blockers
  - Nifedipine
  - Amlodipine
  - Felodipine

**Diabetes Mellitus Medications**

May increase body weight:
- Most insulins
- Sulfonylureas
- Thiazolidinediones
- Meglitinides

May decrease body weight:
- Metformin
- Glucagon-like peptide-1 agonists
- Sodium glucose co-transporter 2 inhibitors
- Alpha glucosidase inhibitors

Reference/s: [7] [18] [63] [76]

Obesity

* Leading cause of preventable death in the US
* The American Medical Association (AMA), World Health Organization (W.H.O.), along with National and International medical and scientific societies, recognize obesity as a chronic progressive disease
* U.S. spent $190 billion on obesity-related health care expenses in 2005
Obesity and Related Illness and Disease

- Migraines: 57% Resolved
- Dyslipidemia: 96% Resolved
- Depression: 55% Resolved
- Obstructive Sleep Apnea: 74-98% Resolved
- Asthma: 82% Improved or Resolved
- Cardiovascular Disease: 82% Risk Reduction
- Gerd: 72-98% Resolved
- Stress Urinary Incontinence: 44-88% Resolved
- In Women: Polycystic Ovarian Syndrome
  - 79% Resolution of Hirsutism
  - 100% Resolution Menstrual Dysfunction
- Venous Stasis Disease: 95% Resolved
- Degenerative Joint Disease: 41-76% Resolved
- Gout: 77% Resolved

Type II Diabetes: 83% Resolved
Quality of Life: Improved 95% in Patients
Metabolic Syndrome: 80% Resolved
Nutritional Therapy for Obesity

Energy consumption intended to cause negative calorie balance and loss of fat mass

Low-calorie diets: 1,200-1,800 kcal/day
- Restricted fat diet
  - Low-fat diet: <30% fat calories
  - Very low-fat diet: <10% fat calories
- Restricted carbohydrate diet
  - Low-glycemic diet:
  - Low-carbohydrate diet 50-150 grams/day
  - Very low carbohydrate diet <50 grams/day (with or without nutritional ketosis)

Very low-calorie diets: Less than 800 kcal/day
- Physician supervision recommended
- Recommended for shorter durations
- Full meal-replacement programs

Reference/s: [91] [92] [94] [95] [96] [97] [509]

<table>
<thead>
<tr>
<th>Weight Category</th>
<th>BMI Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>≤ 19</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>19 - 25</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>26 - 29</td>
<td>BMI 40 = approximately 100 lbs above ideal weight</td>
</tr>
<tr>
<td>Obese Class I</td>
<td>30 - 35</td>
<td></td>
</tr>
<tr>
<td>Obese Class II</td>
<td>35 - 39.9</td>
<td></td>
</tr>
<tr>
<td>Morbid Obesity</td>
<td>≥ 40</td>
<td></td>
</tr>
<tr>
<td>Super Obesity</td>
<td>≥ 50</td>
<td></td>
</tr>
</tbody>
</table>
IGT aged 20-79 by region 2010 and 2030
Long-Term Mortality after Gastric Bypass

* 7.1 years follow-up
* Overall deaths dropped 40% with Surgery
* Heart Disease Deaths dropped 56%
* Diabetes deaths dropped 92%
* Cancer deaths dropped 60%

Kearsten lost over 130 pounds along with multiple medical conditions and prescriptions pills!
Successful Weight Loss Surgery

Restrictive Procedures

- **Adjustable Gastric Band (AGB)**
  - Advanced platform Standard (APS) and Large (APL)
  - Realize C
- **Roux-en-Y Gastric Bypass (Roux 100 cm)**
- **Vertical Sleeve Gastrectomy (VSG)**
How Dangerous is Surgery?

* BOLD National Data – 57918 patients…
* Average in hospital mortality = 0.043%
* Average mortality 30 days = 0.089%
* **Surgery is less risky than the disease itself for 1 month**

DeMaria EJ et al SOARD 6(2010) 347-355
Screening Children for Type 2 Diabetes and Prediabetes

Consider for all children who are overweight* and have ≥2 of any of the following risk factors:

- Family history of type 2 diabetes in first- or second-degree relative
- Native American, African American, Latino, Asian American or Pacific Islander
- Signs of insulin resistance or conditions associated with insulin resistance†
- Maternal history of diabetes or GDM during child’s gestation

Test every 3 yrs using A1C beginning at age 10 or puberty onset

Children: age ≤18 yrs

*BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% ideal for height
†Acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome, or small-for-gestational-age birth weight
BMI=body mass index; GDM=gestational diabetes mellitus

McGill University: Compared 5,746 morbidly obese patients managed medically with 1,035 patients who underwent surgery

* sex, age, and duration matched

* Medical: 5-year mortality was 6.17%

* Surgical: 5-year mortality was 0.68%

>9 X

IRIS: Pioglitazone Lowers Rate of Progression to Diabetes Vs Placebo

Rate of progression to diabetes

HR = 0.48 (0.33, 0.69)  
P < 0.001  
7.7%  
(n = 149)

Pioglitazone  
(n = 1,937)

Placebo  
(n = 1,937)

3.8%  
(n = 73)

About the trial

Multicenter, double-blind trial assessed whether pioglitazone may benefit patients with cerebrovascular disease. N = 3,876 patients with recent ischemic stroke or TIA and insulin resistance randomized to pioglitazone (target 45 mg/d; n = 1,939) or placebo (n = 1,937). Primary outcome: fatal or nonfatal stroke, or MI over 4.8 years.

Absolute risk reduction

IRIS = Insulin Resistance Intervention after Stroke
MI = myocardial infarction; SBP = systolic blood pressure

1. Inzucchi SE, et al. Presented at the American Diabetes Association 75th Scientific Sessions, June 5-9, 2015; Boston, Massachusetts. 380-OR
Kernan WN, et al; for the IRIS Trial Investigators  
IRIS: Pioglitazone Lowers Risk for Stroke and TIA Vs Placebo

Rate of fatal or nonfatal stroke, or MI

<table>
<thead>
<tr>
<th>% Subjects</th>
<th>Pioglitazone (n=1,939)</th>
<th>Placebo (n=1,937)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9.0% (n=175)</td>
<td>11.8% (n=228)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR=0.76 (0.32, 0.93)  
P=0.007

Stroke*  
<table>
<thead>
<tr>
<th>% Subjects</th>
<th>Stroke (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.3% (n=150)</td>
</tr>
<tr>
<td>4</td>
<td>7.7% (n=123)</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

MI  
<table>
<thead>
<tr>
<th>% Subjects</th>
<th>MI (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.7% (n=78)</td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

About the trial
Multicenter, double-blind trial assessed whether pioglitazone may benefit patients with cerebrovascular disease. N=3,876 patients with recent ischemic stroke or TIA and insulin resistance randomized to pioglitazone (target 45 mg/d; n=1,939) or placebo (n=1,937). Primary outcome: fatal or nonfatal stroke, or MI over 4.8 years.

*First event only
IRIS=Insulin Resistance Intervention after Stroke  
MI=myocardial infarction

Kernan WN, et al; for the IRIS Trial Investigators.  
Lower All-Cause & CV Mortality With Empagliflozin Vs Placebo in High-Risk Patients

**EMPA-REG OUTCOME**

**EASD 2015**

- **Placebo (n=2,333)**
- **Empagliflozin (n=4,687)**

**Death from any cause**

<table>
<thead>
<tr>
<th>% Subjects</th>
<th>Placebo (8.3%)</th>
<th>Empagliflozin (5.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RRR=32%**

- **HR=0.68 (0.57-0.82)**
- **P<0.001**

**Death from CV causes**

<table>
<thead>
<tr>
<th>% Subjects</th>
<th>Placebo (5.9%)</th>
<th>Empagliflozin (3.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RRR=38%**

- **HR=0.62 (0.49-0.87)**
- **P<0.001**

39 patients would need to be treated over 3 years to prevent 1 death.

---

CV=cardiovascular; MI=myocardial infarction; RRR=relative risk reduction

### SEQUEL Subanalysis: Percent Weight Loss from Baseline at Wk 108 Primary Endpoint

- **PHEN 7.5 mg plus TPM 46 mg qd plus lifestyle modifications (n=115):** -10.9%
- **PHEN 15 mg plus TPM 92 mg qd plus lifestyle modifications (n=201):** -12.9%
- **Placebo qd plus lifestyle modifications (n=159):** -2.5%

Subjects: overweight/obese adults (BMI 27-45 kg/m²) with ≥2 weight-related comorbidities and prediabetes or metabolic syndrome

ER=extended release; PHEN=phentermine; TPM=topiramate

SEQUEL Subanalysis: Annualized Incidence of Type 2 Diabetes at Wk 108

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Annualized incidence rate at Wk 108</th>
<th>Subjects: overweight/obese adults (BMI 27-45 kg/m²) with ≥2 weight-related comorbidities and prediabetes or metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHEN 7.5 mg plus TPM 46 mg qd plus lifestyle modifications (n=115)</td>
<td>1.8 (P&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>PHEN 15 mg plus TPM 92 mg qd plus lifestyle modifications (n=201)</td>
<td>1.3 (P&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Placebo qd plus lifestyle modifications (n=159)</td>
<td>6.1</td>
<td></td>
</tr>
</tbody>
</table>

PHEN/TPM ER is not approved to prevent and/or reduce the progression of type 2 diabetes by the U.S. Food and Drug Administration. ER=extended release; PHEN=phentermine; TPM=topiramate.

**SEQUEL Subanalysis:**
Reduction of Type 2 Diabetes Incidence Related to Greater Weight Loss

<table>
<thead>
<tr>
<th>Weight loss at 108 Wks</th>
<th>Annualized type 2 diabetes incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>6.3</td>
</tr>
<tr>
<td>≥5% to &gt;10%</td>
<td>1.3</td>
</tr>
<tr>
<td>≥10% to &gt;15%</td>
<td>1.3</td>
</tr>
<tr>
<td>≥15%</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*P*<0.05 vs <5% weight loss for all comparisons

Greater weight loss associated with greater reduction in incidence of type 2 diabetes, regardless of treatment group

PHEN/TPM ER is not approved to prevent and/or reduce the progression of type 2 diabetes by the U.S. Food and Drug Administration.

ER=extended release; PHEN=phentermine; TPM=topiramate

Physical Activity Recommendations

**Adults with diabetes**

Physical activity recommendations

- ≥150 min/wk moderate-intensity aerobic activity (50%–70% max heart rate), spread over ≥3 days/wk with no more than 2 consecutive days without exercise
- Resistance training ≥2 times/wk (in absence of contraindications)*
- Reduce sedentary time: break up ≥90 mins spent sitting

Evaluate patients for contraindications prohibiting certain types of exercise before recommending exercise program†

Consider age and previous level of physical activity

**Children with diabetes, prediabetes**

Physical activity recommendations

- ≥60 min physical activity/day

*Adults with type 2 diabetes
†Eg, uncontrolled hypertension, severe autonomic or peripheral neuropathy, history of foot lesions, unstable proliferative retinopathy

# Treatment for Overweight and Obesity in Type 2 Diabetes

## Treatment recommendations for overweight and obese individuals with type 2 diabetes

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>25.0-26.9</th>
<th>27.0-29.9</th>
<th>30.0-34.9</th>
<th>35.0-39.9</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet, physical activity, behavioral therapy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pharmacologic therapy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Lower BMI cutoff points for Asian Americans: 23.0; 23.0-27.4; 27.5-37.4; 37.5

Lifestyle Changes for Obesity Management

Diet, physical activity, and behavior therapy designed to achieve 5% weight loss for overweight and obese individuals with type 2 diabetes who are motivated to lose weight:
- High-intensity interventions (≥16 sessions in 6 months)
- Focus on diet, physical activities, behavioral strategies to achieve a 500-750 kcal/day deficit

Individuals who achieve short-term weight loss:
- Prescribe long-term (≥1 yr) comprehensive weight management program
- At least monthly contact and ongoing monitoring of body weight
- Reduced calorie diet
- High levels of physical activity (200-300 min/wk)

To achieve long-term weight loss >5%:
- Short-term (3-month) high-intensity lifestyle interventions that use very low-calorie diets (≤800 kcal/day)
- Long-term comprehensive weight management counseling to maintain weight loss

# Screening for Prediabetes and Type 2 Diabetes

**US Preventive Services Task Force: Glucose Screening & Type 2 Diabetes**

**Screening for Prediabetes and Type 2 Diabetes**

- Adults aged 40-70 years who are overweight or obese
  - Screen for abnormal blood glucose as part of CV risk assessment
  - Offer or refer patients with abnormal glucose to intensive behavioral counseling interventions

<table>
<thead>
<tr>
<th>Screening tests</th>
<th>A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FPG</td>
</tr>
<tr>
<td></td>
<td>2-hr OGGT</td>
</tr>
</tbody>
</table>

*Confirm IFG, IGT, or type 2 diabetes diagnosis with repeat testing*

<table>
<thead>
<tr>
<th>Screening interval</th>
<th>Limited evidence on optimal rescreening interval for adults with initial normal glucose test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rescreening every 3 years may be reasonable</td>
</tr>
</tbody>
</table>

*S* Same test on a different day

FPG=fasting plasma glucose; OGTT=oral glucose tolerance test

---

Pharmacologic Therapy for Obesity Management

Glucose-lowering medications may affect weight in individuals with type 2 diabetes who are overweight or obese
- Consider weight effects before prescribing type 2 diabetes medications
- Minimize, where possible, the medications for comorbid conditions that are associated with weight gain

Among selected individuals with type 2 diabetes and
BMI $\geq 27$ kg/m²
- Weight loss medications may be effective as adjuncts to diet, physical activity, and behavioral counseling
- Balance potential benefits against risks

<5% weight loss after 3 months of weight loss medications or safety/tolerability issues:
- Discontinue medication
- Use alternative medication or treatment approach

### Blood Glucose Values Indicating Prediabetes or Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>IFG or IGT</th>
<th>Type 2 Diabetes</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1C</strong></td>
<td>5.7-6.4%</td>
<td>≥6.5%</td>
<td>&lt;5.7%</td>
</tr>
<tr>
<td><strong>FPG</strong></td>
<td>100-125 mg/dL (5.6-6.9 mmol/L)</td>
<td>≥126 mg/dL (≥7.0 mmol/L)</td>
<td>&lt;100 mg/dL 5.6 mmol/L</td>
</tr>
<tr>
<td><strong>2-Hr OGTT</strong></td>
<td>140-199 mg/dL (7.8-11.0 mmol/L)</td>
<td>≥200 mg/dL (≥11.1 mmol/L)</td>
<td>7.8 mmol/L</td>
</tr>
</tbody>
</table>

FPG=fasting plasma glucose; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; OGTT=oral glucose tolerance test

Management of Patients Who Are Overweight or Obese

Diet, exercise, and behavioral modification for all individuals with BMI ≥25

Adjuncts:
- Pharmacotherapy with BMI ≥27 with comorbidity or BMI >30
- Bariatric surgery with BMI ≥35 with comorbidity or BMI >40

History of unsuccessfully losing and maintaining weight with lifestyle?

Candidates for pharmacotherapy*

Assess efficacy and safety of pharmacotherapy at least monthly for first 3 months, then at least every 3 months

- Weight loss medications reinforce behavioral changes, promote adherence to lifestyle, and increase physical activity potential
- Lifestyle changes are needed when using a weight loss medication
  — Weight loss medications will not work alone
  — Addition of a weight loss medication to lifestyle will likely result in greater weight loss

*Must meet label indications

<table>
<thead>
<tr>
<th>Match Weight Loss Medications to Patient Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine and diethylpropion associated with BP elevations</td>
</tr>
<tr>
<td>Better choice: lorcaserin</td>
</tr>
<tr>
<td>Patient with obesity and depression taking an SSRI or SNRI</td>
</tr>
<tr>
<td>Better choice: phentermine/topiramate or phentermine alone</td>
</tr>
<tr>
<td>Orlistat likely safe in all instances</td>
</tr>
</tbody>
</table>

SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor

### Recommended Dosing for Obesity Treatment

- **Dose escalation based on efficacy and tolerability to the recommended dose**
  - Do not exceed upper-approved dose boundary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>120 mg TID</td>
<td>Favorable safety, efficacy profile at 120 mg TID</td>
</tr>
<tr>
<td>Phentermine/topiramate</td>
<td>7.5 mg/46 mg QD</td>
<td>Start at 3.75/23 QD for 2 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If tolerable, increase to 7.5/46</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>10 mg BID</td>
<td></td>
</tr>
<tr>
<td>Naltrexone/bupropion</td>
<td>8 mg/90 mg, 2 tablets BID</td>
<td>1 tablet in morning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 1 wk, add 1 tablet before dinner</td>
</tr>
<tr>
<td></td>
<td></td>
<td>As tolerated: increase to 2 tablets in morning 3rd wk, 2 tablets before dinner 4th wk to max 2 tablets BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If side effects, no increases until tolerable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinue if patient has not lost &gt;5% body weight at 12 wks</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>3.0 mg SC QD</td>
<td>Start at 0.6 mg SC QD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase by 0.6 per wk to 3.0 max</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No increases until tolerable if side effects</td>
</tr>
</tbody>
</table>

Refer to full manufacturer’s prescribing information for dosing indications.

BID=twice daily; QD=once daily; SC=subcutaneous; TID=three times daily.
Off-Label Long-Term Use of Phentermine

- Phentermine is the most widely prescribed weight loss medication
  - It is not approved for long-term use
  - No long-term controlled safety and efficacy data
- Reasonable for clinicians to prescribe phentermine long term providing the patient:
  1. Has no evidence of serious CVD
  2. Does not have serious psychiatric disease or history of substance abuse
  3. Knows that other weight-loss medications have documented efficacy and safety for long-term treatment and phentermine does not
  4. Does not demonstrate a clinically significant increase in pulse or BP while on phentermine
  5. Demonstrates significant weight loss while on phentermine
- Start at 7.5 or 15 mg QD
  - Increase only if no clinically significant weight loss
  - Follow patient at least monthly during escalation, at least every 3 months when on stable dose

Guidelines for Children and Adolescents With Type 2 Diabetes: Lifestyle Changes, Metformin for All

In all instances except ketosis, diabetic ketoacidosis, unclear distinction between types 1 and 2

- At type 2 diabetes diagnosis, initiate
  - Lifestyle changes
    - Nutrition interventions
    - Physical activity
  - Metformin
    - Confirm type 2 diabetes diagnosis prior to initiation
    - Start at low dose (500 mg/d) due to possible GI effects
    - Monitor for glycemic deterioration
    - Add insulin, other antihyperglycemic therapy if needed

GI=gastrointestinal
Metformin and insulin are the only antihyperglycemic agents approved for use in children/adolescents by the US Food and Drug Administration.

Guidelines for Children and Adolescents With Type 2 Diabetes: Weight Loss, Diet (2 of 2)

- Refer patients to registered dietician
- Provide nutrition education
  - Consume 3 planned meals with snacks/day
  - No eating while watching TV, using computer
  - Use smaller plates to make portions seem larger
  - Leave small amounts of food on plate

General Recommendations
- Eat regular meals and snacks
- Reduce portion size
- Choose calorie-free drinks (except milk)
- Increase fruit, vegetable intake
- Consume 3-4 servings low-fat dairy/day
- Limit
  - Juice to 1 cup/day
  - High-fat food intake
  - Frequency, size of snacks
- Reduce calories from fast-food meals

Guidelines for Children and Adolescents With Type 2 Diabetes: Physical Activity

- Moderate-to-vigorous exercise: ≥60 min/day
  - Create individualized plan with patient and family
  - Provide written exercise “prescription” describing ideal duration, intensity, and frequency
  - Include activities that can be incorporated into daily routine
- Limit nonacademic screen time to <2 hrs/day
  - Discourage presence of video screens, TVs in bedroom

Treatment to Fail Algorithm does not address physiology (Use of Insulin has gone up 500%)

At diagnosis:
Lifestyle + Metformin

- Lifestyle + Metformin + Basal Insulin
- Lifestyle + Metformin + Intensive Insulin
- Lifestyle + Metformin + Sulfonylurea
After Metformin DZ modifying therapy

GLP 1 (wt loss, - hypo, beta cell fx, durability > 4 yr)

SGLT 2 (wt loss, - hypo)

DPP4 (wt neutral, - hypo)

TZD (IS, beta cell, - hypo, wt durability greater than SU and metformin)

Basal Insulin (wt gain, + hypo, BS monitoring * consider adding GLP 1 to basal prior to going to prandial insulin)
Long-Term Mortality after Gastric Bypass

* 1984 to 2002
* 9949 Surgery
* 9628 Medical/Control
* 7925 matched for age, sex, and BMI

Adams TJ et al NEJM Volume 357:753-761
August 23, 2007 Number 8
Major Obstacle in maintaining control is progressive beta cell failure and hypoglycemia

Hypoglycemia is associated with increased mortality and morbidity

Hyperglycemia is the major factor responsible for microvascular complx, 1% decrease A1c 35 % decrease risk of complx