Type 2 diabetes mellitus (T2DM) is closely associated with obesity, primarily through the link of insulin resistance. 87.5% of those with T2DM have overweight or obesity; over 60% have a BMI ≥30 kg/m². Insulin resistance can be fueled by poor diet quality and/or energy imbalance that favors weight gain. As individuals gain fat mass, the adipose tissue promotes a pro-inflammatory environment that further worsens insulin resistance. Therefore, effective treatment strategies for obesity in the setting of T2DM should address insulin resistance by altering energy balance and diet composition.

The primary goal of any treatment for obesity is to initiate and sustain a negative energy balance. The negative energy balance is primarily achieved through modification of calorie intake and increases in physical activity. Lifestyle modification with behavioral therapy can be an effective first step. Pharmacotherapy as an adjunct to lifestyle modification is effective for increasing the number of responders, the magnitude of response, and the duration of that response. Bariatric surgery is available as a treatment option for those with T2DM when the BMI is 35 kg/m² or higher. Weight loss interventions in T2DM can be done safely, but the clinician should manage the risk of hypoglycemia expectantly to avoid adverse events and the need for extra calories to resolve hypoglycemia.

Weight reduction in those with T2DM can lead to improved risk factor control and improved glycemic control. Some individuals can also achieve diabetes remission—defined as sustained normal glycemia without the need for antidiabetes medication. Predictors of increased probability of remission include younger age, shorter duration of diabetes, non-use of insulin, and larger amounts of weight loss. Surgical treatments are more likely to be associated with diabetes remission, but intensive medical weight loss can be effective as well.
Obesity Management in Patients with Diabetes

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Our Objectives Today

- Benefits of weight reduction for control of diabetes
- Strategies to create energy deficit in patients with diabetes
- Minimize risk of harm during weight loss
- Diabetes remission with weight loss

Key Points

- Individuals with Type 2 Diabetes (T2D) and Obesity should be advised to lose weight
- The benefits of weight loss include improved glycemic control with the potential for less medication
- Some people can achieve diabetes remission— likelihood is associated with the strategy and amount of weight lost achieved
- Weight loss can be done safely if we pay attention to the effects of calorie restriction, increased activity, and diet composition on insulin resistance

Type 2 Diabetes (T2DM) and Overweight/Obesity Are Linked

- 87.5% of those with T2DM are overweight/obese
- 43.5% have a BMI ≥ 30 kg/m²
- 17.8% have a BMI ≥ 40 kg/m²

The Link is Insulin Resistance

- Poor Diet Quality
- Energy imbalance
- Excess calorie intake
- Decreased physical activity
- Increased Adiposity
- Increased visceral fat mass
- Overweight/Obesity
- Liver: increased glucose production
- Muscle: altered glucose uptake

CDC National Diabetes Statistics Report, 2017

Age adjusted prevalence of obesity and diabetes by US state in 1994, 2003 and 2012

Disclosures

- Research support
  - Nestle Healthcare Nutrition
  - Vivus, Inc
- Consulting
  - Nestle Healthcare Nutrition
The Link is Insulin Resistance

Poor Diet Quality
- Energy Imbalance
- Excess calorie intake
- Decreased physical activity

Increased Adiposity
- Increased visceral fat mass
- Overweight/Obesity

Insulin Resistance
- Liver: increased glucose production
- Muscle: altered glucose uptake

Dysglycemia
- Pre Diabetes
- Type 2 Diabetes

Behavior Modification is Essential

Surgical Intervention

Primarily for BMI ≥ 40 or ≥ 35 with significant co-morbidities
- Following serious attempts at lifestyle modification

Bariatric Surgery Options
- Roux-en-Y gastric bypass
- Vertical sleeve gastrectomy

Pharmacotherapeutic options for weight management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Withdrawn</th>
<th>Currently available</th>
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</thead>
<tbody>
<tr>
<td>Fenfluramine, phentermine</td>
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<td></td>
</tr>
<tr>
<td>Sibutramine</td>
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<td></td>
</tr>
<tr>
<td>Phentermine*</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Orlistat</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Phentermine, topiramate ER</td>
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<td></td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Liraglutide 3.0 mg</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bupropion, naltrexone SR</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacotherapy can play a key role in improving adherence to a lifestyle change plan

Pharmacotherapy added to effective lifestyle intervention can:
- Increase the number of people who respond to lifestyle intervention
- Increase the magnitude of that response
- Increase the duration of that response

Effect of phentermine and topiramate ER on weight in patients with and without T2DM

Conquer 10-week data and SEQUEL T2DM subgroup 2-year data

- Mean reduction in HbA1c at week 108 was greater in T2DM phentermine and topiramate ER treated groups compared with placebo

Effect of naltrexone ER/bupropion on weight in patients with and without T2DM

Mean reduction in HbA1c was significantly greater in the T2DM naltrexone ER/bupropion treated group compared with placebo.

Naltrexone ER 32 mg/bupropion 360 mg

Placebo

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Change in weight (%)</th>
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<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>8</td>
<td>-6</td>
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<td>48</td>
<td>-17</td>
</tr>
<tr>
<td>56</td>
<td>-17</td>
</tr>
</tbody>
</table>

Change in weight (%)

COR-Diabetes: 56-week data


What are the indications for pharmacotherapy?

BMI = 27-29.9 kg/m² + co-morbid condition
BMI = 30+

When should pharmacotherapy be used?

1. Early hunger
2. Poor satiation
3. Persistent food thoughts
4. Strong hedonic response to food, eating
5. Less than robust response to dietary/PA plan

How long should pharmacotherapy be used?

INDEFINITELY

• Obesity is a chronic, relapsing disorder
• If treatment is withdrawn, the probability of weight regain increases

Intensive Medical Weight Management

• Case and Management Keys

Case: Ms. SJ

Presents with 6-year history of poorly controlled type 2 DM

BMI = 34 kg/m², initial HbA1c = 9.5%

Currently on 70 units per day of Lantus insulin + 15 units regular insulin AC

She will start on full meal replacement
Low calorie diet: 960 kcal/d, 56 g protein
Type 2 Diabetes

On initial presentation
1. Tightly controlled (HbA1c < 7%)
2. Moderate control (7-9%)
3. Poor control (>9%)

Tightly controlled
Discontinue all sulfonylureas
Likely able to quickly discontinue other meds
- Depends on duration of diabetes, weight loss response, activity
Consider metformin for maintenance

Moderate control
Can target improvement in control (HbA1c < 7) but need to avoid hypoglycemia
Discontinue secretagogues and/or insulin upon program initiation
- Substitute agents that are associated with weight loss or weight neutral if needed

Associated weight changes with T2DM meds

Weight gain: sulfonylureas, TZDs, insulin
Neutral: DPP IV inhibitors
Weight loss: metformin, SGLT-2 inhibitors, GLP-1 RA

Poor control
Improve control but minimize use of weight gain associated meds
- Decrease total dose of insulin by up to 50%
- Eliminate/decrease meal time dosing of short acting insulin
- Avoid dosing based on carbs per meal (not appropriate in low calorie setting)
- Substitute agents that are associated with weight loss or weight neutral if needed

Diabetes management options

Eliminate meal time insulin (~40% reduction in total insulin)
Drop Lantus when fasting blood sugars <126 (~20% reduction)
At later point, add agent that might allow for more rapid reduction of insulin e.g., metformin, DPP IV inhibitor, GLP-1 RA, SGLT-2 inhibitor
Diabetes Remission with Weight Reduction

The Question

Can the disease of diabetes be modified to a point of no longer being abnormal?

i.e., is it possible to put diabetes into remission with weight reduction, thereby modifying the progressive nature of the disease?

Definition of Remission

Achieving glycemia below the diabetic range in the absence of active pharmacologic or surgical (ongoing procedures such as repeated replacements of endoluminal devices) therapy.

Buse et al. Diabetes Care November 2009 vol. 32 no. 11 2133-2135

• Partial Remission
  • Sub-diabetic hyperglycemia of at least 1 year’s duration
  • A1C <6.5%
  • Fasting glucose 100–125 mg/dl

• Complete Remission
  • Return to normoglycemia of at least 1 year’s duration
  • A1C < 5.7%
  • Fasting glucose < 100 mg/dl

What types of therapies lead to diabetes remission?

• Prolonged remission
  • Maintenance of normoglycemia for 5 years’ duration

• Partial Remission
  • Intensive medical weight loss

• Complete Remission
  • Bariatric surgery

Buse et al. Diabetes Care November 2009 vol. 32 no. 11 2133-2135
STAMPEDE Trial

RCT of medical therapy vs. sleeve gastrectomy vs. RYGB

Followed for 5 years

N= 150, BMI 27-43, age 20-60

Results of the DIRECT trial

• RCT of intensive medical weight loss with total diet replacement (835-853 kcal/d) in primary care offices in England
• Comparison intervention: guideline driven practice
• N= 149 per group
  • 23 intervention practices
  • 29 control practices
• Endpoint: HbA1c < 6.5% after 2 months off diabetes meds = remission

• 46% of intervention group achieved remission
• 80% of those who lose 15 kg achieved remission
• Average weight loss at 1 year: 10 ± 8 kg in active intervention vs 1 ± 3.7 kg in control

What types of therapies lead to diabetes remission?

• Behavioral weight loss intervention
• From The Look AHEAD (Action for Health for Diabetes) study

The UI group was significantly more likely to experience any remission (partial or complete), with prevalences of 11.5% (95% CI, 10.1%-12.8%) during the first year and 7.3% (95% CI, 6.2%-8.4%) at year 4, compared with 2.0% for the DSE group at both time points. JAMA. 2012;308(23):2489-2496

Summary

• Diabetes and overweight/obesity are closely linked
• Improving weight with effective treatment strategies can lead to significant improvements in glycemia and even remission
• Effective strategies for weight control include behavioral, pharmacological, and surgical interventions

• To avoid adverse events, namely hypoglycemia, adjust medication treatment aggressively
• Larger volume weight loss is typically associated with remission
• Younger age, recent onset of diabetes, and nonuse of insulin are other predictors of remission
• Identify these patients and advise of the benefits of weight loss!