Type 2 Diabetes Management

Nicolas Musi, MD
Director
Geriatric Research, Education and Clinical Center (GRECC)
Audie L Murphy VA Medical Center
Barshop Institute
University of Texas Health Science Center
San Antonio, TX
Age, Glucose Homeostasis and Diabetes

• Epidemiology
• Pathophysiology
• Recommendations
Age-Specific Prevalence of the Metabolic Syndrome by Sex and Race/Ethnicity

Prevalence of Metabolic Syndrome, %

Ages 20-39 y

Sex
- Males
- Females

Race/ethnicity
- Non-Hispanic white
- Black
- Hispanic
- Other

Overall Sex Race/Ethnicity

Ages 40-59 y

Overall Sex Race/Ethnicity

Ages ≥60 y

Overall Sex Race/Ethnicity

One in every two people age 65 and older have diabetes or pre-diabetes.
Why Diabetes Risk Increases With Age?
Pathophysiology of Type 2 Diabetes

- Excessive glucose production
- Reduced glucose uptake
- Excessive lipolysis
- Resistance to the action of insulin
- Defective \(\beta\)-cell secretion

Carbohydrate digestive enzymes
Effect of Age on Insulin Secretion

- Young
- Older Normal Glucose Tolerant
- Old Impaired Glucose Tolerant

Blood Glucose (mg/dl)

Insulin (mU/ml)
Type 2 Diabetes in Aging

Peripheral Insulin Resistance

- β Cell Failure
- Low Physical Activity
- Sarcopenia
- Decreased Insulin Action in Muscle
- Visceral Adiposity
Are Older Patients More Insulin-Resistant?

Peripheral Insulin Sensitivity

- Glucose Infusion Rate (kg.min)
- P<0.05
- 26 ± 1 vs 62 ± 1 Age (years)
Age and Insulin Resistance

Mitochondrial Function

Insulin Resistance
Mechanism of Insulin Resistance in Aging

- Glucose
- Insulin
- PI3-K
- IRS
- IKK-NFκB
- ROS
- Mitochondrial Dysfunction

Fatty Acids

Lipids

DAG

Ceramides
Effect of Age on Lipid Content

Magnetic Resonance Spectroscopy

Intramyocellular Lipid Content

(Petersen, Science, 2003)
Needle Muscle Biopsy
Effect of Age on Mitochondrial ATP Production

Luciferase assay (ATP synthesis rate)

Mitochondrial ATP Production

*P<0.05 vs. older group
Aerobic Training Program

- **Week 1**
  - **Warm up**
  - **Week 2 - Week 4**
    - 60% of effort
    - 3 Day/week
    - 20 mins/time
  - **Week 5 - Week 7**
    - 65% of effort
    - 3 Day/week
    - 25 mins/time
  - **Week 8 - Week 11**
    - 70% of effort
    - 4 Day/week
    - 35 mins/time
  - **Week 12 - Week 15**
    - 80% of effort
    - 4 Day/week
    - 45 mins/time

- **VO2 max**
- **VO2max and Insulin Sensitivity ~10%**
Effect of Aerobic Exercise on Mitochondrial ATP Production in Older Subjects

S+R: Succinate + Rotenone; G+M: Glutamate + Malate; P+M: Pyruvate + Malate

*, $P<0.05$ vs. older group before exercise.
Recommendations

• Should we treat diabetes?
• Older subjects with diabetes
  – Higher rates of premature death, functional disability, HTN, CHD, and stroke
  – Higher rates of geriatric syndromes: polypharmacy, depression, cognitive impairment, urinary incontinence, falls, pain
# ACCORD, ADVANCE and VADT Study Design

<table>
<thead>
<tr>
<th>Study</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Endpoints</td>
<td>CV death, Non-fatal MI/Stroke</td>
<td>CV death, Non-fatal MI/Stroke, macrovacs event</td>
<td>CV death, Non-fatal MI/Stroke, CHF macrovacs event</td>
</tr>
<tr>
<td>Study</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
</tr>
<tr>
<td>Design</td>
<td>Glucose Intensive vs Standard Arm 2x2 BP control +/-fenofibrate v placebo</td>
<td>Glucose Intensive vs Standard Arm 2x2 Perindopril +indamide v placebo</td>
<td>Glucose Intensive vs Standard Arm 2x1 All received BP and Lipid Rx</td>
</tr>
</tbody>
</table>

# ACCORD, ADVANCE and VADT Demographics

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td># Participants</td>
<td>10,251</td>
<td>11,140</td>
<td>1,791</td>
</tr>
<tr>
<td>Population</td>
<td>North America</td>
<td>Europe /Asia</td>
<td>US</td>
</tr>
<tr>
<td>Male</td>
<td>62%</td>
<td>58%</td>
<td>97%</td>
</tr>
<tr>
<td>Age group mean age</td>
<td>40-79</td>
<td>&gt;55 yrs</td>
<td>&gt;40yrs</td>
</tr>
<tr>
<td></td>
<td>62.2</td>
<td>66</td>
<td>60.5</td>
</tr>
<tr>
<td>Non-Hispanic White Ethnic Representation</td>
<td>27% Hispanic, African Am</td>
<td>37% Asian</td>
<td>38% Hispanic, African Am, Native Am</td>
</tr>
</tbody>
</table>

## ACCORD, ADVANCE and VADT Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>93.5</td>
<td>78 kg</td>
<td>97.2</td>
</tr>
<tr>
<td>BMI</td>
<td>32.2</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>Duration DM</td>
<td>10</td>
<td>8</td>
<td>11.5</td>
</tr>
<tr>
<td>Baseline A1c</td>
<td>8.3</td>
<td>7.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Prior CVD</td>
<td>35%</td>
<td>32%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Therapeutic Approach: ACCORD, ADVANCE and VADT

<table>
<thead>
<tr>
<th>Protocol</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provider Directed</td>
<td>Provider Directed Formulary-based Poly-pharmacy</td>
<td>Stepped Approach: SU, Met, TZD, Insulin</td>
<td>Stepped Approach: Met BMI ≥27; SU BMI &lt;27, TZD, Insulin</td>
</tr>
<tr>
<td>Meds (Inten v Std)</td>
<td>Metformin 95 v 87 %</td>
<td>74 v 67 %</td>
<td>75 v 71%</td>
</tr>
<tr>
<td></td>
<td>TZD (Rosi) 91 v 58 %</td>
<td>17 v 11%</td>
<td>85 v 78%</td>
</tr>
<tr>
<td></td>
<td>Oral Hypoglycemic 87 v 74 %</td>
<td>94 v 84 %</td>
<td>55 v 45%</td>
</tr>
<tr>
<td></td>
<td>Insulin 73 v 58 %</td>
<td>41 v 24 %</td>
<td>90 v 74%</td>
</tr>
<tr>
<td></td>
<td>Exenatide 12 v 4 %</td>
<td>- - -</td>
<td>- - -</td>
</tr>
<tr>
<td>Follow-up intensive group</td>
<td>Q mo x 4, then q 2 mo</td>
<td>Q mo x 4, then Q 3 mo</td>
<td>-</td>
</tr>
</tbody>
</table>

VADT Study Results ADA Scientific Session San Francisco, 2008; Diabetes Obesity and Metabolism, 2008
**Outcomes: Summary of ACCORD, ADVANCE and VADT**

<table>
<thead>
<tr>
<th></th>
<th>ACCORD*</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1C (%)</strong></td>
<td>6.4 vs. 7.5 †</td>
<td>6.4 vs. 7.0 †</td>
<td>6.9 vs. 8.4 †</td>
</tr>
<tr>
<td>(Intensive vs. Std)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nonfatal MI (%)</strong></td>
<td>3.6 vs. 4.6% †</td>
<td>2.7 vs. 2.8</td>
<td>6.3 vs. 6.1</td>
</tr>
<tr>
<td>(Intensive vs. Std)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CV Death (%)</strong></td>
<td>2.6 vs. 1.8 † (1.35 Hazard Ratio)</td>
<td>4.5 vs. 5.2</td>
<td>2.1 vs. 1.7</td>
</tr>
<tr>
<td>(Intensive vs. Std)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Microvascular</strong></td>
<td>-</td>
<td>nephropathy ↓ 21%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>retinopathy ↓ 5% NS</td>
<td></td>
</tr>
<tr>
<td><strong>Take home</strong></td>
<td>↓ risk MIs, but ↑ risk death in intensive arm</td>
<td>Glucose control has no impact on CV events, but ↓ Microvascular risk</td>
<td>Glucose control has no impact on CV events</td>
</tr>
</tbody>
</table>

*ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial halted intensive glucose group (2/6/08)
† significant difference between intensive and standard group

VADT Study Results ADA Scientific Session San Francisco, 2008; Diabetes Obesity and Metabolism, 2008
### Adverse Outcomes: ACCORD, ADVANCE and VADT

<table>
<thead>
<tr>
<th>Intensive vs Std</th>
<th>ACCORD*</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Hypoglycemia (% per yr)</td>
<td>3.0 vs 1.0</td>
<td>0.7 vs 0.4</td>
<td>-</td>
</tr>
<tr>
<td>Hypoglycemia requiring assistance (% per year)</td>
<td>4.6 vs 1.5</td>
<td>1.8 vs 0.6</td>
<td>2.3 vs 1.1</td>
</tr>
<tr>
<td>Weight Gain &gt; 10Kg</td>
<td>27.8 % vs 14.1%</td>
<td>0.0 vs -1.0</td>
<td>-</td>
</tr>
<tr>
<td>Wt gain (Kg) Intensive group</td>
<td>3.5</td>
<td>0.7</td>
<td>6.8</td>
</tr>
<tr>
<td>Increased Mortality Rosiglitazone?</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

ACCORD, ADVANCE, and VADT Lessons Learned

• Intensive glucose control does not reduce CVD mortality in T2DM, and *may* increase risk, especially in patients with pre-existing CHD

• Aggressive A1c targets (<6.5%) were associated with a 3-fold increased risk of hypoglycemia

• No excess CVD mortality was seen with rosigliatazone
• Intensive control associated with reduced risk for nephropathy in ADVANCE.

• To reach and maintain A1c targets of <6.5 required frequent adjustments of multiple anti-diabetic medications

• Aggressive targets (<6.5) are probably reasonable for healthy patients to reduce risk of microvascular complications
Recommendations (ADA, AGS)

Goals of Treatment (Tight Control?)

Consider:

1) Functional Status
2) Life expectancy
3) Cognitive Function
4) Clinical Heterogeneity (prone to complications?)
Recommendations (ADA, AGS)

Goals of Treatment (Tight Control?)

- Functional, Cognitively Intact, Significant Life Expectancy:
  - Similar Goals as Younger Person
  - A1c ~ 7%
Recommendations (ADA, AGS)

Goals of Treatment (Tight Control?)

Decreased Function/Cognition, Short Life Expectancy:

- Glycemic control can be relaxed

- Avoid hyperglycemic complications!
Oral Agents for the Treatment of T2DM

Liver

†Sulfonylureas

Impaired Insulin

Pancreas

†HGP

†Metformin

†Rosiglitazone

†Pioglitazone

HGP = hepatic glucose production.

Incretin-mimetics:

Exenatide (~GLP-1)

DPP-4 Inhibitors

↑ GLP-1

Gut

↓ Acarbose

Muscle

Insulin resistance

↓ Glucose uptake

Glucose

Hyperglycemia

↑HGP

↑ Metformin

↑ Rosiglitazone

↑ Pioglitazone

HGP = hepatic glucose production.
Antihyperglycemic therapy T2DM (ADA Standards, 2016)
Sulfonylureas

- Stimulate insulin release
- Lower A1c 1.5-2%
- Weight Gain
- Hypoglycemia 1-20%

Half life: Chloropropamide 36 h
         Glipizide    2-5 h
         Glyburide  10 h
         Glimepiride 5-9 h

* Aging: Half lives are prolonged
Metformin

- Decrease Hepatic Glucose Output
- Lower A1c 1.4-2%
- No Weight Gain/Loss
- No Hypoglycemia
- Aging: Decreased Renal Clearance
- Precautions:
  - Lactic Acidosis Rare
  - Caution Age>80: Check Cr. Clearance
  - Contraindication: CHF, Renal/Liver Disease
TZDs (Pioglitazone/Rosiglitazone)

- Agonist of PPAR gamma nuclear receptor
- Improve insulin action in muscle and liver
- Lower A1c 0.3-1.9%
- Weight gain
- Hypoglycemia very rare (0.6%)
- Decreased bone density / increase bone fractures
- Aging: No difference in safety or effectiveness
- Precautions:
  - Check LFTs within 2 months then periodic.
  - Contraindication: CHF, Edema, Liver Disease, LFT >2.5 ULN
Incretin System

- Delay Emptying
- Insulin ↑
- Glucagon ↓
- GLP-1
- Gut
- Cleaved by DPP IV
- Suppress Appetite
Incretin-Mimetics

**Exenatide**
- Agonist of GLP-1 (Incretin)
- Increase Insulin Release/Inhibit Glucagon
- Delay Gastric Emptying
- Significant Weight Loss
- No hypoglycemia unless used with Insulin or SU
- Main Side Effect: Nausea (1/3)
  - Aging: No Difference in Safety or Effectiveness

**Liraglutide**

**Sitagliptin**
- Inhibitors of DPP-IV (Breaks Down GLP-1)
- Given Orally Once Daily
- Increase Insulin Release/Inhibit Glucagon
- No Weight Gain/Loss
- No hypoglycemia unless used with Insulin or SU
- Well Tolerated
  - Aging: No Difference in Safety or Effectiveness

**Saxagliptin**

**Linagliptin**
Sodium-Glucose Transporter (SGLT)2 Inhibitors

• 180 g of glucose filtered daily
• All glucose is reabsorbed by proximal tubules (SGLT1 – 10% and SGLT2 – 90%)
• Dapagliflozin (5-10 mg), canagliflozin (100-300 mg), empagliflozin (10-25 mg) – all PO; once a Day
• A1c reduction – 0.7 – 1%
• Low risk of hypoglycemia
• Added benefits: weight loss (0.5-3 kg) and BP reduction (mean SBP reduced by 4 mmHg)
Sodium-Glucose Transporter (SGLT)2 Inhibitors

• Contraindicated: Severe liver and kidney failure (GFR less than 45-60 mL/min/1.73 m²)
• Aging: Use low doses
• Issues:
  – Fungal infections (genitalia), UTI
  – Dehydration
  – Increase DKA
  – Decrease bone density / increase fracture risk
Summary

• Plan for Izzy?
Back to Dr. Liu
Izzy

• Visited PCP for checkup.

• Izzy recalled an ad campaign urging all baby boomers to get screened for chronic hepatitis C.

• While running bloodwork, her PCP ordered an HCV antibody test.
  – Her results came back AB+ and a subsequent HCV RNA test confirmed she had chronic HCV.
  – She was told she had genotype 1a and that she should go see Dr. Lawitz...
HCV: Is Metabolic Syndrome a Negative Predictive Factor?

Eric Lawitz, MD
Professor of Medicine
University of Texas Health Science Center, San Antonio
Vice President, Scientific and Research Development
The Texas Liver Institute
San Antonio, Texas
Chronic Hepatitis C

• Approximately 170 million people infected with HCV worldwide.
• Until 2011, only therapy available was peginterferon + ribavirin offering cures rates ~40%.
  – Primarily targeted towards the host.
• Standard of care now offers >90% cure rates with direct acting antiviral (DAA) agents.
  – Solely targeted towards the virus.
HCV Can Now Be Cured in Most Patients

• Unlike HIV and HBV infection, HCV infection is a curable disease
  – HCV does not archive its genome

• What does cure mean?
  – Undetectable HCV RNA 12 weeks after completion of antiviral therapy
  – SVR12 is almost invariably durable

SVR and All-cause Mortality in CHC Patients with Advanced Fibrosis

Baseline factors significantly associated with all-cause mortality:

- Older age
- GT 3 (2-fold increase in mortality and HCC)
- Higher Ishak fibrosis score
- Diabetes
- Severe alcohol use

530 patients followed for a median of 8.4 years

Factors Associated With Accelerated Fibrosis Progression

• **Modifiable**
  – Alcohol consumption
  – Nonalcoholic fatty liver disease
  – Obesity
  – Insulin resistance

• **Viral**
  – Genotype 3
  – Coinfection with HBV or HIV

• **Non-modifiable**
  – Fibrosis stage
  – Inflammation grade
  – Older age at time of infection
  – Male sex
  – Organ transplant

Interplay Between Metabolic Factors and Chronic Hepatitis C (CHC)

HCV and Metabolic Syndrome Factors

• Individuals with HCV infection are predisposed to develop T2DM at least one decade earlier than those without HCV infection.\(^1\)

• Eradication of HCV infection is associated with reduced incidence of glucose metabolism disturbances after treatment, independent of other predisposing factors.\(^2\)

• Pioglitazone does not produce significant reductions in viral load.\(^3\)

Peginterferon + Ribavirin: The Distant Past
Peginterferon/Ribavirin in GT1: Presence of Metabolic Syndrome Led to Lower Response Rates

Sulkowski M et al., EASL 2010
The Higher Number of Metabolic Syndrome Criteria Met, The Lower The Chance of Cure (SVR) with PEG-IFN/RBV Treatment

Sulkowski M et al., EASL 2010
Insulin Resistance Defined by HOMA-IR > 2 and Achievement of SVR with PEG-IFN/RBV

• Differences greatest in individuals with higher insulin resistance and individuals with advanced fibrosis

Eslam M et al., *Alimentary Pharmacology and Therapeutics*, 2011; 34: 297-305
Is Direct-Acting Antiviral Therapy Also Negatively Impacted by Metabolic Syndrome?
The HCV Lifecycle: Multiple Targets

FDA Approved Direct-Acting Antiviral Agents (DAAs) from Multiple Classes

Note the common root name for each drug class
Principles of All Oral Regimens for HCV

• Combine drugs from different classes
  – Target multiple targets to increase efficacy
  – Decrease risk of viral resistance
• If done properly
  – Near universal efficacy
  – Shortened duration of therapy
  – Adverse events have minimal impact on patient’s quality of life
Ombitasvir/Paritaprevir/r + Dasabuvir + RBV: SAPPHIRE-I

Genotype 1, treatment-naïve, noncirrhotic, 12 weeks, n=473

SAPPHIRE-II & PEARL-II
Ombitasvir/Paritaprevir/r + Dasabuvir, No Cirrhosis

- Ombitasvir/paritaprevir/r + dasabuvir
- Treatment-experienced patients (PEG/RBV)
- Duration: 12 weeks
- SAPPHIRE-II
  - 1a and 1b
  - Ribavirin for all
  - Sample size 394
- PEARL-II
  - 1b only
  - +/- ribavirin
  - Sample size 179

ION-3: Ledipasvir/Sofosbuvir ± RBV GT1 Treatment Naïve Noncirrhotic: 8 Weeks vs 12 Weeks

C-EDGE: Grazoprevir/Elbasvir (GZR/EBR) for 12 Weeks in GT 1 Treatment-Naïve Patients

- 67% of failures due to relapse
- Most common adverse events were headache, fatigue, nausea and arthralgia (no difference from placebo arm)

Zeuzem et al., Abstract G07, EASL 2015; published online at Ann Intern Med (www.annals.org) on 24APR15.
ASTRAL-1: Sofosbuvir/Velpatasvir ± RBV x 12 Weeks in Tx-naïve Patients

Overall

618/624

99

GT1

323/328

98.5

SVR12 %

Velpatasvir (VEL, GS-5816): pangenotypic HCV NS5A inhibitor; 22.3% Cirrhosis

Feld JJ, et al. NEJM 2015
Is the patient taking any drugs that could have a potential drug:drug interaction with a DAA?

- Antiarrhythmics e.g. digoxin, amiodarone
- PPIs/acid reducing agents
- Herbal supplements
- HIV antivirals e.g. tenofovir, lopinavir/ritonavir
- Drugs that are renally cleared

Is a co-medication contraindicated or is a dose adjustment required?

Can plasma levels of co-medications be easily monitored to ensure they remain within the established therapeutic range?

Great reference tool: www.hep-druginteractions.org
Summary

• Treating patients with diabetes and other components of metabolic syndrome is safe and highly efficacious.
• Multiple all-oral options with cure rates >95%.
• Typical treatment duration is 12 weeks (as short as 8 weeks in some; up to 24 weeks in others).
• Important to review concomitant medications and make appropriate modifications, if necessary.
Back to Dr. Liu
Izzy

• Treated with a DAA regimen, achieved SVR12 and was cured of HCV.
• 3 months later was involved in motor vehicle accident requiring 6 months of PT.
• In that time period, she stopped exercising and gained 30 lbs.
• BMI now 37.
• Hypertension, T2DM and dyslipidemia under control.
• Her friend recently underwent bariatric surgery and looked great and Izzy wants to know if she can do the same...
Obesity Management

Nicole Basa, M.D., F.A.C.S.
Assistant Professor of Surgery,
Texas A&M Medical School
Cedar Park Surgeons, P.L.L.C.
Cedar Park, Texas
Obesity Pandemic

• In the United States it is more common to be overweight than not.
  - Over 2/3 of the population meet the criteria
    • BMI over 25
  - Over 1/3 are obese
    • BMI over 30
Strategies for Weight Loss

• Diet and Exercise
• Medications
• Surgery
Diets

• An estimated 60 million Americans go on some form of diet each year.

• Over $50 billion a year is spent on diets, pills and other dietary products.

• Programs tend to be good at initial weight loss but does not include counseling to sustain weight loss.

• Research has shown that 95% of those who lose weight gain it back within 3 years.
Diet and Exercise

• Persistent Metabolic Adaptation 6 years after “The Biggest Loser” Competition, *Obesity Biology and Integrated Physiology* 2016
  – 14 out of 16 “Biggest Loser” competitors from season 8 were followed for 6 years
  • Resting Metabolic Rate Measured
    – RMR at baseline was 2607 kcal/day and fell to 1996 kcal/day after the 30 week competition
    – “Metabolic Adaptation” or “adaptive thermogenesis,” occurs
Metabolic Adaptation

• Weight loss is accompanied by a slowing of resting metabolic rate (RMR)
• The RMR after weight loss is lower than would be expected based on the measured changes in body composition
• In a study several years ago 16 people who competed in “Biggest Loser” body composition was measured
  – Weight was lost primary from fat mass (FM) with relative preservation of fat-free mass (FFM)
Diet and Exercise vs. Surgery

• Metabolic Adaptation increased 6 years after the “Biggest Loser” competition

• Bariatric Surgery- Roux en Y Gastric Bypass patients had significant metabolic adaptation 6 months after surgery and no detectable metabolic adaptation after 1 year
  – It is possible that the lack of long-term metabolic adaptation may reflect a permanent resetting of the body weight set-point
Weight Loss Long-term

Figure 3. The weight loss curves for patients treated conservatively and surgically (Adapted from Martin FL et al. Comparison of the costs associated with medical and surgical treatment of obesity. Surgery 1995; 118: 599-607. Used with permission).
Medications

• Qsymia (Phentermine/Topiramate)
  – 5-10% weight loss

• Lorcaserin (Belviq)
  – Serotonin 2C receptor agonist in hypothalamus

• Liraglutide 3.0 mg (Saxenda)
  – GLP 1 agonist
Bariatric Surgery

- Basic Criteria:
  - BMI ≥ 40 or
  - BMI ≥ 35 with one or more obesity related comorbidity

Most likely insurance approved comorbidities:
1. Sleep Apnea
2. Diabetes Mellitus
3. Hypertension on multiple medications
Mortality Reduction

Surgical Patients Had Nine Times Lower Risk of Dying Within the Study Period

* Includes perioperative (30-day) mortality of 0.4%

Gastric Bypass

- Malabsorptive
- Restrictive
- 75% Excess Wt. Loss

Sleeve

- 65% Excess Wt. Loss

Lap Band

- 40% Excess Wt. Loss
- Restrictive
Hunger Hormones

• Ghrelin
  – Increases right before a meal
  – Appetite stimulant
“Fullness” Hormones

- GLP-1 and Insulin
  - Decreases food intake
  - Appetite suppressant

- Peptide YY
  - Causes fullness after a meal
  - Appetite suppressant
Neurohormonal control of appetite
Lap Band
Lap Band

• Peak placement in 2008
• Currently only 10% of bariatric procedures worldwide
• Banding exerts a temporary weight loss
  – Weight loss due to decreased food intake
  – No direct neuro-hormonal effects
  – Ghrelin levels are elevated
Ghrelin - Hunger

Korner et al. Differential effects of Gastric Bypass and Banding on Circulating Gut hormone and Leptin Level, Obesity, Sept 2006
GLP-1 Causes Fullness

PYY Causes Fullness

# Lap Band Outcomes

<table>
<thead>
<tr>
<th>Studies</th>
<th>Length of Follow up (mean)</th>
<th>Patient number</th>
<th>Reoperations (% of patients)</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolonen et al.</td>
<td>7 years</td>
<td>123</td>
<td>25%</td>
<td>Failure rate 15% 1-3yr 40% 8-9 yrs</td>
</tr>
<tr>
<td>Suter et al.</td>
<td>8 years</td>
<td>317</td>
<td>21.7%</td>
<td>Failure rate 40% at 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>33% developed late complications</td>
<td></td>
</tr>
<tr>
<td>Camerini et al.</td>
<td>13 years</td>
<td>45</td>
<td>60% of bands removed</td>
<td>Longest Follow up. Discouraged band placement</td>
</tr>
</tbody>
</table>
Sleeve Gastrectomy
Remnant Stomach
Comorbidity Resolution with the Sleeve Gastrectomy

Table 2
Comorbidity resolution after sleeve gastrectomy

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Follow-up</th>
<th>T2DM</th>
<th>HTN</th>
<th>Hyperlipidemia</th>
<th>Sleep apnea</th>
<th>DJD/joint pain</th>
<th>GERD</th>
<th>Peripheral edema</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cottam et al (2006)³</td>
<td>126</td>
<td>1 yr</td>
<td>81% R</td>
<td>78% R</td>
<td>73% R</td>
<td>80% R</td>
<td>85% R</td>
<td>70% R</td>
<td>91% R</td>
<td>67% R</td>
</tr>
<tr>
<td>Hamoui et al (2005)⁴</td>
<td>118</td>
<td>2 yr</td>
<td>47% R</td>
<td>15% R</td>
<td>5% I</td>
<td>7% I</td>
<td>6% I</td>
<td>8% I</td>
<td>3% I</td>
<td>9% I</td>
</tr>
<tr>
<td>Moon Han et al (2005)⁵</td>
<td>60</td>
<td>1 yr</td>
<td>100% R</td>
<td>93% R</td>
<td>45% R</td>
<td>100% R</td>
<td>76% R</td>
<td>80% R</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Silecchia et al (2006)⁶</td>
<td>41</td>
<td>18 mo</td>
<td>79.6% R</td>
<td>62.5% R</td>
<td>30% I</td>
<td>56.2% R</td>
<td>24% I</td>
<td>20% I</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

T2DM = Type 2 diabetes mellitus; HTN = hypertension; DJD = degenerative joint disease; GERD = gastroesophageal reflux; R = resolved; I = improved.

- Vidal from Spain reports that at 4 months the resolution of Type II DM was similar in Lap Sleeve (51.4%) patients compared to the Lap Roux en Y Gastric Bypass (62%) patients

Roux-en-Gastric Bypass
Roux en Y Gastric Bypass

• Gold standard procedure
• Works through restriction and malabsorption
• Resolution of diabetes prior to weight loss
• Decrease in hunger hormones
• Increase in satiety
<table>
<thead>
<tr>
<th></th>
<th>RYGB</th>
<th>AGB</th>
<th>VSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid homeostasis</td>
<td>Elevated HDL</td>
<td>Elevated HDL</td>
<td>Elevated HDL</td>
</tr>
<tr>
<td></td>
<td>Reduced triglycerides</td>
<td>Reduction in triglycerides not as dramatic as RYGB or VSG</td>
<td>Reduced triglycerides</td>
</tr>
<tr>
<td></td>
<td>Reduced total cholesterol, LDL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose homeostasis</td>
<td>Improved fasting blood glucose</td>
<td>Improvements are slower and not</td>
<td>Improved fasting blood glucose</td>
</tr>
<tr>
<td></td>
<td>and insulin sensitivity, prior to</td>
<td>as dramatic as after VSG or RYGB</td>
<td>and insulin sensitivity, prior to</td>
</tr>
<tr>
<td></td>
<td>weight loss</td>
<td></td>
<td>weight loss</td>
</tr>
<tr>
<td>Role of gastric restriction</td>
<td>Has not yet been directly tested</td>
<td>Failure of band leads to less</td>
<td>Gastric restriction is not the critical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gastric restriction and less</td>
<td>factor preventing hyperphagia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>weight loss</td>
<td></td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>Few published studies</td>
<td>No overall change in gastric emptying rate;</td>
<td>Most papers show increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emptying rate of proximal pouch created by band is enhanced</td>
<td></td>
</tr>
<tr>
<td>Energy expenditure</td>
<td>Controversial</td>
<td>Not reported</td>
<td>Unchanged, but only reported in one study</td>
</tr>
<tr>
<td>Leptin</td>
<td>Circulating leptin levels lower than expected for body weight; Changes to leptin sensitivity not tested</td>
<td>Plasma leptin reduced, as expected for body weight; Changes to leptin sensitivity not tested</td>
<td>Circulating leptin levels lower than expected for body weight; Body weight changes not driven by changes to leptin sensitivity</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Reduced total ghrelin; Controversial, but no change in acyl-glycerin levels</td>
<td>Increased circulating ghrelin</td>
<td>Reduced total ghrelin; Controversial, but no change in acyl-glycerin levels</td>
</tr>
<tr>
<td>CCK</td>
<td>No change</td>
<td>No change</td>
<td>Not measured</td>
</tr>
<tr>
<td>GLP-1 (postprandial)</td>
<td>Weight loss-independent postprandial increase</td>
<td>Increased circulating GLP-1 but much less than RYGB or VSG</td>
<td>Weight loss-independent increase comparable to RYGB</td>
</tr>
<tr>
<td>PYY (postprandial)</td>
<td>Increased postprandial PYY levels; Reduced body weight loss in PYY knockout mice</td>
<td>No change</td>
<td>Increased postprandial PYY levels, comparable to levels after RYGB</td>
</tr>
<tr>
<td>Bile acids</td>
<td>Increased plasma bile acids</td>
<td>Not reported</td>
<td>Increased plasma bile acids</td>
</tr>
<tr>
<td>Diet Change</td>
<td>Decreased fat intake, more fruits and vegetables</td>
<td>Decrease bread intake and increase in caloric liquids; Greater fat intake and fewer fruits/vegetables than RYGB</td>
<td>Decreased fat intake, similar to RYGB</td>
</tr>
<tr>
<td>Food Intolerance</td>
<td>Some dumping syndrome, usually well-tolerated</td>
<td>More persistent and problematic than RYGB; Mainly vomiting</td>
<td>Little or none</td>
</tr>
</tbody>
</table>
Sleeve and Gastric Bypass Hormonal Changes

- Ghrelin decreased
- Peptide YY increased
- GLP-1 increased
- Leptin decreased
- Resistin decreased
2016 ADA Guidelines

**Table 6.1—Treatment for overweight and obesity in type 2 diabetes**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>23.0* or 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, and behavioral therapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</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>

+ Treatment may be indicated for selected motivated patients.
* Cutoff points for Asian American individuals.
Izzy (2007)

- Izzy undergoes lap band procedure.
- Over 6-9 months, successfully achieves substantial weight loss; hypertension, diabetes and dyslipidemia well controlled.
- She swears that she will eat well and exercise regularly in order to maintain the weight loss.
Panel Discussion/Q&A