Use of GLP1-Receptor Agonists and Obesity Management in the Transplant Patient

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Objectives

- Define obesity as a disease and its prevalence
- Describe mechanisms that contribute to obesity
- Identify common comorbidities
- Explain the relationship between obesity and the transplant patient
- Identify treatment options:
  - Lifestyle modifications
  - Bariatric surgery
  - Pharmacologic options, including GLP-1 Receptor Agonists

What is obesity?

"Obesity is defined as a **chronic**, **progressive**, **relapsing**, and **treatable multi-factorial, neurobehavioral disease,** wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences."

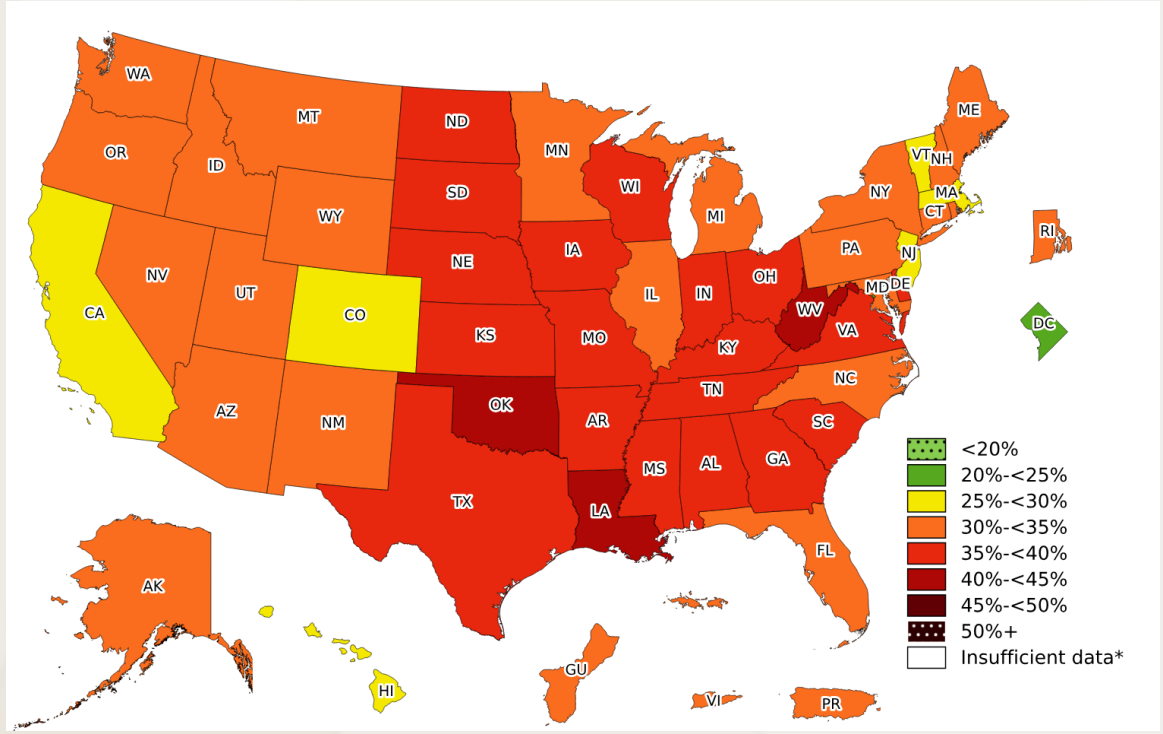
– The Obesity Medicine Association

What is obesity?

BMI	Classification
<18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Overweight
≥ 30	Obesity
30.0-34.9	Class I
35.0-39.9	Class II
≥ 40	Class III

Obesity Statistics

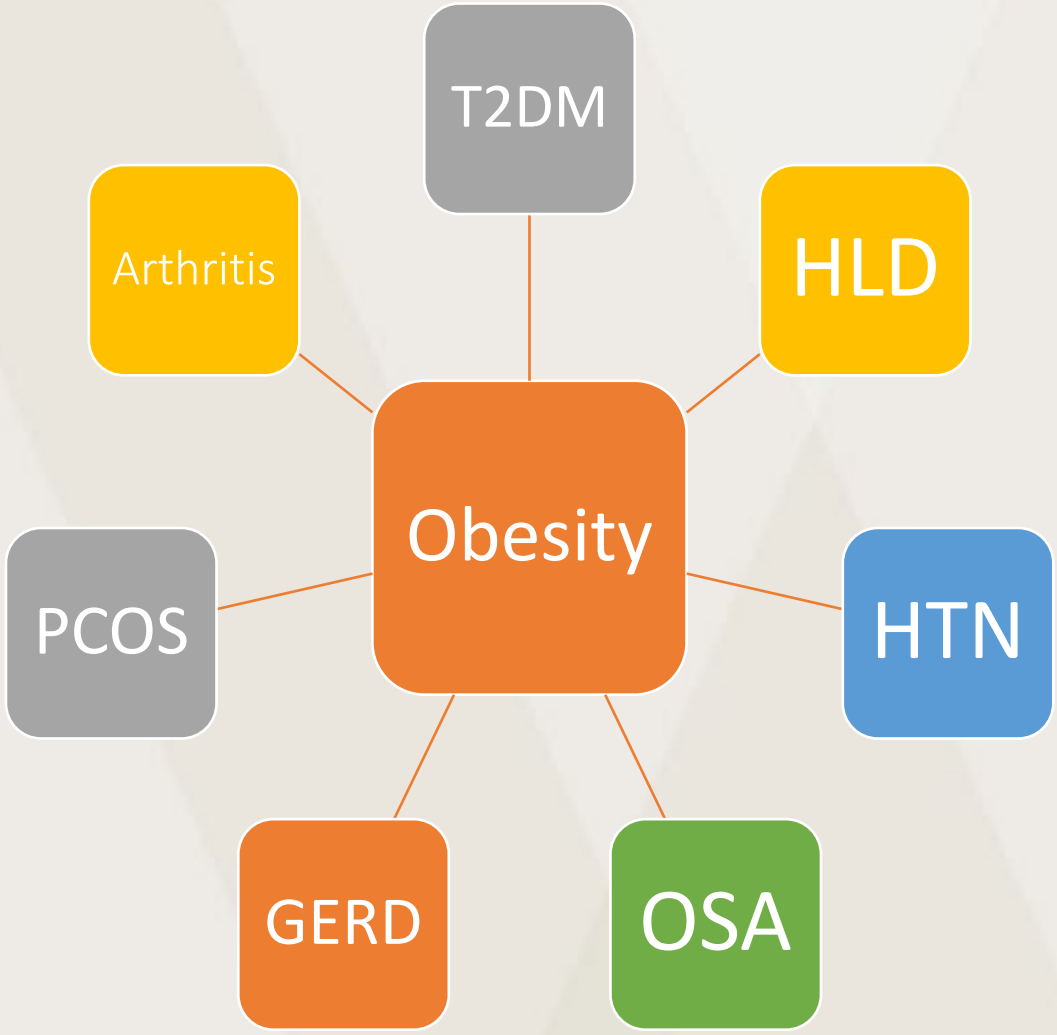
- NHANES/CDC National data: 2020
  - 30.7% of adults are overweight
  - 42.4% of adults suffer from obesity
  - 19.7% children and adolescents
- State of TN
  - 38.9% of adults suffer from obesity
- Cost of obesity?
  - 173 billion dollars per year (2019)



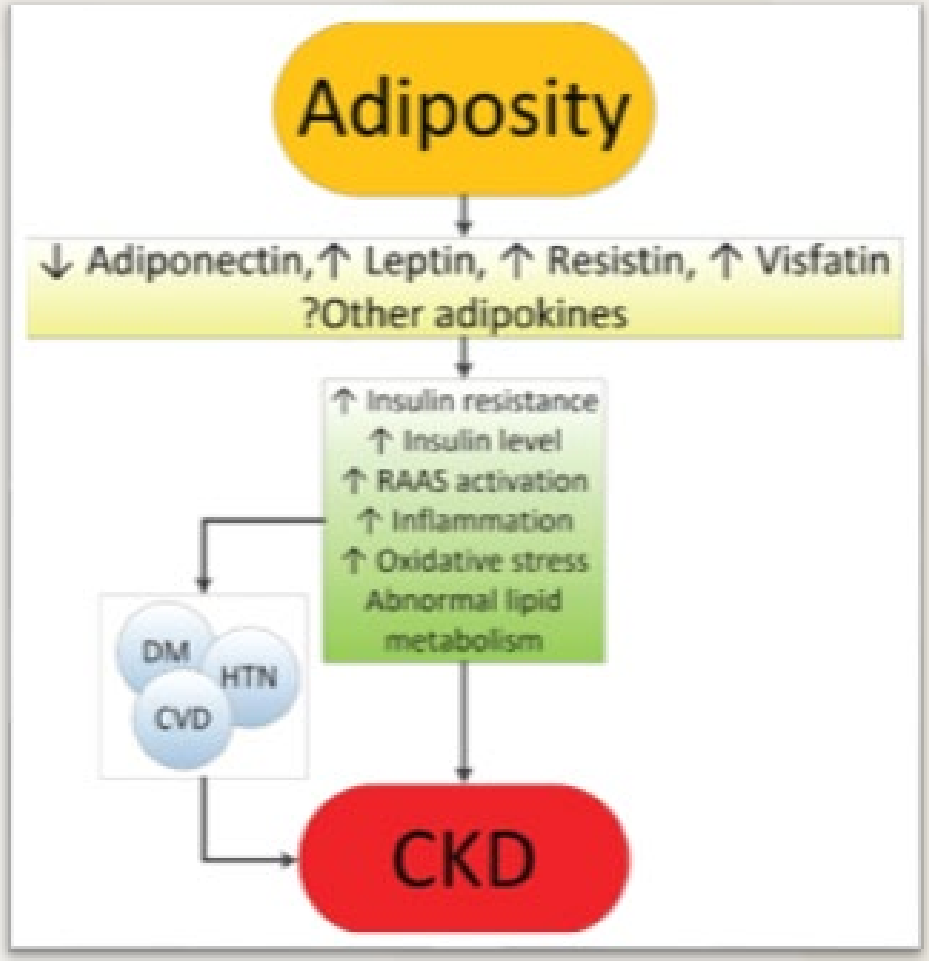
Contributing Factors to Obesity

Genetics/Biology	Insulin Resistance	Eating Disorders	Behavioral Health disorders	Medications
Environmental	Developmental	Psychosocial	Early Life Events	Stress
Lack of Exercise	Pregnancy/Hormone imbalances	Substance use	Eating choices and behaviors	Sleep

Comorbidities Associated with Obesity



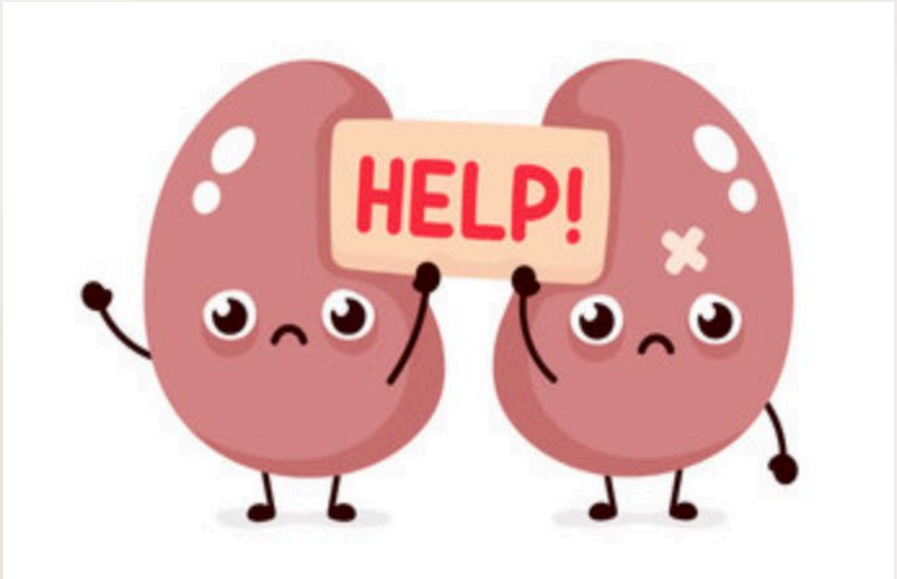
Obesity and CKD



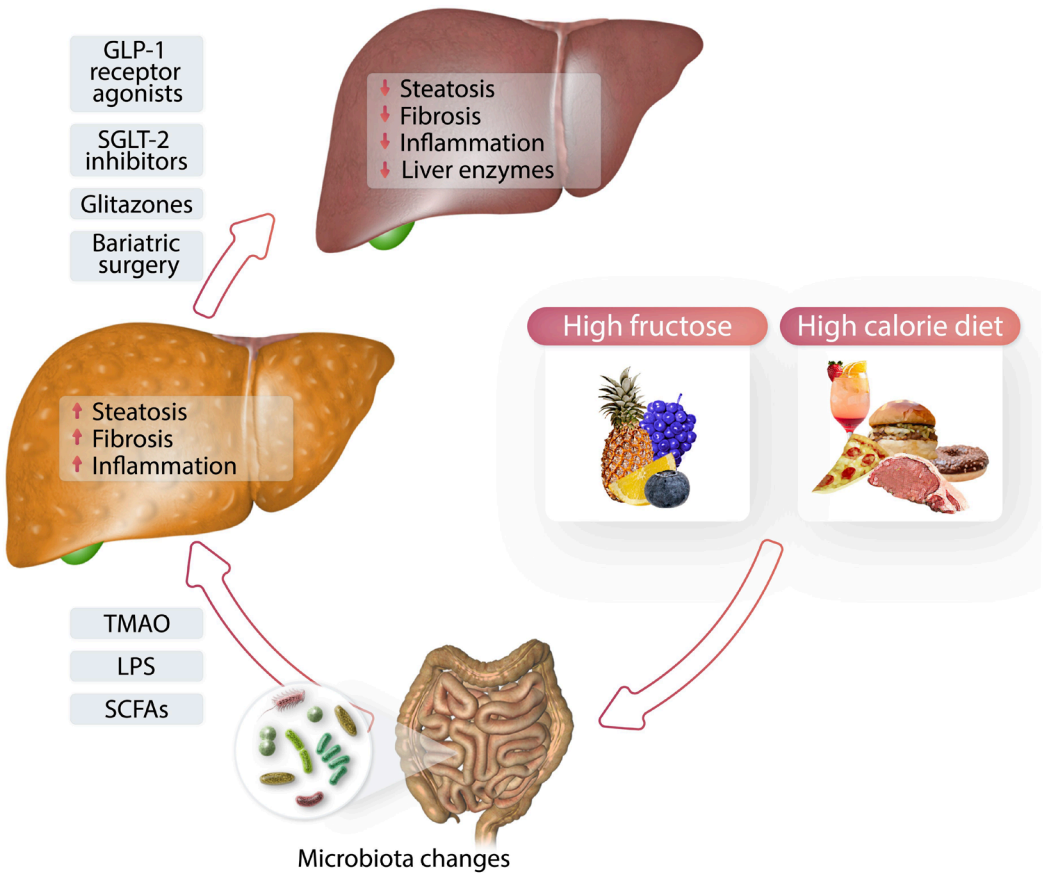
- Intrarenal fat accumulation along proximal tubule and glomeruli → hyperfiltration → glomerular injury → impaired GFR and albuminuria
- Comorbid CVD, T2DM, HTN worsens CKD
- Weight loss associated with reduction in albuminuria

Obesity and Kidney Transplant

- Patients with obesity are at higher risk of complications post-transplant:
  - Wound complications/infections
  - Cardiac disease, T2DM
  - Longer length of hospital stay
  - Delayed graft function/acute rejection
  - Morbidity and mortality



Obesity and NAFL/NASH

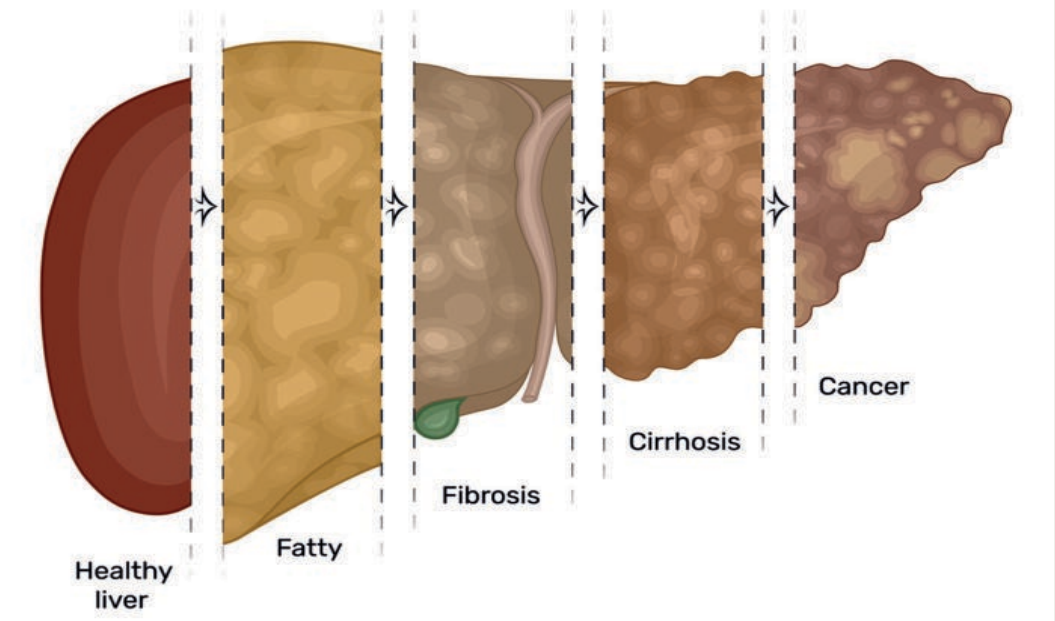


Grander, et al.,2023

- NAFLD expected to become leading cause of liver transplant by 2030
- NAFL: excess hepatic fat
- NASH: excessive hepatic fat + liver inflammation, may lead to fibrosis and cirrhosis and cancer
- Dietary byproducts cause inflammatory changes of liver
- At least 7-10% weight loss is needed for improvement

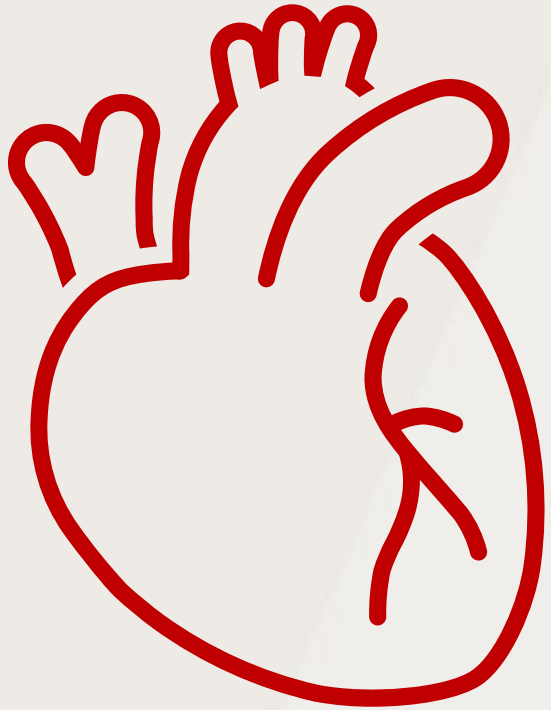
Obesity and Liver Transplant

- Obesity can affect liver transplant patients
- Increased recurrence of NAFLD and NASH
- Increased CV death risk
- Obesity rates following liver transplant
  - 1 year out: 33.7%
  - 5 years out: 40.3%



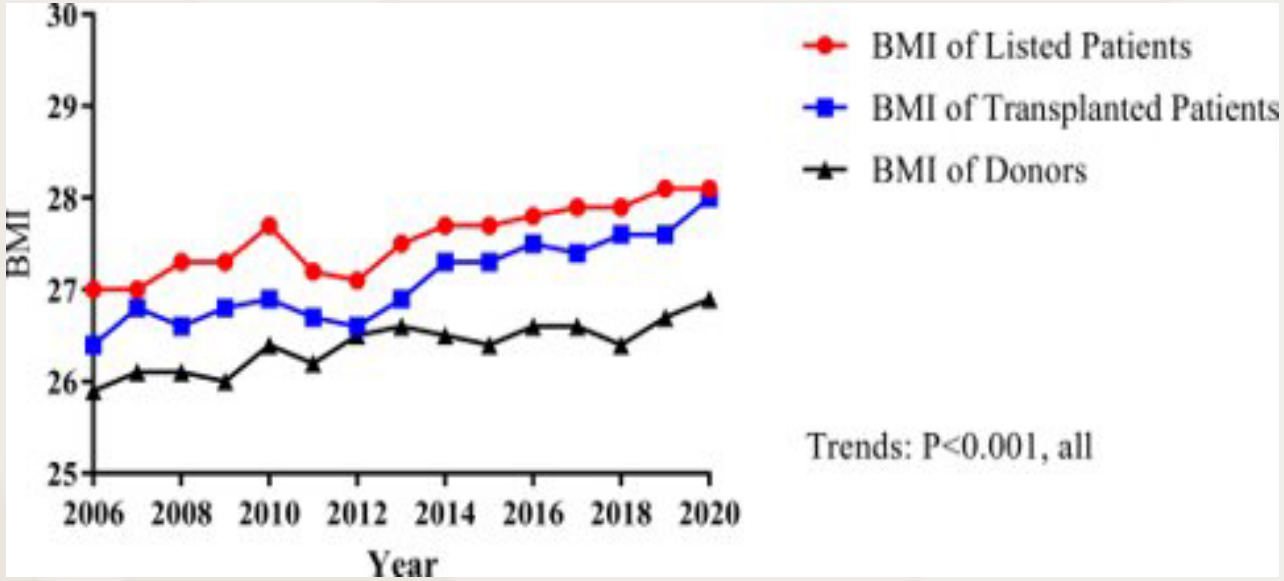
Obesity and Heart Disease

- Insulin resistance/T2DM
- Lipid abnormalities
- HTN
- Left ventricular remodeling
- Central obesity is associated with abnormal cardiac mechanics (i.e., impaired echocardiographic systolic and diastolic strain)
- Sleep disorders
- Endothelial dysfunction



Obesity and Heart Transplant

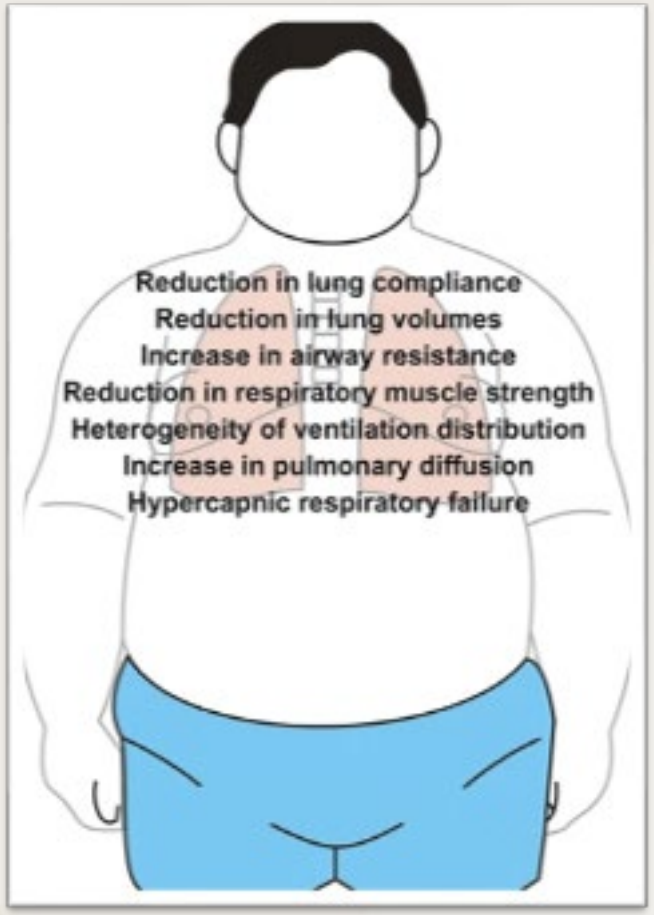
- Patients with obesity are at higher-risk of complications post-transplant:
  - Renal dysfunction
  - Diabetes
  - Stroke
  - Acute rejection
  - Cardiac allograft vasculopathy
  - Malignancy
  - Mortality



Chouairi et al., 2021

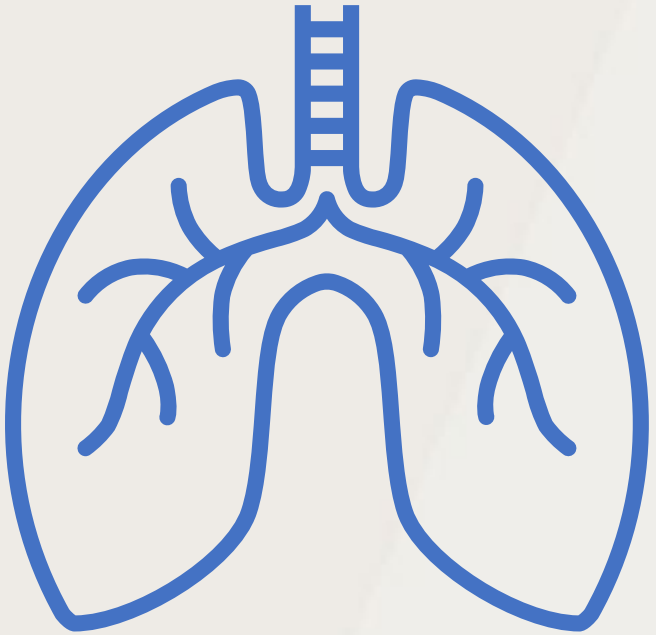
Obesity and Lung Disease

- Restrictive pulmonary damage
- Decreased respiratory compliance, increased pulmonary resistance, and reduced respiratory muscle strength
- Inflammatory changes in obesity



Obesity and Lung Transplant

- Higher BMI after lung transplant associated with longer LOS
- Increase mortality rate in patients with obesity
- Abdominal obesity reduces lung compliance → higher post-operative complication risk
- Increased risk of graft dysfunction



Transplant Patient Demographics at VUMC

- BMI cut-offs for transplant at VUMC
  - Liver: absolute is 50; ideal <40
  - Lung: 35
  - Kidney: 35, can consider above 35 if other comorbidities are present
  - Heart: 40 in general; can consider in low 40s if patient is very sick or more muscular build

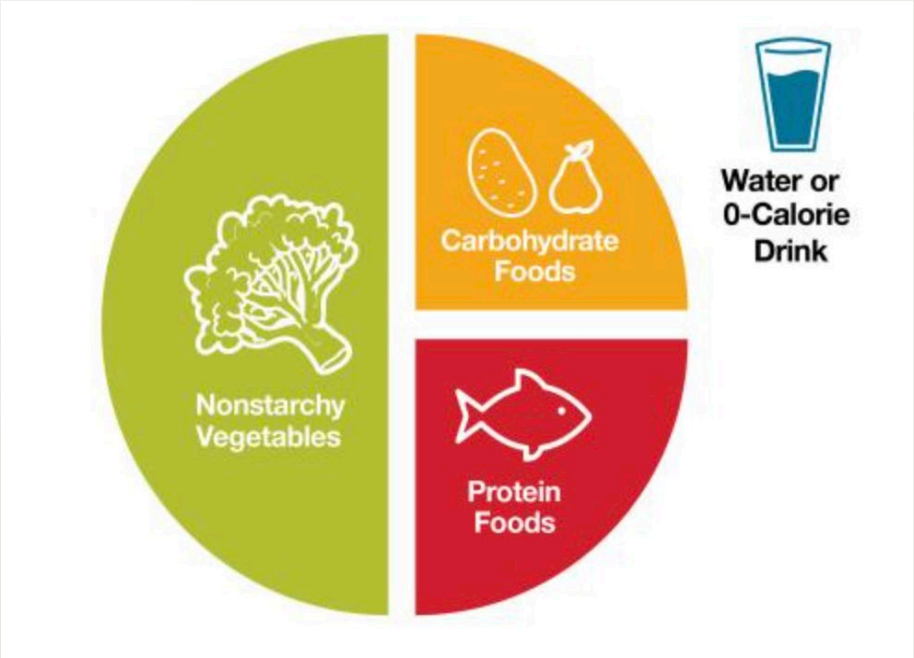
Effect of Immunosuppressants on the Transplant Patient

Glucocorticoids	Calcineurin Inhibitors (Cyclosporin, Tacrolimus)	MTOR Inhibitors (Sirolimus)	Azothioprine, Mycophenalate Mofetil	Selective T-Cell Costimulation Blocker (Belatocept)
↑ blood glucose ↓ insulin secretion (beta cell apoptosis) ↓ expression of glucose transporters ↑ body weight, blood pressure, and blood lipids	↓ insulin secretion Toxic effect on pancreatic beta cells Cause hypomagnesemia (↑ risk of PTDM) ↑ body weight & components of metabolic syndrome	Impair insulin secretion ↓ insulin signal transduction ↑ body weight & components of metabolic syndrome	Have not been shown to induce Post-transplant DM	Lower PTDM rates than those on CNIs

Treatment Options for Obesity Management

Lifestyle Interventions

- 5-15% weight loss produces great benefits
- Dietary intake, behavior modification, exercise, stress management and good sleep are key for maintenance
- Must monitor weight maintenance closely
- Weight regain is common



ADA, Plate Method

Bariatric Surgery

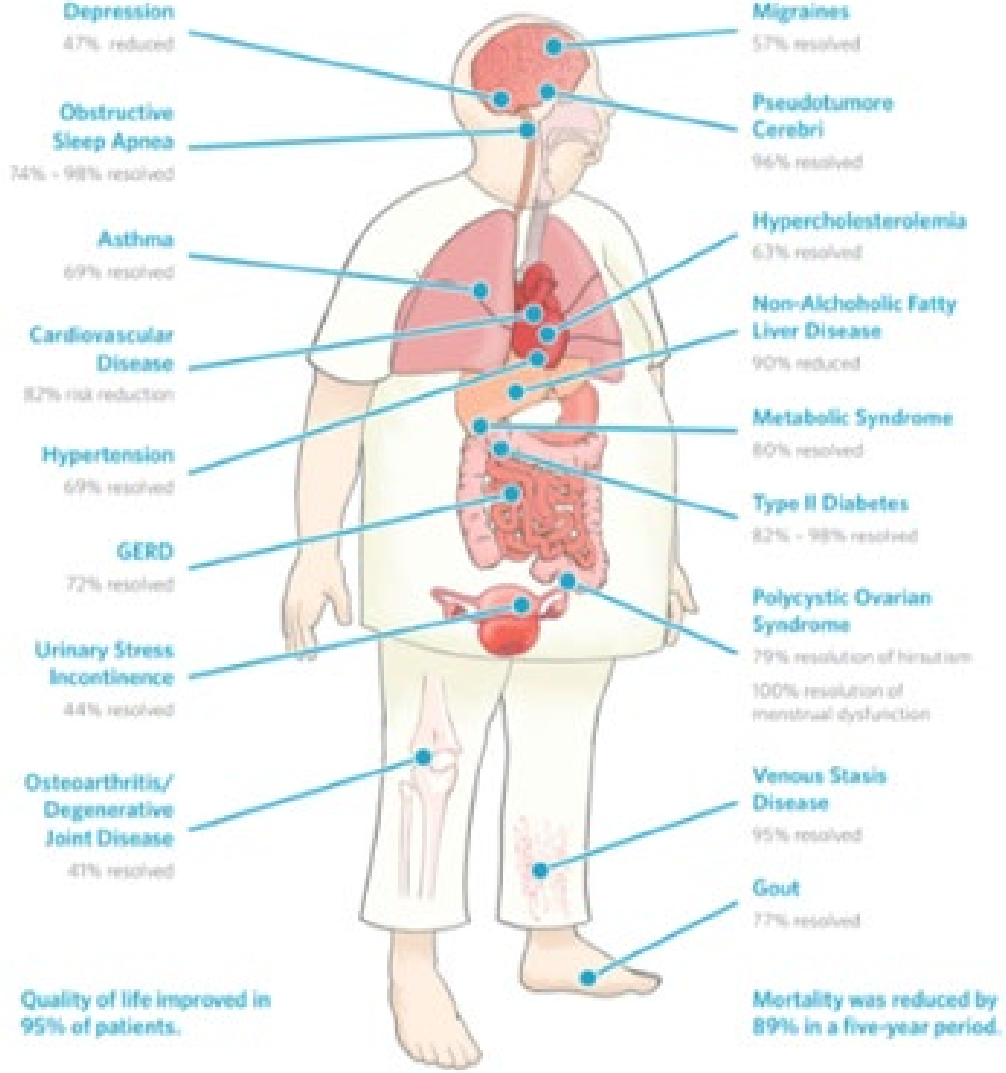
- Safe and effective treatment for obesity

  Mortality rate from bariatric surgery is 0.08%

- Roux-en-Y Gastric Bypass (RYGB)
- Vertical Sleeve Gastrectomy (VSG)
- Adjustable Gastric Band (AGB)

Benefits of Bariatric Surgery

Losing 50% to 70% of excess weight may be just the beginning...



Depression
47% reduced

Obstructive Sleep Apnea
74% - 98% resolved

Asthma
69% resolved

Cardiovascular Disease
82% risk reduction

Hypertension
69% resolved

GERD
72% resolved

Urinary Stress Incontinence
44% resolved

Osteoarthritis/ Degenerative Joint Disease
41% resolved

Migraines
57% resolved

Pseudotumore Cerebri
96% resolved

Hypercholesterolemia
63% resolved

Non-Alchoholic Fatty Liver Disease
90% reduced

Metabolic Syndrome
80% resolved

Type II Diabetes
82% - 98% resolved

Polycystic Ovarian Syndrome
79% resolution of hirsutism
100% resolution of menstrual dysfunction

Venous Stasis Disease
95% resolved

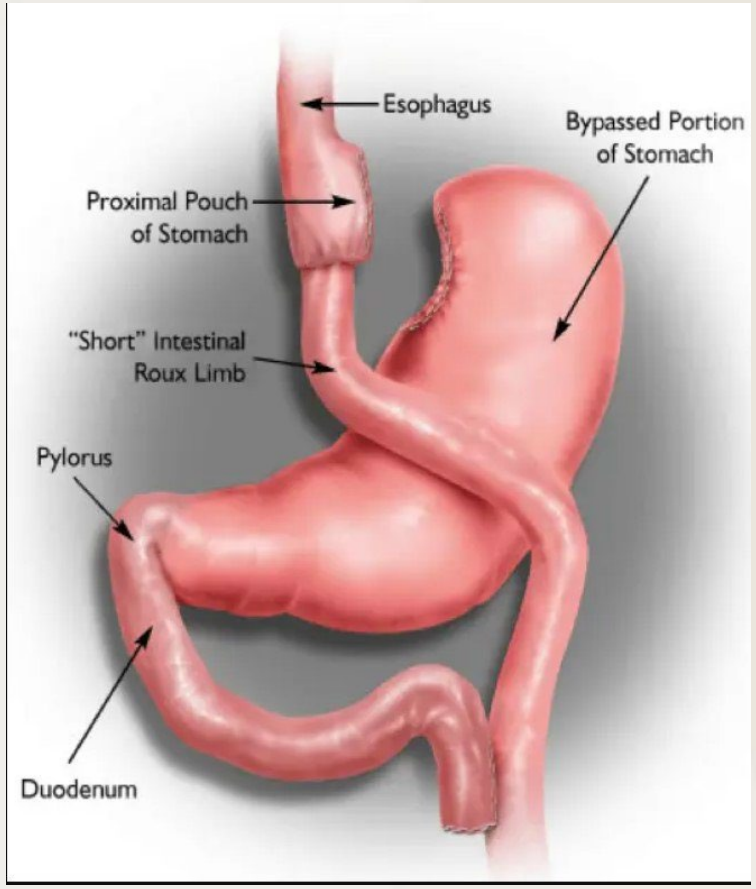
Gout
77% resolved

Quality of life improved in 95% of patients.

Mortality was reduced by 89% in a five-year period.

Roux-en-Y Gastric Bypass

Restrictive and Malabsorptive

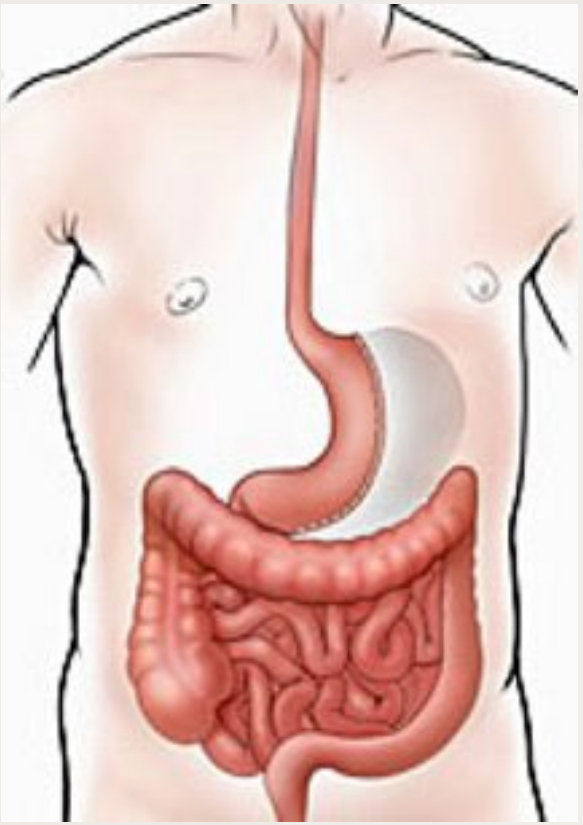


- Weight loss of 60-70% of EBW at 12-18 months post-op
- Small gastric pouch empties directly into the jejunum
- Malabsorption is one of the key components of the surgery
- Patients are required (for life) to take MVI & Calcium supplements daily

Sleeve Gastrectomy (VSG)

Restrictive Procedure

- Weight loss of 60% EBW at 12-18 months post op
- Vitamin deficiencies possible
  - Decreased acid production
  - Loss of intrinsic factors
  - Decreased PO intake
- Gastrectomy leaves a gastric pouch of 100-150 mL in size
- Maintains pylorus function
- No small bowel involved and irreversible



Bariatric Surgery and the Transplant Patient

- Goals of bariatric surgery PRIOR to transplant
- Considerations POST-transplant
- Consensus
  - More research needed, but overall may be a safe option for this patient population

Pharmacology

- Anti-Obesity Medications
  - BMI $\geq$ 27 + 1 weight-related comorbidity and BMI $\geq$ 30
- Goals of therapy:
  - Treat the disease of obesity
  - Facilitate eating behavior changes
  - Reduce weight regain
  - Improve quality of life and overall health
  - Adjunct therapy to bariatric surgery

How do medications work?

- Reduce caloric intake
- Decrease hunger
- Increase satiety
- Change food preferences
- Reduce calorie absorption
- Increase energy expenditure
- Reduce reward value of food
- Treat insulin resistance

FDA-approved Anti-Obesity Medications (AOM)

FDA approved AOM, long-term use

- Qsymia (phentermine/topiramate)
- Contrave (buproprion/naltrexone)
- Xenical (orlistat)
- Saxenda (liraglutide)
- Wegovy (semaglutide)
- Plenity
- Setmelanotide
- For binge eating disorder: Vyvanse

FDA approved AOM, short-term use

- Phentermine

Off-label AOMs

- Topiramate
- Zonisamide
- Bupropion
- Naltrexone

- Diabetic agents
  - Metformin
  - SGLT-2 inhibitors
  - Pramlintide
  - GLP-1/GIP-Receptor Agonist (Tirzepatide)
  - GLP-1 Receptor Agonists
    - Ozempic (Semaglutide)
    - Victoza (Liraglutide)
    - Trulicity (Dulaglutide)
    - Byetta, Bydureon (Exenatide)

AOMs in the Transplant Patient

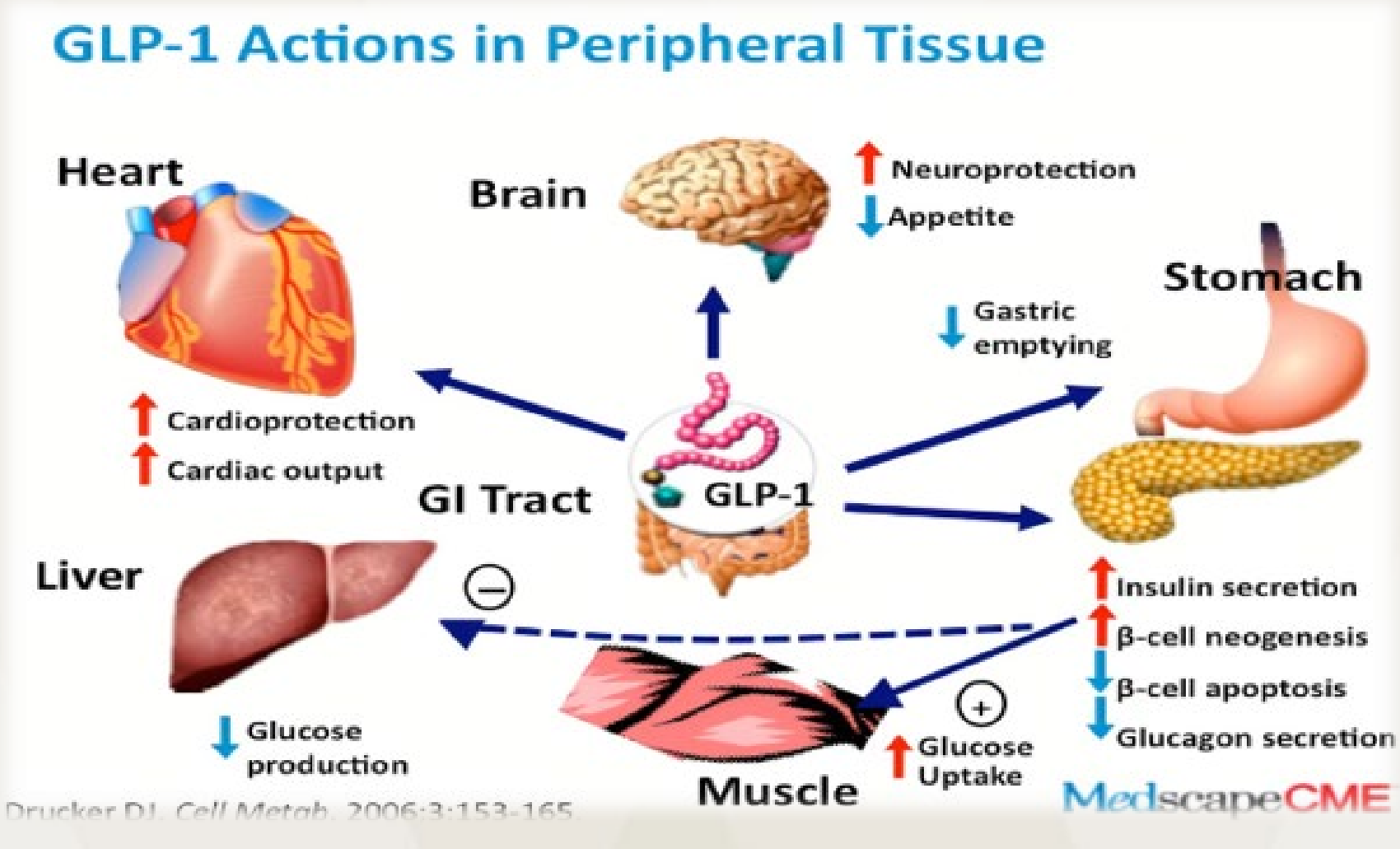
- Phentermine
  - Concerns about side-effect profile & potential for abuse
  - Solid organ transplant (SOT) population at higher risk for cardiovascular morbidity at baseline
- Topiramate
  - May interfere with CNI metabolism
- Bupropion/Naltrexone (Contrave)
  - Need to be cautious with SOT patients → frequent monitoring while on therapy
  - Adverse effects (tremor, seizure, hypertension) may be additive with immunosuppressants
- Orlistat
  - Use of orlistat with tacrolimus and MMF may worsen gastrointestinal-related toxicities
  - Use of orlistat with cyclosporine is generally not recommended due to increased risk of graft rejection

Now, let's talk about GLP-1 Receptor Agonists....

Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs)

- **Benefits:** reduction in energy consumption, changes in food preferences, decreased appetite, increased satiety
- **Side-effects:** nausea, vomiting, constipation, diarrhea, gallstones, possible pancreatitis
- **Contraindications:** medullary thyroid cancer, MEN-2 syndrome, necrotizing/chronic pancreatitis*

GLP-1 RA mechanisms

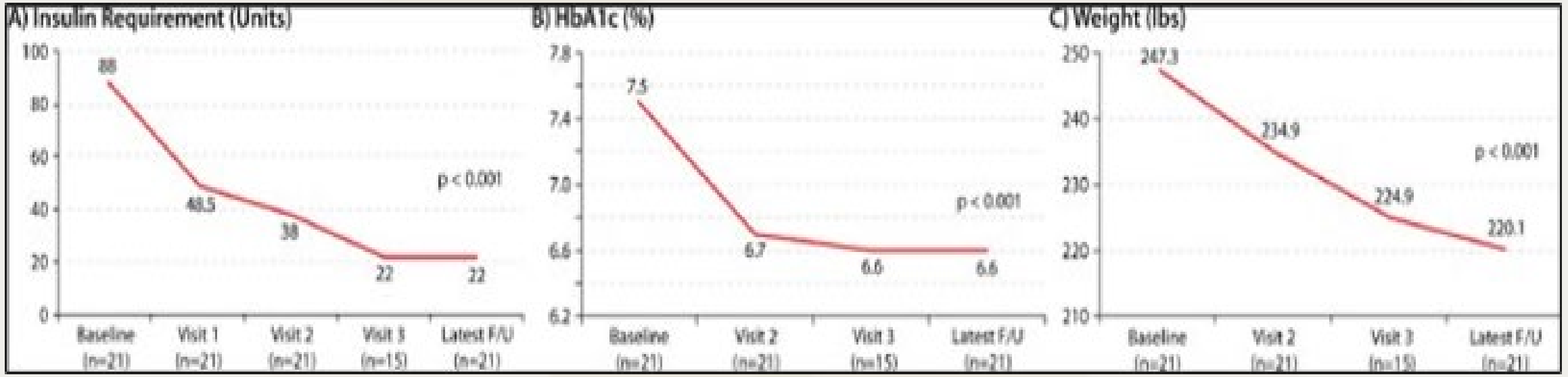


Effects of GLP-1 RAs on Weight

Medication	% Weight Loss
Mounjaro	15-21%
Ozempic/Wegovy	10-16%
Saxenda/Victoza	6-7.5%
Rybelsus	4-7%
Trulicity	4-6%

Use of GLP-1 RA in the Transplant Patient

- BMI reduction
- Improved management of DM
- Limitations in the literature



(Sammour et al. 2021)

Use of GLP-1 RAs in the Transplant Patient

- Side Effects
  - Similar side-effect profile for non-transplant patients
  - Adverse Outcomes
  - Effect on Immunosuppression
    - Several studies identified that GLP-1 RA therapy did not demonstrate impact on immunosuppression

GLP-1 RA Impact on Cardiac & Kidney Outcomes

Dulaglutide

- AWARD-7
  - Delayed decline in eGFR in patients with T2DM & CKD compared to insulin

Liraglutide

- LEADER trial
  - Decreased CV risk
  - Decrease in albuminuria and new onset proteinuria
  - No progression of eGFR

Semaglutide

- SUSTAIN-6
  - Reduces risk of persistent proteinuria
- SELECT
  - Reduces risk of MACE by 20% in patient that are overweight/obese & have established CVD

Tirzepatide

- SURPASS-4
  - Slow the rate of eGFR decline & reduce UACR in patients with T2DM compared to insulin

Special Mention: Mounjaro

- Tirzepatide (Mounjaro)
  - Combination GLP-1 receptor agonist + GIP receptor agonist
  - SURPASS I and II
    - 13.1% weight loss after 40 weeks
    - Tirzepatide for adolescents trial ongoing (SURPASS-PEDS)
  - SURMOUNT I and II
    - 22.5% weight loss at 72 weeks
    - Predicting to have FDA approval for obesity management late 2023
  - SYNERGY–NASH
    - Phase 2 trial ongoing to evaluate of effect of Tirzepatide vs. placebo once weekly for treatment of NASH

Up and coming...

- Retatrutide
  - Triple hormone receptor agonist (GIP, GLP-1, and glucagon receptors)
  - Currently in phase 3 trials
  - Up to 24.4% reduction in body weight at 48 weeks of treatment with highest dose
  - 9/10 patients had resolution of NAFLD after 48 weeks on two highest doses

Case Study

- 66 y.o F s/p heart transplant in 2012 & kidney transplant in 2021
- PMH: Class 3 Obesity, HTN,
  OSA, HLD, GERD, fibromyalgia, PTDM
- Established care with Medical Weight Loss Clinic in August 2022
  - Initial weight 227lb, BMI 42.8
- AOM progression:
  - 8/22 start Trulicity (dulaglutide)
  - 12/22 transitioned to Ozempic (semaglutide)
- Last follow-up June 2023:
  - Weight 153lb, BMI 27.1
  - 74 lb weight loss (32% of body weight)

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Questions?

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