Treating Obesity in the Setting of Diabetes

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We have no conflict(s) with commercial interest companies to disclose.

Objectives

• Describe the treatment of obesity as a disease, including evidence-based comprehensive lifestyle programs
• Compare and contrast medical treatment options for patients with diabetes and obesity
• Discuss the results (breakthroughs and barriers) of the interprofessional obesity clinic initiative

Is Obesity a Disease????

• What is a disease?
  • A disorder of structure or function in a human, animal or plant, especially one that produces specific signs or symptoms that affect a specific location and is not simply a direct result of physical injury. (Oxford)

• Why is obesity not being considered a disease?
  • Lack of universal way to measure obesity
  • BMI is not accurate in all individuals
  • Being obese is not a guarantee to having other health problems
  • Hard to separate out what is caused by personal choice and what is related to genetics
  • Though this is true for many health conditions e.g. - cancers, CAD, hyperlipidemia
  • Some health care providers feel defining obesity as a disease may lead to discrimination
Obesity as a Disease

• Obesity is recognized as a disease by
  • American Medical Association (AMA) - 2013
  • World Health Organization (WHO)
  • World Obesity Federation
  • Canadian Medical Association
  • Obesity Canada

• The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) stated that "Obesity is a complex, adiposity based chronic disease" in their 2016 Obesity Clinical Practice Guidelines

What is Obesity?

• Obesity is a term used to describe excess body fat – and is an adiposity-based chronic disease – needs anthropometric measures and clinical complications to define and classify its severity.
• BMI
  • > or = 30 kg/m²
• Classifications
  • Class I: 30 – 34.9 kg/m²
  • Class II: 35 – 39.9 kg/m²
  • Class III: > 40 kg/m² (morbid obesity)

Obesity: Role of Hormones

• Ghrelin (gut hormone-primarily from stomach)
  • Has stimulatory effects on growth hormone release, food intake, and fat deposition
  • Inhibits insulin secretion and regulates gluconeogenesis and glycogenolysis

• Leptin (protein secreted by adipocytes)
  • Regulates energy homoeostasis, neuroendocrine function, and metabolism
  • Acts on the brain to regulate appetite
  • Involved in motivation for and reward of feeding
  • Interacts with brainstem to contribute to satiety
  • Often high in obese patients and they are often resistant to it

*Endocrine Practice 2016
*Annals of Internal Medicine, 2011
## Obesity: Role of Hormones

**Growth Hormone**
- Hormone made in the pituitary gland
- Stimulates release of the hormone somatomedin (somatotropin) by the liver which causes growth
- Excess growth hormone causes insulin resistance and hyperglycemia

*Nature Reviews Endocrinology, 2007*

**Cortisol (steroid hormone)**
- Regulate blood sugars and metabolism
- Reduce inflammation
- Assist with memory formation
- Control salt and water balance and blood pressure
- Elevated levels causes rapid weight gain in face, abdomen and chest
- "stress" hormone
  - Used to boost energy in fight-or-flight response and turn off non-vital functions at that time
  - Chronic stress can cause long-term exposure to cortisol, which can lead to obesity, heart disease, anxiety and depression

*Endocrine Society- hormone.org*

## Obesity Statistics

- Prevalence of obesity in 2015-16 was 39.8% of U.S. adults
- ~160 million Americans are either obese or overweight
- Nearly three-quarters of American men and more than 60% of women are obese or overweight
- In 2015, 30.3 million Americans, or 9.4% had diabetes, of these approximately 1.25 million American children and adults have type 1 diabetes

*Centers For Disease Control and Prevention (CDC), HealthData.org, American Diabetes Association*
Impact of Obesity

- Obesity and its sequelae are expensive to treat
  - Obesity-related conditions including heart disease, stroke, type 2 diabetes, and certain types of cancer are some of the leading causes of preventable, premature death
  - Estimated annual medical cost of obesity in the U.S. was $147 billion in 2008; medical cost for obese people was $1,429 higher than normal weight people
  - Diabetes patients have average annual medical costs of $16,752, of which about $9,601 is from diabetes. This is on average 2.3 times higher than someone without diabetes.

Impact of Obesity: Complications

- Pre-diabetes
- Diabetes Mellitus Type 2
- Dyslipidemia
- Hypertension (HTN)
- Cardiovascular Disease (CVD) and CVD mortality
- NAFLD/NASH
- PCOS
- Female Infertility

- Obstructive Sleep Apnea (OSA)
- Asthma and Reactive Airway Disease (RAD)
- Male hypogonadism
- Osteoarthritis
- Urinary stress incontinence
- Gastro-esophageal Reflux Disease (GERD)
- Depression

Obesity and Diabetes

- Overlap with diabetes – “Diabesity”
  - 34% of U.S. adults have obesity
  - more than 11% of U.S. adults have diabetes and prevalence expected to reach 21% by 2050
  - Obesity and weight gain were shown to adversely affect psychological well-being in patients with diabetes
    - Cause feelings of inadequacy
    - Negatively affect treatment satisfaction
    - These psychological effects were associated with greater noncompliance with therapy
  - Obesity can worsen dyslipidemia, HTN, and CVD risk in patients with and without diabetes
Obesity and Diabetes

T2DM is an end-stage disease arising from insulin resistance and progression of cardiometabolic disease.

Several studies found on average only 12% of patients had a normal body weight at diagnosis with DM2.

Obesity Management

- Weight loss of as little as 5% is linked to
  - Delay the progression from prediabetes to type 2 diabetes
  - Improve glycemic control
  - Reduce the need for glucose-lowering medications
- More likely to occur early in the natural history of type 2 diabetes
- Use of very low-calorie diets (<800) and total meal replacements may be prescribed for carefully selected patients by trained practitioners in medical care settings with close medical monitoring.

Diabetes Care 2019; Look AHEAD 2014; Endocrine Practice 2016

Obesity Management

- At each patient encounter, BMI should be calculated, documented and discussed with the patient
- Providers should assess each patient’s readiness to achieve weight-loss goals and intervention strategies
  - Interventions should be high intensity (> 16 sessions in 6 months)
    - Individual or group settings

Diabetes Care 2019
Obesity Management

- Physical Activity
- Behavioral Changes
- Meal Plan
- Weight Loss

Management Obesity

<table>
<thead>
<tr>
<th>Meal Plan</th>
<th>Physical Activity</th>
<th>Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reduce-calorie healthy meal plan</td>
<td>• Aerobic physical activity progressing to ≥30 minutes/week on 3–5 separate days</td>
<td>• Self-monitoring</td>
</tr>
<tr>
<td>• ~500–750 kcal daily deficit</td>
<td>• Resistance exercise: involving major muscle groups: 2–3 times/week</td>
<td>• Goal setting</td>
</tr>
<tr>
<td>• Individual: personal and cultural preferences</td>
<td>• Reduce sedentary behavior: Individualized: preferences and physical limitations</td>
<td>• Education</td>
</tr>
<tr>
<td>Dietician or health educator</td>
<td>Exercise trainer, physical/occupational therapist</td>
<td>• Problem-solving strategies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stimulus control</td>
</tr>
</tbody>
</table>

Diabetes Management - Promoting Weight Loss

Focus should be on agents that are cause weight reduction and/or are weight neutral

Diabetes Care 2019, ADA/EASD 2018
Diabetes Management- GLP-1

- **How it works:**
  - Increases insulin release when food is eaten
  - Makes you feel full faster and longer
- **A1c lowering potential:** ~1-1.5%
- **Administration:** subcutaneous injection
- **Side effects:**
  - Upset stomach
  - Pancreatitis

Diabetes Management- GLP-1

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Weight loss (in months)</th>
<th>% weight loss</th>
</tr>
</thead>
</table>
| Semaglutide  | 0.25 mg weekly x 4 weeks, then increase to 0.5 mg | 0.5 mg: 4.4 – 5.6%  
  1 mg: 5 – 6.2% | --            |
| Liraglutide  | 0.6 mg daily x 7 days, then increase to 1.2 mg | 1.8 mg: 2.6 – 3.6%  
  2.4 mg: 3.6 – 4.1% | --            |
| Dulaglutide  | 0.75 mg weekly, 1 mg increase to 1.5 mg | 0.75 mg: 3.8%  
  1.5 mg: 3.9% | --            |
| Exenatide ER | 2 mg weekly               | 1.6 – 3.7%              | 17.7%        |
| Exenatide    | 5 mg twice daily, May increase to 10 mg | 10 mg: 1.5 – 4%  
  14 mg: 2.6 – 4% | --            |
| Lixisenatide | 10 mg daily x 14 days, then increase to 20 mg | 1.6 – 3%  
  20 mg: 3.4 – 6% | --            |

SGLT-2 Overview

- **How it works:**
  - Getting rid of blood sugar through the urine
- **A1c lowering potential:** 1%
- **Administration:**
  - Oral tablets
- **Side effects:**
  - Urinary tract infections
  - Increased urination
Diabetes Management - SGLT2

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Weight loss (1-year)</th>
<th>&gt;5% weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>100 mg daily</td>
<td>100 mg: 2.1%</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>300 mg daily</td>
<td>100 mg: 2.4%</td>
<td>---</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10 mg daily</td>
<td>10 mg: 1.96%</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>25 mg daily</td>
<td>10 mg: 1.99%</td>
<td>---</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>5 mg daily</td>
<td>5 mg: 3.1%</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>10 mg daily</td>
<td>5 mg: 3.6%</td>
<td>---</td>
</tr>
<tr>
<td>Ertogliflozin</td>
<td>5 mg daily</td>
<td>5 mg: 3.3%</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>15 mg daily</td>
<td>5 mg: 3.4%</td>
<td>---</td>
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Obesity Management

- Pharmacotherapy for weight loss should only be used as an adjunct to lifestyle therapy and not alone
- Nearly all FDA approved weight loss medications have been shown to improve glycemic control in patients with type 2 diabetes and delay progression to type 2 diabetes in patients at risk
- Help patients to more consistently adhere to low-calorie diets and to reinforce lifestyle changes

Obesity Management

- Prevents the absorption of dietary fats
  - Administer during or up to 1 hour after each main meal containing fat
- Precautions
  - May cause malabsorption of fat-soluble vitamins
  - Many drug interactions
  - Increases the risk of cholelithiasis and nephrolithiasis
**Obesity Management**

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</tr>
</thead>
<tbody>
<tr>
<td>Lorcaserin</td>
<td>10 mg BID</td>
<td>4.5 – 8%</td>
<td>47.2%</td>
<td>Headache, nausea, dizziness, fatigue</td>
</tr>
<tr>
<td>Lorcaserin XR</td>
<td>20 mg daily</td>
<td>~4.5 – 8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Activates serotonin 5-HT<sub>2C</sub> receptors
- Results in feeling full and eating less

**Precautions**
- Serotonin syndrome with other serotonergic agents
- Avoid in liver and renal failure (eGFR < 30)
- May have abuse potential, euphoria as higher than recommended doses
- Pre-existing bradycardia

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<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine/</td>
<td>7.5 / 46 mg daily</td>
<td>~8 – 9%</td>
<td>62%</td>
<td>Constipation, paresthesia, insomnia</td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
<td>~10 – 12%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Phentermine: reduces appetite by stimulating the release of norepinephrine (controls hunger)
- Topiramate: causes appetite suppression and satiety enhancement (resists cravings)

**Initial dosing**
- Start with 3.75/23 mg daily for 14 days, then increase to 7.5/46 mg daily x 12 weeks, assess weight loss
- 11.25/69 mg daily for 14 days, then increase to 15/92 mg daily

**Precautions**
- Need to taper off if discontinuing (decrease by 1 dose every other day for at least 1 week)
- May increase resting heart rate
- Can cause cognitive dysfunction and mood disorders
- May cause worsening glaucoma, should not be used in pre-existing glaucoma
- eGFR < 50: max dose is 7.5/46
- Do not use in pregnancy

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<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone/</td>
<td>32 / 360 mg</td>
<td>~6 – 8%</td>
<td>48%</td>
<td>Constipation, nausea, headache, serotonina</td>
</tr>
<tr>
<td>Bupropion</td>
<td></td>
<td>~10 – 12%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Naltrexone/Bupropion: work together to regulate hormones in the hunger and reward centers of the brain
- Initial dosing (tablet strength 8/90 mg)
  - Start with 1 tablet morning x 1 week
  - Increase one tablet a week until usual dose

**Precautions**
- Do not use in patients with seizure history or uncontrolled hypertension
- May cause worsening glaucoma, should not be used in pre-existing glaucoma
- eGFR < 50: max dose is 8/90 mg daily
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</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>3 mg</td>
<td>~8 - 9%</td>
<td>63.2%</td>
<td>Hypoglycemia, constipation, nausea, headache, indigestion</td>
</tr>
</tbody>
</table>

- Increases satiety and slows down gastric emptying
- **Dosing**
  - 0.6 mg subcutaneously once daily x 7 days, increase by 0.6 mg every 7 days until usual dose
- **Precautions**
  - Pancreatitis?
  - Thyroid C-cell tumors

Obesity Management – with or without diabetes

- Efficacy and safety should be assessed at least monthly for the first 3 months of treatment with certain weight loss medications
- If a patient's response is deemed insufficient after 3 months or if there are significant safety or tolerability issues at any time, the medication should be discontinued and alternative medication or treatment approaches should be considered
- Consideration for Bariatric Surgery recommendation – BMI ≥ 40 or ≥ 35 plus an obesity-related complication

Obesity Management – with or without diabetes

- **Discuss the results (breakthroughs and barriers) of the interprofessional obesity clinic initiative**
  - Vision: team consisting of Physician(s) and/or Nurse Practitioner(s), RD, psychologist or therapist, and exercise specialist ideally.
  - Payment for meds: lack of coverage by many insurance plans; insurance coverage may stop if weight loss is not proven at certain intervals does not take into account many of the struggles patients can have in their weight-loss journey; meds are costly-copy cards may help
  - Reimbursement limitations for office visits: need to follow up monthly for some medications obesity alone not considered a “billable diagnosis”
  - Shared medical appointment: serve as cohort, possible support structure, save valuable time for all healthcare providers involved in the team
Obesity Management

• Weight loss with lifestyle therapy or in combination with medications led to improvement in diabetes control at all phases of DM2

• In the UKPDS (newly-diagnosed DM2 patients treated with lifestyle therapy) and Look Ahead studies (84% were on diabetes meds—nearly half on multiple meds and 15% on insulin – with average duration of diabetes 6.8 years) - greater weight loss led to progressive lowering of A1c levels

Obesity Management – Costs and Consequences of NOT treating

• Typical cost of weight loss surgery can be from $20,000 to $25,000.

• Doesn’t it make sense to treat obesity more aggressively with intensive lifestyle intervention and medications readily to help alter the course of its path? Complications of obesity can be very costly, often progressive and potentially debilitating.

• Making obesity a “billable diagnosis” could help expand access for obese patients to seek proven treatments and necessary ongoing monitoring from appropriate healthcare providers

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