Diabetes and Obesity
Considerations for weight loss management in prevention and treatment of type 2 diabetes

Liana K. Billings, MD, MMSc
Adult Endocrinology Medical Group
Diabetes and Obesity Research Program
Clinical Assistant Professor of Medicine
Pritzker School of Medicine, University of Chicago

November 1, 2019

Healthcare for what’s next.
Disclosures

- Novo Nordisk – Consultant, Speaking Honoraria
- Sanofi – Consultant
- Lilly - Consultant
1. “Diabesity”
2. Diabetes prevention
3. Effects of weight loss in diabetes
4. Choosing anti-diabetes pharmacotherapy
5. Choosing surgery
6. Medication adjustment
By 2050 there will be roughly 84 million (21% of population)
Costs for diabetes in the US $327 billion in 2017

CDC, October 2019
Illinois
Health and Economic Burden

- Prevalence 9.9% = 971,000 people
- Incidence 66,000 new diagnosed cases/yr
- Total Cost $8,585,600,000 per year
Diabetes and Obesity Prevalence

% of Diabetes Among BMI > 25
150,000 patients

- Diabetes
- No Diabetes

30%
70%
The New England Journal of Medicine

REDUCTION IN THE Incidence OF Type 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

Diabetes Prevention Program Research Group*
Inclusion Criteria:
• >25 y/o
• Fasting glucose 95-124 mg/dl
• 2hr post 75g OGTT 140-199 mg/dl

Diabetes Prevention Program (DPP)
Study Design

3234 Subjects

Randomised 1:1:1

Mean 2.8 years

Metformin 850 mg BID

Intensive Lifestyle

Placebo BID

Endpoint: Diabetes Incidence

DPP.NEJM.2002
DPP: Standard vs Intensive Lifestyle

**Standard Lifestyle**
- Written Instructions
- 20-30 minute individual session
- Reference to healthy diets
- Increase exercise

**Intensive Lifestyle**
- Weight loss (7% body weight)
- Healthy low calorie, low-fat diet
- 150 minutes/week of moderate intensity physical activity
- 16-lesson curriculum in-person one-on-one during first 24 weeks
Weight loss by treatment group
Lifestyle group lost on average 7% body weight

DPP.NEJM.2002
DPP Results – Weight loss is important

Key take-away – Lower risk and low number needed to treat to prevent diabetes

- Risk of DM was:
  - 58% lower in Lifestyle
  - 31% lower in Metformin compared to placebo

- Number need to treat (NNT) to prevent DM:
  - 7 people in Lifestyle
  - 14 in Metformin

DPP.NEJM.2002
The participants in the Diabetes Prevention trial were randomized to standard of care with placebo pill, metformin 850mg twice daily, or lifestyle intervention. Compared to placebo the following interventions lowered diabetes risk as follows:

A) Metformin 20%, Lifestyle 10%
B) Metformin 10%, Lifestyle 30%
C) Metformin 31%, Lifestyle 58%
The participants in the Diabetes Prevention trial were randomized to standard of care with placebo pill, metformin 850mg twice daily, or lifestyle intervention. Compared to placebo the following interventions lowered diabetes risk as follows:

A) Metformin 20%, Lifestyle 10%
B) Metformin 10%, Lifestyle 30%
C) Metformin 31%, Lifestyle 58%
Long-term follow-up in DPP → DPPOS
10 years of follow-up since randomization

Risk of DM was:
35% lower in Lifestyle
18% lower in Metformin compared to placebo

DPPOS. *Lancet.* 2009
An illustration of metabolic memory

DPPOS. Lancet. 2009
Weight loss is worth the investment

Diabetes Incidence %

DPPOS. Lancet. 2015
Weight loss in diabetes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*
Inclusion Criteria:
• >45-75 y/o
• T2D
• BMI ≥ 25
• HbA1c ≤ 11%

Endpoint:
4P MACE Composite
CV death
Nonfatal MI
Nonfatal stroke
Hospitalization for angina

5145 Subjects

Control

Intensive Lifestyle

0 Randomised
1:1

Median 9.5 years
Stopped on the basis of futility

Look AHEAD. NEJM. 2013
Look AHEAD: No benefit in terms of 4P MACE

Look AHEAD. NEJM. 2013
A1c and weight loss in Look AHEAD

Look AHEAD. *NEJM*. 2013
Weight loss in T2D influences CKD risk
Lower cumulative risk of high-risk CKD in patients in the Intensive Arm

Outcome: High-risk CKD
- eGFR less than 30, or
- eGFR less than 45 and urine ACR at least 30
- eGFR less than 60 mL/min and urine ACR
- than 300
- Renal replacement therapy

Look AHEAD. Lancet Diabetes Endo. 2014
Magnitude of weight loss influence outcomes

Outcomes
- **Primary**: 4P MACE
- **Secondary**: 4P MACE plus
  - coronary artery bypass grafting
  - carotid endartectomy
  - percutaneous coronary intervention
  - hospitalization for CHF
  - PVD
  - total mortality

Choosing Anti-diabetes therapy that promote weight loss
Supported by ADA guidelines

GLP-1RA

SGLT2i/GLP-1RA (oral semaglutide)
GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN

ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

Either OR

GLP-1 RA with proven CVD benefit or SGLT2i with proven CVD benefit, if eGFR adequate

If HbA1c above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin
- T2D
- SU

If HbA1c above target

HF OR CKD PREDOMINATES

Either OR

SGT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate, add GLP-1 RA with proven CVD benefit

If HbA1c above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
- SU
- T2D
- Basal insulin

If HbA1c above target

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

If HbA1c above target

GLP-1 RA with good efficacy for weight loss

SGLT2i

If HbA1c above target

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

Without established ASCVD or CKD

COST IS A MAJOR ISSUE

If HbA1c above target

GLP-1 RA with good efficacy for weight loss

SGLT2i

If HbA1c above target

SU

If HbA1c above target

T2D

If HbA1c above target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider DPP-4i OR SGLT2i with lowest acquisition cost

If HbA1c above target

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
- SU
- T2D
- Basal insulin

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA, strongest evidence for liraglutide = exenatide extended release. For SGLT2i, evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
5. Low dose
6. Choose 1
7. Degludec / glargine U300 = glargine U100 / detemir = NPH insulin
8. Semaglutide = liraglutide = dulaglutide = exenatide = lixisenatide
9. If no specific comorbidities like, no established CVD, low risk of hypoglycemia, and lower

NorthShore University HealthSystem
Targeting the underlying pathophysiology
Actions of a GLP-1RA

- **BRAIN**
  - Decreased energy intake
  - Increased satiety

- **PANCREAS**
  - Glucose-dependent insulin and glucagon secretion
  - Insulin synthesis

- **LIVER**
  - Inhibition of hepatic glucose production

- **GI TRACT**
  - Inhibition of gastric emptying

**GLP-1RA**
- Exenatide
- Exenatide ER
- Liraglutide
- Lixisenatide
- Dulaglutide
- Semaglutide
- Semaglutide (Oral)

Weight change for GLP-1RAs: Head to Head

SGLT2 inhibitors
Block reabsorption of glucose at the proximal tubule of the kidney

- Canagliflozin
- Dapagliflozin
- Empagliflozin
- Ertugliflozin
- Sotagliflozin

Weight loss: 2-3 kg

Prevent weight gain when you are considering adding insulin

**Scenario #1**

HbA1c > 7% on oral medications

Next step: Basal insulin?

Study: DUAL V

**Scenario #2**

HbA1c > 7% on oral meds and basal

Next step: Bolus insulin?

Study: DUAL VII

Adding a GLP1RA can negate weight gain from insulin!

Consider fixed-ratio combination (iDegLira or IGlarLixi) or Insulin plus GLP1 alone
DUAL V: Glargine v iDegLira on oral med

HbA1c

Weight (kg)

Lingvay. JAMA. 2016
DUAL VII: Basal-bolus v iDegLira add on to basal

Billings LK. Diabetes Care. 2018
GLP-1RA and SGLT1i are effective in reducing composite MACE

Major Adverse Cardiac Events

MACE 3-Point Composite
• Non-fatal MI
• Non-fatal Stroke
• CV-related death

LEADER (Liraglutide)
SUSTAIN (Semaglutide)
REWIND (Dulaglutide)
EMPA-REG (Empagliflozin)
CANVAS (Canagliflozin)
Which medication reduced major adverse cardiovascular events in long-term cardiovascular outcome trials?

a) Liraglutide
b) Exenatide
c) Dulaglutide
d) Canagliflozin
e) Empagliflozin
f) a, b, c
g) a, c, d, e
h) d, e
Which medication reduced major adverse cardiovascular events in long-term cardiovascular outcome trials?

a) Liraglutide
b) Exenatide
c) Dulaglutide
d) Canagliflozin
e) Empagliflozin
f) a, b, c

**g)** a, c, d, e

h) d, e
Metabolic Surgery for weight loss and glucose management

Ikramuddin. *JAMA*. 2018
Medication adjustments when starting a low carbohydrate diet (LCD) <130 grams/day in T2D

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Hypo risk?</th>
<th>Clinical Suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas</td>
<td>Yes</td>
<td>Reduce (50%)/Stop; Promote weight gain</td>
</tr>
<tr>
<td>Insulin</td>
<td>Yes</td>
<td>Reduce/stop. Wean by 30-50%*</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>No</td>
<td>Continue**</td>
</tr>
<tr>
<td>Metformin</td>
<td>No</td>
<td>Continue</td>
</tr>
<tr>
<td>GLP-1RA</td>
<td>No</td>
<td>Continue</td>
</tr>
<tr>
<td>TZD</td>
<td>No</td>
<td>Stop if possible, promote weight gain</td>
</tr>
<tr>
<td>DPP-4i</td>
<td>No</td>
<td>Consider stop; Minimal efficacy; $$</td>
</tr>
<tr>
<td>SMBG/CGM</td>
<td>N/A</td>
<td>Ensure adequate testing for patients on hypo-risk meds</td>
</tr>
</tbody>
</table>

*Caution when reducing insulin if clinical suspicion of endogenous insulin insufficiency, keep 0.3u/kg/day
**SGLT2i have increased risk of DKA in insulin deficiency

Adapted. Murdoch. *Brit J of Gen Practice. 2019*
Thank you!

lbillings@northshore.org
diabetesresearch@northshore.org
Research Office 847-663-8346