Medical Management of Common Co-Morbid Problems of Obesity

Ken Fujioka, M.D.
Scripps Clinic, Dept of Endocrine
San Diego, California

Disclosure

• Consultant: Amgen, Boehringer-Ingelheim, Gelesis, Janssen Global Services, KVK Tech, Novo Nordisk, Phenomix, Roivant, Sunovion Pharmaceuticals
• Advisory Board: Novo Nordisk
• Speakers Bureau/Honorarium: Novo Nordisk
Patient that is Overweight and Hypertensive

- Joe presents for his annual physical
- He sees himself in “good shape” but has put on a few pounds over the past 5 years
- He is turning 50 and wants to get “checked out”
- He has no complaints
- He moved up in his company the last few years from sales to in house executive but still has to go out to do lunch meetings
- He admits to not exercising regularly and does not smoke tobacco
- Family history is remarkable for obesity and a “heart attack” in his Dad at age 56

Physical Exam 49 Year Old Male

- Weight is 224 pounds
- Height is 5 feet 9 inches
- BMI is 34
- Waist is 44 inches
- Blood pressure is 178/84, repeat after sitting is 172/84
- Pulse is 80
- Legs have trace to +1 edema
- Happy, nice guy, funny, friendly, and very well dressed
History of Hypertension and Obesity

• The first study to prospectively show weight is associated with HTN was the:
  • Framingham Heart Study in the 1960s

• Until the Mid-1980s scientist and physicians did not know why obesity caused HTN
  • Central obesity or Visceral obesity was closely related to HTN
  • 65%-75% of HTN in the US is due to visceral obesity
  • Insulin resistance or increased insulin levels were associated with visceral obesity and HTN


Insulin and Hypertension

• Insulin effects include:
  • Increase in Sympathetic Nervous System activity
  • Direct effect on Kidneys to retain Sodium
  • If you increase insulin you increase blood pressure
  • If you lower insulin you lower blood pressure

Why Does Someone with Obesity Become Hypertensive?

• 1. Physical compression of the kidneys by fat
  • fat in the kidneys
  • fat around the kidneys
• 2. Activation of the renin-angiotensin-aldosterone system (RAAS)
• 3. Increased sympathetic nervous system (SNS) activity

• Natural history of untreated obesity induced hypertension is renal damage (and other end organ damage) that results in very difficult to treat hypertension requiring multiple medications to treat
• The mechanisms of obesity induce HTN is the same in children as are the treatments

The Renin-angiotensin-aldosterone System (RAAS)

• The RAAS system is activated by the renal compression by fat as well as sympathetic stimulation
• The renin-angiotensin-aldosterone system (RAAS) is activated in obesity
  • Sympathetic (SNS) stimulation of Renin with the generation of angiotensin II
  • angiotensinogen production is increase in fat cells with the generation of angiotensin II and aldosterone
• This leads to a hyper-Renin, hyper-Angiotensin, and hyper-Aldosterone state
Obesity and Sodium Reabsorption

• Obesity directs the Kidneys to reabsorb Sodium
  • Neural: Sympathetic Nervous System
  • Hormonal: Aldosterone and Insulin
  • Renovascular: Angiotensin II
• Higher sodium shifts the pressure natriuresis curve to the right
• Thus the body needs to increase arterial pressure to excrete sodium to maintain sodium and volume balance
  • Yes obesity induced HTN is salt sensitive

Treatment Options for: Obesity induced Hypertension

• Weight loss
  • All the guidelines say this (especially for kids)
  • We will spend more time on this in the next lecture
• Dietary Approaches to Stop Hypertension (DASH) diet
  • Salt restriction
• As far as weight loss no diet is is better than another
  • Just find what the patient is willing to do
• Alcohol moderation
• Behavioral modification

Physical Activity

• Physical activity:
  • exercise as the only intervention for weight loss
    • Typical weight loss is 3.5 pounds
    • Exercise alone will drop BP about 3mm Hg
  • Exercise combined with calorie restriction will drop BP much more


Alcohol and Obesity Induced HTN

• Systolic blood pressure goes up 1 mmHg for every 10 grams of ETOH
• Paradoxical effect in that low levels of ETOH appear to have cardio-protective effects
• Combined weight loss with lowering of ETOH intake will lower blood pressure 14/9 mmHg
• Take home message, the moderate to heavy overweight drinkers will benefit if they can decrease their ETOH intake

Diuretics the Perfect Drug?
Obesity induced HTN has Increased Na Absorption and is Salt Sensitive

• Hydrochlorothiazide
  • MOA: Hydrochlorothiazide increases excretion of sodium and chloride
• Side effects of HCTZ
  • Insulin resistance which can lead to diabetes
  • Dyslipidemia (increased triglycerides)
• Recommendation:
  • Use low to moderate dose HCTZ (12.5mgs to 25 mgs)

ACE inhibitors and ARBs: First Line

• The renin-angiotensin-aldosterone system (RAAS) is activated in obesity
• Most experts feel ACE inhibitors and ARBs should be the first line treatment for obesity induced HTN
  • No insulin resistance (no increased risk of diabetes)
  • No weight gain
  • Renal Protection in Diabetes
  • No Dyslipidemia
  • Most important they work
Beta Blockers: Use Carefully

- Obesity activates the Sympathetic Nervous System
- Beta Blockers are effective for lowering blood pressure in obesity induced HTN
- Side effects
  - Insulin resistance
  - Weight gain
  - weight-matched β-blocker users, diet-induced thermogenesis, fat oxidation rate and weekly habitual activity were lower by 50%, 32%, and 30%
- Limit to patients with Cardiovascular issues (s/p Myocardial infarction)
- Use B-blockers with a vasodilating component
  - less of a potential for weight gain and insulin resistance

Calcium Channel Blockers

- Effective at lowering blood pressure
- Preferred add on to ACE or ARB medications
  - Improved Cardiovascular outcomes (better than HCTZ with ACE) in normal weight and overweight
  - No difference (HCTZ vs Calcium Channel blocker add on) in Obese
- Neutral effects on lipids and insulin resistance
Patient with uncontrolled diabetes: Which to treat first
1. Blood Sugar
2. Weight

52 year old female presents with obesity and type 2 diabetes of 6 years duration
She is on metformin and glimepiride (sulfonylurea) and her diabetes is uncontrolled with an A1c of 8.6
Since starting diabetes treatment she has gained 20 pounds and now has a BMI of 34.
You are considering insulin treatment to get her A1c to goal
In the past when she lost weight her diabetes “went away”

What is the goal or goals for our patient with diabetes type 2 and Obesity
- Improve the blood sugar (A1c)
- Improve the comorbid problems of diabetes
  - Hypertension
  - Micro albuminuria and nephropathy
  - Neuropathy
  - Decrease the risk of cardiovascular disease (both cardiac disease and risk of stroke)
- Improve the patient's quality of life
  - Weight loss improves quality of life
• Current 2020 Diabetes Optimal Care Bundle
  • 2 HbA1c tests; most recent A1c < 8%
  • most recent blood pressures < 140/90
  • LDL < 100 or on a statin
  • attention for nephropathy (proteinuria) within the past 12 months
• The bundle is “all or nothing”
• all 4 of the components must be met to qualify for payment

How Much Weight Loss Is Needed to Improve Glycemic Control?

Improvement begins with >2% weight loss

![Change in A1C (%) by Weight-Loss Category](image)

A1C = glycated hemoglobin.
How Much Weight Loss Is Needed to Improve BP?

Effect of amount of weight loss on SBP and DBP: direct and linear

<table>
<thead>
<tr>
<th>Change in BP by Weight-Loss Category</th>
<th>Gained &gt;2%</th>
<th>Gained ≤2%</th>
<th>Lost &gt;2%</th>
<th>Lost ≤2%</th>
<th>Lost ≥5%</th>
<th>Lost &gt;10%</th>
<th>Lost ≥15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP: P &lt; .0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP: P &lt; .0005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DBP = diastolic blood pressure; SBP = systolic blood pressure.

How Much Weight Loss Is Needed to Improve Lipids?

Effect of amount of weight loss on HDL-C and TGs is direct and linear; effect on LDL-C is less pronounced

<table>
<thead>
<tr>
<th>Change in TGs by Weight-Loss Category</th>
<th>Gained &gt;2%</th>
<th>Gained ≤2%</th>
<th>Lost &gt;2%</th>
<th>Lost ≤2%</th>
<th>Lost ≥5%</th>
<th>Lost &gt;10%</th>
<th>Lost ≥15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C: P &lt; .0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C: P = .3614</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
Bottom line on LDL cholesterol

Neither weight loss or improving Blood sugar will always improve LDL

Strongly consider statin therapy

Weight Loss Improves Micro Albuminuria

2-year Dietary Intervention Randomized Controlled Trial (DIRECT) randomized 318 subjects to:
- low-fat diet
- Mediterranean
- low-carbohydrate diets (higher protein diet)

- All groups had an improvement in
  - GFR
  - Urine microalbumin-to-creatinine ratio
    - Even those subjects that already had known microalbuminuria

Treating just the Blood Sugar the Downside

• Patients with Diabetes have a high chance of death from cardiovascular disease
  • Cardiac disease
  • Or CVA (stroke)

• Mixed data but it appears that there are negative cardiovascular effects with
  • Insulin
  • Sulfonylureas

Adding Insulin and the Potential for Increased Cardiovascular Events

• Well known that insulin resistance is associated with cardiovascular disease

• Adding insulin to other diabetic drugs (as opposed to just the other diabetic drugs alone) has been associated with an increase in primary cardiovascular disease

• basal insulin (HR, 2.03; 95% CI, 1.81-2.27)

Khatib J, Shao Y, Shi L, Fonseca V. Impact of Insulin Treatment on Primary Outcomes in Cardiovascular Outcome Trials. Diabetes 2019, Jun; 68(Supplement 1)
Insulin Dose and Cardiovascular Disease

- Case controlled (836pts)
  - Patients that had a recent Cardiovascular event on oral agents and Insulin
- Matched by sex, age, duration of diabetes and type of oral antidiabetic to patients with out a recent cardiovascular event
- Risk of a Cardiovascular event went up with the dose of Insulin
- Patients on > 53 units of insulin (cardiovascular event risk 3.0)
- Patients on > 24 units of insulin (cardiovascular event risk 2.0)


Insulin and Renal Disease

- T2DM study evaluated insulin therapy with end-stage renal disease outcomes. (n = 188,544; 1.5 million-years follow-up)
- Insulin users had >2-fold incidence of end-stage renal disease as compared to non-insulin users.
- Insulin therapy increased risk throughout the range of A1c levels, strongly suggesting the exogenous insulin may be nephrotoxic

Sulfonylureas and Increased Cardiovascular Risk

- The comparative risk of cardiovascular events is higher after starting treatment with sulfonylureas (HR, 1.36; 95% CI, 1.23-1.49),
- Risk also elevated for a secondary cardiac event
- The risk does not appear as high but the patients on Sulfonylureas usually have less advanced diabetes (compared to patients starting insulin)
- Compared to metformin using a sulfonylurea will have more Cardiovascular risk
- It would appear; that compared to treating weight using a sulfonylurea will have more Cardiovascular risk

Khatib J, Shae Y, Shi, Fonesa V. Impact of Insulin Treatment on Primary Outcomes in Cardiovascular Outcome Trials. Diabetes 2019, Jun; 68(Supplement 1)

Factors Associated with Insulin-Induced Weight Gain (IIWG)

- The more insulin you give the more the patient is susceptible to weight gain
  - Anything close to or higher than 0.5 units of Insulin per kg
- Adding short acting (bolus insulin)
- Starting at a lower BMI (less than 30)
- Average weight gain is 10 to 20 pounds the first year

Physiology of Weight Gain with Insulin

- Insulin is an anabolic hormone
  - Inhibits protein catabolism
  - Inhibits lipolysis
  - Promotes lipogenesis = central obesity => Insulin resistance

- Increase in caloric intake
  - Defensive eating (perceived fear of hypoglycemia)
  - DCCT patients who experienced severe hypoglycemia had more weight gain vs patients who did not
  - Increase appetite is an early, adaptive response to low blood sugar levels

Diabetic Medications that Lower the Risk of Cardiovascular Disease and Produce Weight Loss

- GLP-1
  - 3-15% weight loss
- SGLT-2 inhibitors
  - 2-3% weight loss
- Metformin
  - 2-3% weight loss

PM O’Neil, AL, Rohr, B. Mechanisms of weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial www.thelancet.com Published online August 16, 2010
David Polski, AJ, Sangis; Randy, Sen; Kevin D. Hall How strongly does appetite counter weight loss? Quantification of the homeostatic control of human energy intake Obesity Volume 24, Issue 11, pages 2289-2295
Treatment options to treat the weight first in a patient with DM2

- Diet: no risks in the diabetic
- Exercise: no risk if done with care
- Weight loss medications
- Bariatric surgery

Diet and Exercise in the Diabetic

- Diet: “one size does not fit all”
- The guidelines say “use what works”
- Don’t be afraid to use a low carb diet (< 100 grams per day)
  - Low carb diets have not been shown to have more hypoglycemia
  - Quite a few studies showing better A1c control (with low carb)
  - Use caution in patients on SGLT-2 inhibitors

- Exercise: what is the best exercise to improve A1c
  - A1c improves most with cardio, or resistance training, or?
• **Participants** (n = 262):
  - Sedentary individuals with diabetes
  - HbA1c: >6.5% but <11.0%

• **Goal**: Compare benefit to HbA1c of:
  - Control group
    - Stretching and relaxation
  - Aerobic training
    - 12 kcal/kg/week
  - Resistance training
    - 3 days per week: 21 sets per day
  - Combination of resistance & aerobic (Combo)
    - 10 kcal/kg/week & 1 set of 9 RT 2 days/week

• **9 Month Intervention**
• All exercise supervised (@ 20,000 sessions)
Actual Time Exercising

<table>
<thead>
<tr>
<th>Mode</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance</td>
<td>141 min/wk</td>
</tr>
<tr>
<td>Aerobic</td>
<td>140 (130 -150) min/wk</td>
</tr>
<tr>
<td>Combo</td>
<td>RT: 30-40 min/wk</td>
</tr>
<tr>
<td></td>
<td>AT: 110 (100-120) min/wk</td>
</tr>
</tbody>
</table>

HbA1c by Month and Group

Intention-to-Treat Analysis (n=262)

- Control
- Resistance
- Aerobic
- Combo

Month

0 1 2 3 4 5 6 7 8 9

HbA1c, %

7.20 7.30 7.40 7.50 7.60 7.70 7.80
SGLT-2 Inhibitors

- **Upside:**
  - Lose ~300 calories per day in the urine
  - Lose 2-3% of weight (more if combined with appetite suppression)
  - Improved A1c

- **Downside:**
  - Potential for Ketoacidosis
    - Typically: decrease insulin when starting an SGLT-2 inhibitor and may not have enough insulin to suppress lipolysis and ketosis
    - SGLT-2 inhibitors promote glucagon secretion
    - Possible decrease in excretion of ketones by the kidneys (decreased renal clearance of ketones)

---

Diets that Promote Ketosis

- “Keto diet”, a diet high in fat, protein and very low in carbohydrates
- Any diet with fewer than 50 grams of carbohydrates a day
- Intermittent fasting
  - Between 12 hours and 36 hours of fasting, patients will go into ketosis
- “Keto drinks” drinks that have ketones in them to promote a decrease in hunger
Ketone Drinks Web Ad Claims

- “Boost ketone levels”
- Get back into ketosis
- “Benefits”
  - Support higher energy
  - Support a healthy metabolism
  - Supports mental clarity
- Curb cravings and hunger
- “Keto Lifestyle”
- And don’t forget to get your Ketone meter

Supplement Facts

<table>
<thead>
<tr>
<th>Serving Size 1 scoop approx. (13g/0.46oz)</th>
<th>Servings Per Container 15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amount Per Serving</strong></td>
<td></td>
</tr>
<tr>
<td>Calories 20</td>
<td>Calories from fat 0</td>
</tr>
<tr>
<td>% Daily Value*</td>
<td></td>
</tr>
<tr>
<td>Total Fat 0g</td>
<td>0%</td>
</tr>
<tr>
<td>Saturated Fat 0g</td>
<td>0%</td>
</tr>
<tr>
<td>Sodium (from Sodium Beta-Hydroxybutyrate) 670mg</td>
<td>28%</td>
</tr>
<tr>
<td>Magnesium (from Magnesium Beta-Hydroxybutyrate) 390mg</td>
<td>98%</td>
</tr>
<tr>
<td>Calcium (from Calcium Beta-Hydroxybutyrate) 600mg</td>
<td>60%</td>
</tr>
<tr>
<td>Total Carbohydrate less than 1g</td>
<td>0%</td>
</tr>
<tr>
<td>Protein 0g</td>
<td>0%</td>
</tr>
<tr>
<td>BHB Blend 11,380mg</td>
<td>††</td>
</tr>
</tbody>
</table>

††Daily Values not established.
*Percent Daily Values are based on a 2,000 calorie diet.

Other Ingredients: Natural Flavor, Cocoa Powder, Stevia Leaf Extract, Monk Fruit Extract

Bottom Line on Keto Diet for Diabetics

- If the patient is on insulin the patient should not do a Keto diet
- If the patient is on an SGLT-2 inhibitor and they have advanced diabetes they should not be on a Keto diet
- This author does not recommend Keto drinks
How to Adjust Insulin When Adding Starting Weight Loss or Adding a Weight Loss Medication

Look AHEAD Instructions on Reduction in Insulin Before Starting Diet

- Asked patients to check blood sugars twice daily for one week
  - ≥ 2 blood sugars < 100 mg/dL
    - Reduce insulin 0% to 50%
  - ≥ 3 blood sugars 80 to 100 mg/dL
    - Reduce insulin 25% to 75%
  - ≥ 3 blood sugars < 80 mg/dL or severe hypoglycemia, or symptomatic hypoglycemia > 2
    - Reduce insulin by 50% to 100%
  - Average decrease in insulin was 50% by year one in the Look AHEAD trial


52 Year Old Engineer with Fatty Liver

- The patient is referred to you for an elevated ALT of 100 and an AST of 50.
- Looks like simple fatty liver disease (NAFLD)
- What is the best Diet?

What Do the Recommendations Say?
Bottom line all say lose 7-10% of the weight

- EAST: 500-1000 kcal deficit; weight loss of 500-1000 g/wk with a 7%-10% total weight loss
- NICE: Main recommendations on diet of NICE’s obesity and preventing excess weight gain guidelines
- Asia-Pacific: 500-1000 kcal deficit
- AISF: 1200-1600 kcal/d; fat-low (< 30% of total calories); carbohydrate-low (< 50% of total calories) = Mediterranean diet
- AASLD: 500-1000 kcal deficit
- Keto diet is not excluded
Treatment Options to Lose 7% -10%

- Diet, Exercise and Lifestyle modification
- Diet, exercise, Lifestyle modification and weight loss medications
- Bariatric surgery
  - Sleeve Gastrectomy
  - Gastric Bypass
- What are the odds that the above treatment options can accomplish 7% -10% weight loss?
- Diet, Exercise and Lifestyle = 20%
- Lifestyle with weight loss medications = 60%
- Bariatric surgery = 85%

Basic of NAFLD:
Increased Intrahepatic Triglyceride [IHTG]

- Main pathways contributing to IHTG
  
  - 1. Increased Adipose tissue lipolysis contributes to IHTG (%60-80%)
  - 2. Increased Hepatic de novo lipogenesis (DNL)
    - The process of converting excess carbohydrates into Fatty Acids => DNL
    - Fructose is especially good at promoting de novo lipogenesis
  - 3. Dietary Fat (15%) depending on the type of fat ingested

C M Perdomo G Frühbeck JEscalada Impact of Nutritional Changes on Nonalcoholic Fatty Liver Disease Nutrients 2013, 12, 677
Overfeeding Saturated Fats vs Unsaturated Fats vs Simple Sugars

- Overfed 38 subjects randomized to diets with high Saturated fat, Unsaturated fat, or simple sugars
- 3 weeks of over feeding (1,000 calories per day)
- 1. Simple sugars stimulated Hepatic de novo lipogenesis (DNL)
- 2. Saturated fat induced insulin resistance and lipolysis in fat cells
- 3. Unsaturated fat decreased lipolysis

- Then measure the Intra-Hepatic TriGlycerides (IHTG) pathways contributing to IHTG

P.K. Luukkonen, S. Sa de Brito, Y. Zhou et al. Saturated Fat Is More Metabolically Harmful for the Human Liver Than Unsaturated Fat or Simple Sugars. Diabetes Care 2018;41:1732–1739
Increase in Intrahepatic Triglyceride [IHTG] at the End of 3 Weeks of Overfeeding

![Chart Title]

P. P. Luskienew, S. S. deavetta, Y. Zhou et. al. Saturated Fat Is More Metabolically Harmful for the Human Liver Than Unsaturated Fat or Simple Sugars. Diabetes Care 2018;41:1732–1739

What is Your Advice to Your Patient with Fatty Liver Disease

- It would be advisable to avoid Saturated Fats
  - Keto diets, Atkins, etc.
- Stick with unsaturated fats or monounsaturated fats
- Follow a diet that he or she thinks they can do:
  - Mediterranean diet
  - Intermittent fasting
  - See a Dietitian for a balanced diet low in simple sugars and saturated fats
Other Options for Fatty Liver Disease

• Metformin
• Pioglitazone
• GLP-1 hormones
• Appetite suppressants
• Bariatric surgery

• Will cover the above in the next lecture
• Thanks for listening