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Weight Management: Triggers for Diabetes and Treatment

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PRESENTER DISCLOSURES

Presenter: Kalie Tommerdahl, MD

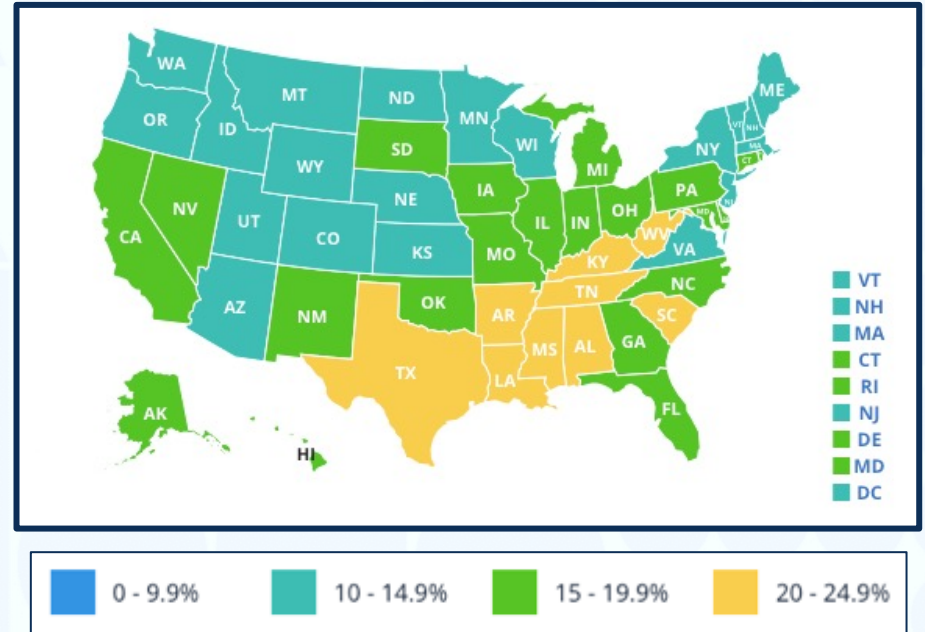
I have no conflicts of interest to disclose.



Pediatric Obesity Epidemic

- Roughly 1 in 6 youth (16.2%) currently have obesity
- Rates of obesity in pediatric patients the United States have remained steady for the past 5 years
- 6 states have significantly higher rates of obesity than the national rate

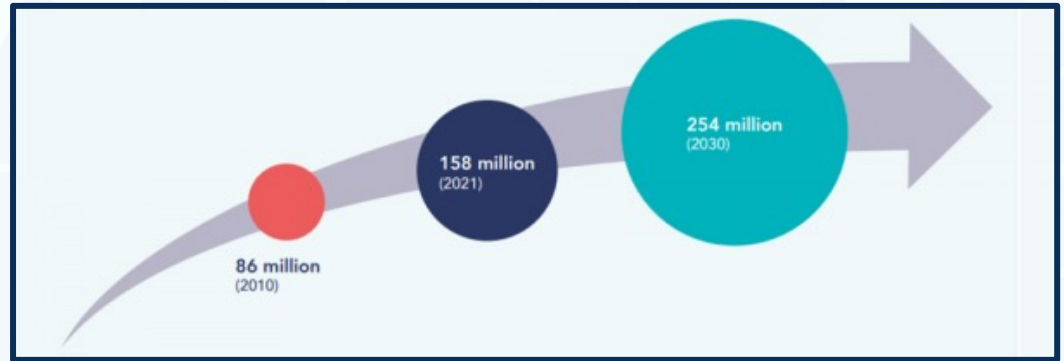
Obesity Rates, Children Ages 10-17 years (2019-2020)



Disparities in Rates of Obesity

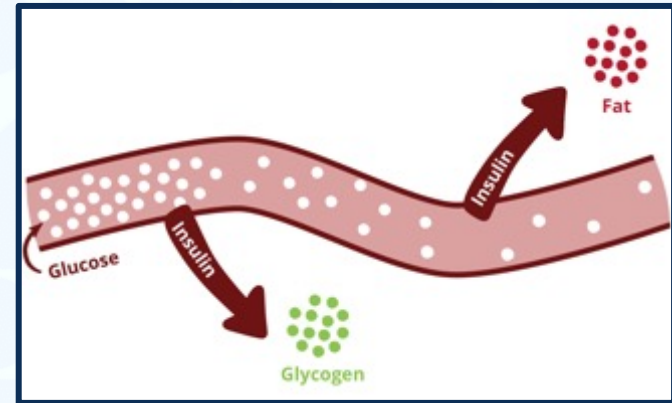
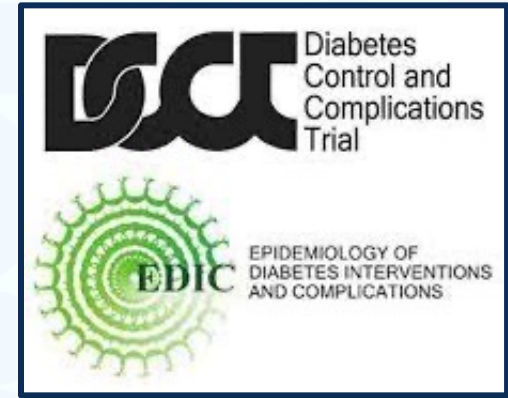
- Distinct disparities in rates of obesity exist by:
- **Race/ethnicity**
 - Non-Hispanic Asian (**8.1%**)
 - Non-Hispanic White (**12.1%**)
 - Hispanic (**21.4%**)
 - Non-Hispanic Black (**23.8%**)
 - Non-Hispanic American Indian/
Alaskan Native (**28.7%**)
- **Socioeconomic status**
 - Highest income group (**8.6%**)
 - Lowest income group (**23.1%**)

Projected number of children aged 5-19 years living with obesity



Obesity and Diabetes

- **Diabetes Control and Complications Trial (DCCT)** showed that intensive insulin management improved glycemia and microvascular complications in type 1 diabetes:
 - Diabetic kidney disease
 - Retinopathy
 - Nephropathy
- However, tight glycemic control is also associated with multiple unintended side effects:
 - Hypoglycemia
 - Weight gain
 - Insulin resistance
 - Inflammation



Purnell JQ et al. JAMA. 1998;280(2):140-6.



Body Mass Index (BMI) Classifications

ADULTS

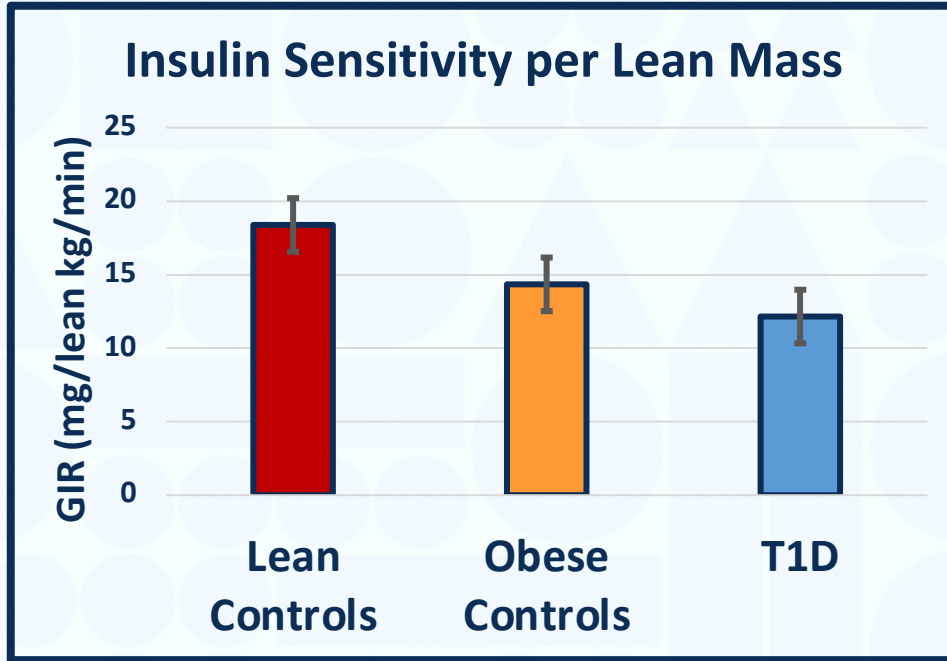
Weight Category	BMI (kg/m ²)
Underweight	<18.5
Normal weight	18.5 to 24.9
Overweight	25.0 to 29.9
Obese	30 to 39.9
Class 3 Obesity	>40

PEDIATRICS

Weight Category	BMI (percentile)
Underweight	<5
Normal weight	5 to 84.9
Overweight	85 to 94.9
Obese	>95



Insulin Sensitivity and Weight



- Type 1 diabetes (T1D) is associated with impaired insulin sensitivity and elevated BMI
- Adolescents with T1D, as compared to matched controls without diabetes, demonstrate decreased:
 - Insulin sensitivity
 - Peak oxygen consumption (VO_2 peak)
 - Peak work rate
- Worse insulin sensitivity and obesity are known risk factors for cardiovascular disease

Nadeau KJ, et al., J Clin Endocrinol Metab, 2010. 95(2): 513-21.

Bjornstad P, et al., Circulation, 2018. 138(25):2895-2907.



EMERALD Study



Hypothesis: Elevated BMI is associated with worse cardiovascular and metabolic outcomes in adolescents with T1D

Pubertal youth aged 12-21 years with T1D and T2D were recruited

RESistance to InSulin in Type 1 ANd Type 2 diabetes (RESISTANT)

Effects of MEtformin on CardiovasculaR Function in AdoLescents with Type 1 Diabetes (EMERALD)



Participants were stratified as:

1. **Lean** (BMI <85%ile),
 2. **Overweight** (BMI 85-<95%ile),
 - or 3. **Obese T1D** (BMI ≥95%ile)
- vs. **T2D**



OUTCOME MEASURES

Participants with T1D or T2D:

- Resting heart rate
- Systolic and diastolic blood pressures
- Mean arterial pressure
- Pulse pressure
- Prevalence of hypertension
- Leptin, adiponectin, and hsCRP

Participants with T1D only:

- Peripheral artery stiffness by Dynapulse
- Aortic shear stress by aortic MRI
- VO_2 peak from maximal exercise by bicycle ergometry



DEMOGRAPHICS

	Lean T1D N=82	Overweight T1D N=28	Obese T1D N=25	T2D N=59
Age (years)	15.7±2.5	16.2±2.3)	15.6±2.1	15.4±2.3
Sex (% female)	50%	79%	32%	71% ^a
Caucasian, n (%)	71 (87%)	26 (93%)	20 (80%)	11 (19%) ^a
Hispanic, n (%)	6 (7%)	0 (0%)	3 (12%)	34 (57%) ^a
BMI (kg/m ²)	20.8±2.2	26.3±2.7	31.1±3.1	33.6±5.9 ^a
Diabetes duration (years)	7.2±4.2	7.3±4.0	5.5±3.6	2.1±1.9 ^a
HbA1c (%)	8.5±1.4	8.6±1.6	8.7±1.5	8.1±2.4

^a $p < 0.05$ T2D vs. obese T1D

Data are expressed as mean ± SD unless otherwise specified



RESULTS: Comparison of CV measures between lean, overweight, and obese participants with T1D vs. T2D

	Lean T1D N=82	Overweight T1D N=28	Obese T1D N=25	T2D N=59
HR (BPM)	68±13	77±13	78±10 ^c	72±13
Systolic BP (mmHg)	114±11	123±9 ^c	124±9 ^c	121±12
Diastolic BP (mmHg)	68±8	73±8 ^c	73±7 ^c	71±11
Prevalence of HTN	10%	26%	44% ^c	12% ^a
Pulse pressure (mmHg)	47±10	51±11 ^c	52±12	51±10
Mean Arterial Pressure (mmHg)	83±8	89±7 ^c	89±5 ^c	87±10 ^a

^a $p < 0.05$ T2D vs. obese T1D

^b $p < 0.05$ obese T1D vs. overweight T1D

^c $p < 0.05$ overweight T1D or obese T1D or T2D vs. lean T1D

Data are expressed as mean ± SD unless otherwise specified



RESULTS: Comparison of CV measures between lean, overweight, and obese participants with T1D vs. T2D

	Lean T1D N=82	Overweight T1D N=28	Obese T1D N=25	T2D N=59
Brachial Artery Distensibility (%/mmHg)	6.26±1.19	5.94±0.90	5.36±0.61 ^c	N/A
VO ₂ peak (mL/kg/min)	31.4±7.2	24.3±5.2 ^c	22.6±3.9 ^{b,c}	N/A
VO ₂ peak (mL/lean kg/min)	43.2±8.1	38.8±6.9	35.7±11.1 ^c	N/A
Descending Aorta Pulse Wave Velocity (m/s)	3.9 (1.2)	4.9 (1.6) ^c	3.6 (1.1) ^b	N/A
Descending Aorta Oscillatory Shear Index	0.04 (0.05)	0.02 (0.01)	0.01 (0.02) ^c	N/A

^a $p < 0.05$ T2D vs. obese T1D

^b $p < 0.05$ obese T1D vs. overweight T1D

^c $p < 0.05$ overweight T1D or obese T1D or T2D vs. lean T1D

Data are expressed as mean ± SD unless otherwise specified



RESULTS: Comparison of CV measures between lean, overweight, and obese participants with T1D vs. T2D continued

	Lean T1D N=82	Overweight T1D N=28	Obese T1D N=25	T2D N=59
Adiponectin ($\mu\text{g/mL}$)	10.7 (9.6, 11.8)	9.7 (7.7, 12.3)	8.6 (7.2, 10.4)	5.1 (4.4, 5.9) ^a
Leptin (ng/mL)	7.7 (6.3, 9.5)	21.5 (16.3, 28.3) ^c	25.9 (21.1, 31.9) ^{b,c}	28.0 (23.3, 33.5)
hsCRP (mg/L)	0.4 (0.3, 0.5)	1.0 (0.6, 1.6) ^c	1.8 (1.2, 2.8) ^{b,c}	2.7 (1.9, 3.7)

^a $p < 0.05$ T2D vs. obese T1D

^b $p < 0.05$ obese T1D vs. overweight T1D

^c $p < 0.05$ overweight T1D or obese T1D or T2D vs. lean T1D

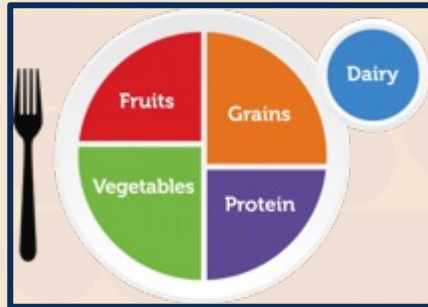
Data are expressed as geometric mean (95% confidence interval)



Obesity Management

Lifestyle

- Healthy food choices
- Portion control
- Daily exercise



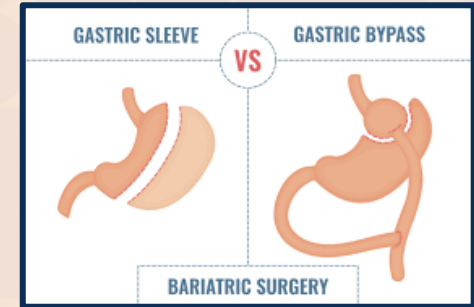
Pharmacologic

- Appetite modifying medications



Surgical

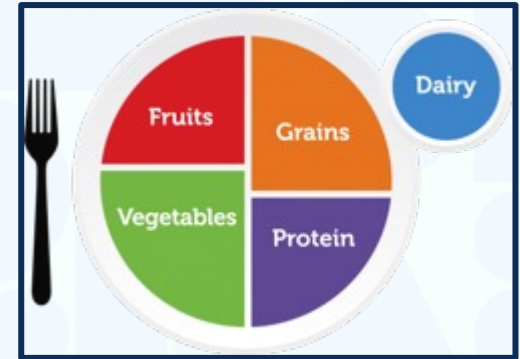
- Gastric sleeve
- Roux-en-Y procedure



Lifestyle Management

- **Healthy food choices:**

- Dietician consultation
- “My Plate” focus
 - Focus on whole fruits, vary your vegetables
 - Make at least half of your grain intake whole grains
 - Vary protein routine
 - Move to low fat or fat free dairy



- **Portion control:**

- Pay attention to appropriate portion sizes, particularly when eating at restaurants

- **Physical activity:**

- Exercise physiotherapist consultation
- 30 to 60 minutes of cardiovascular exercise per day
- Setting achievable goals

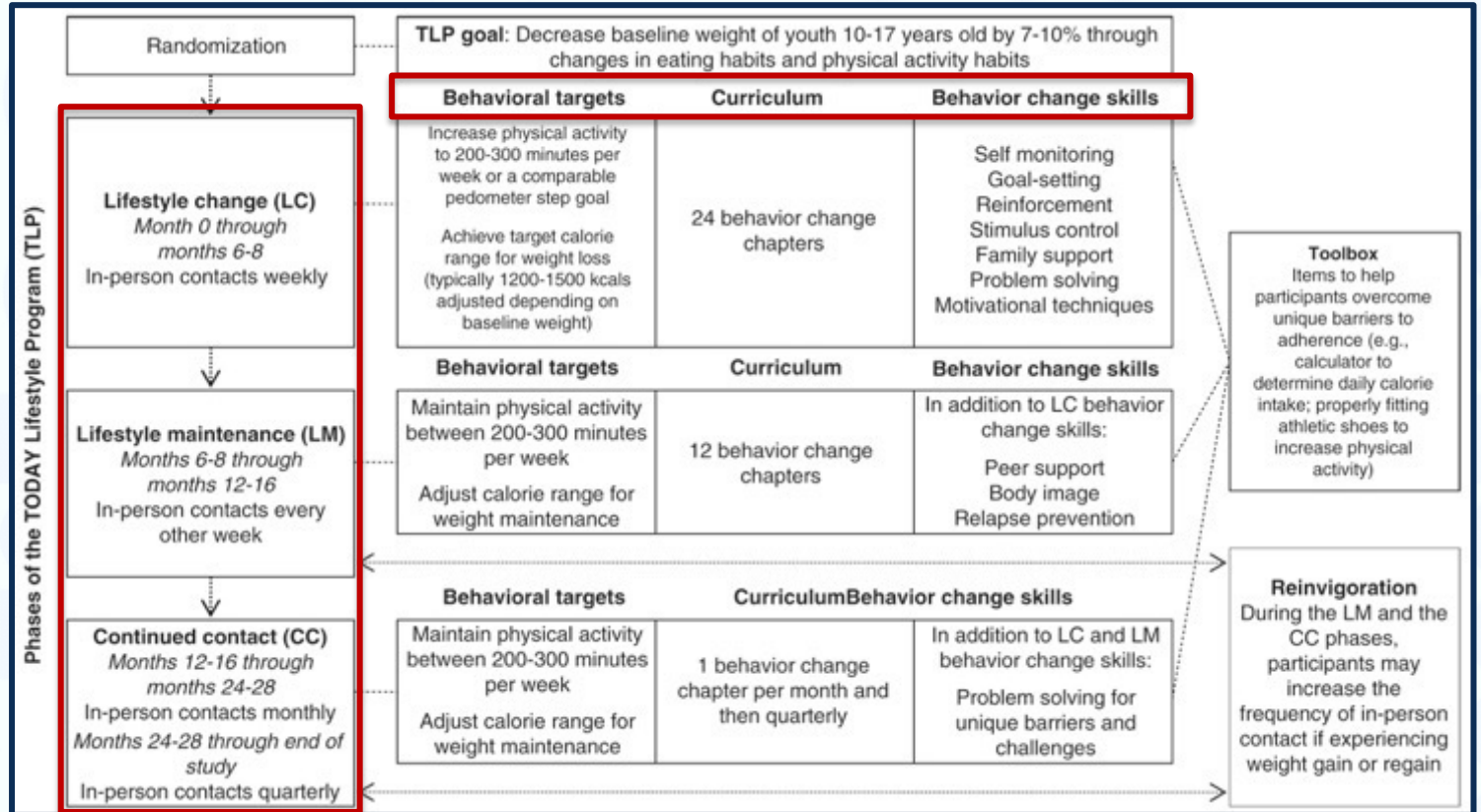


- **Sleep:**

- Focus on age-appropriate sleep duration and good quality sleep



Lifestyle Management: TODAY Study



Pharmacologic Management

- **Metformin/Glucophage (immediate-release or extended-release formulations)**
 - Approved for use in pediatric type 2 diabetes
 - Mechanism: Improves insulin resistance through activation of AMP-activated protein kinase
 - Side effects: Abdominal discomfort, nausea, vomiting, loose stools, lactic acidosis
 - Good for use in girls with PCOS, associated with up to 3% weight loss in pediatrics
- **Phentermine PLUS Topamax**
 - Approved for weight loss in adolescents 17+ years/not approved for weight loss in pediatrics but approved for children 2+ years for seizures
 - Mechanism: Inhibition of norepinephrine reuptake/modulation of GABA
 - Side effects: Increased HR/BP, restlessness, insomnia, potential abuse/dependence; paresthesia, difficulty concentrating, problems with memory, psychomotor slowing, depressed mood
 - Can't be used with pregnancy (teratogenic), MAOI's, hyperthyroidism, hypersensitivity to sympathomimetic amines

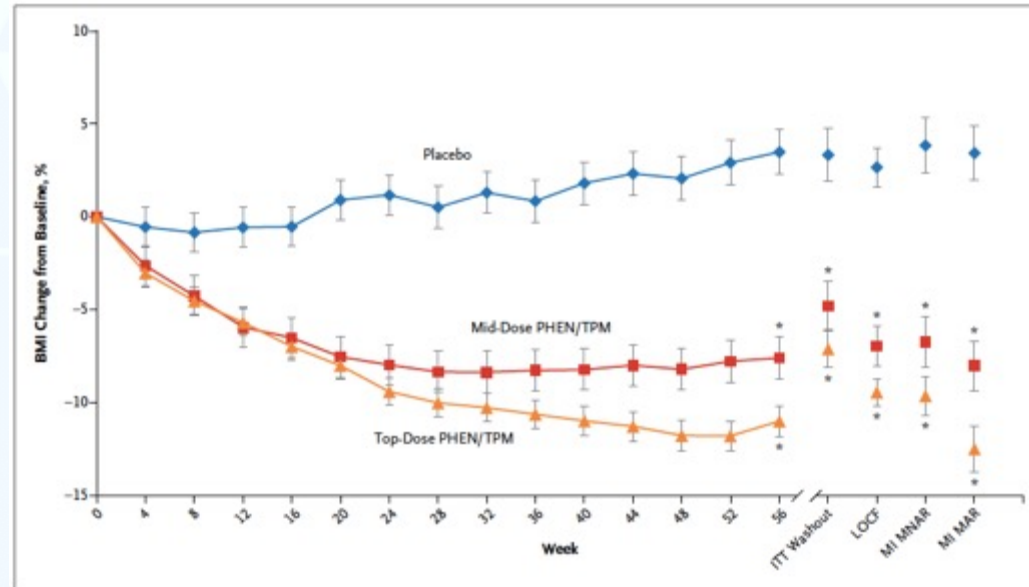


Pharmacologic Management

Phentermine PLUS Topamax

- 56-week, randomized, double-blind trial of obese youth aged 12 to <17 years
- Participants were randomly assigned 1:1:2 to receive placebo (n=556), mid-dose PHEN/TPM (7.5 mg/46 mg; n=554), or top-dose PHEN/TPM (15 mg/92 mg; n=5113), all participants received lifestyle therapy
- Primary end point = mean % BMI change
- RESULTS: Differences from placebo of -10.44 percentage points (95% CI, -13.89 to -6.99; $P < 0.001$) and -8.11 percentage points (95% CI, -11.92 to -4.31; $P < 0.001$) in % change in BMI for the top and mid doses of PHEN/TPM, respectively

Percent Change in BMI Over Time Between Groups



Pharmacologic Management

- **Semaglutide/Rybelsus**

- Not approved in pediatrics for weight loss, available in PO formulation (in addition to once weekly injection formulation Ozempic)
- Mechanism: Glucagon-like peptide-1 receptor agonist (GLP-1 RA)
- Side effects: nausea, vomiting, diarrhea
- Higher doses are most effective for weight loss

- **Orlistat/Alli**

- Approved in 12+ years for weight loss
- Mechanism: Inhibition of gastric/pancreatic lipase
- Side effects: Oily spotting, flatus with discharge, oily stools, decreased absorption of fat-soluble vitamins
- Available to purchase OTC



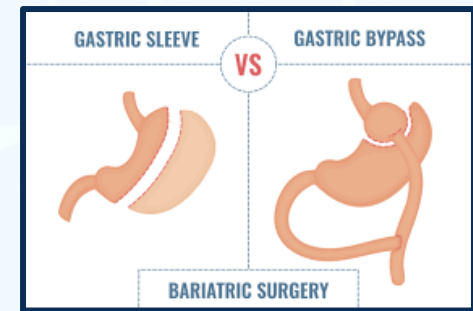
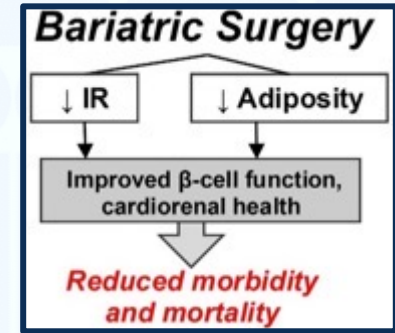
Pharmacologic Management

- **Tirzepatide/LY3298176**
 - Not approved in pediatrics for weight loss
 - Mechanism: Combination GLP-1 RA and glucose-dependent insulinotropic peptide receptor agonist (GIP RA)
 - Side effects: Abdominal discomfort, nausea, vomiting, diarrhea, constipation
 - In a recently published study, participants taking tirzepatide achieved average weight reductions of:
 - 16.0% (35 lb. or 16 kg on 5 mg)
 - 21.4% (49 lb. or 22 kg on 10 mg)
 - 22.5% (52 lb. or 24 kg on 15 mg)
 - compared to placebo (2.4%, 5 lb. or 2 kg)
 - Additionally, 89% (5 mg) and 96% (10 mg and 15 mg) of people taking tirzepatide achieved at least 5% body weight reductions compared to 28% of those taking placebo



Surgical Management

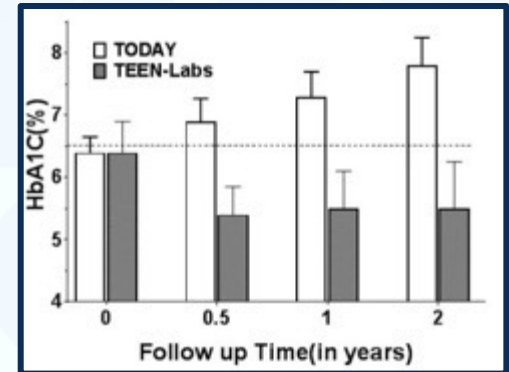
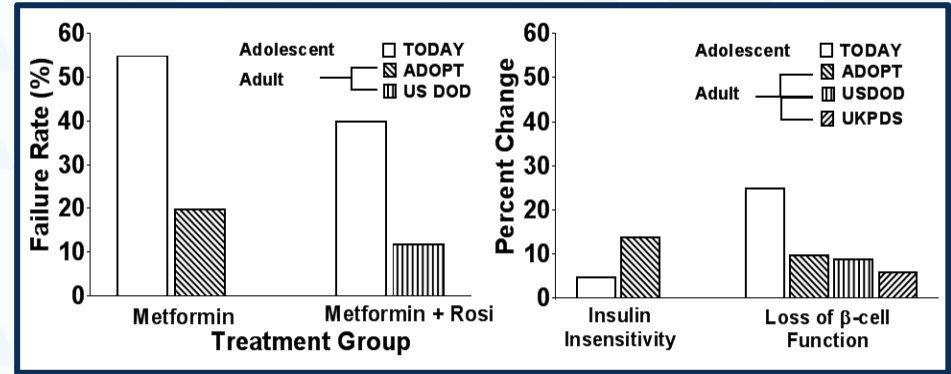
- The American Society for Metabolic and Bariatric Surgery (ASMBS) Pediatric Committee recommend consideration of the following populations for bariatric surgery:
 - *Class II obesity* (BMI at the 120th percentile of the 95th percentile) plus *one comorbidity* (i.e., cardiovascular disease, T2D, OSA, NAFLD, idiopathic intracranial hypertension, orthopedic disease, GER, etc.)
 - *Class III obesity* (BMI at the 140th percentile of the 95th percentile)
- Contraindications for bariatric surgery include:
 - A medically correctable cause of obesity
 - An ongoing substance abuse problem (within the preceding year)
 - A medical, psychiatric, psychosocial, or cognitive condition that prevents adherence to postoperative dietary and medication regimens
 - Current or planned pregnancy within 12 to 18 months of the procedure



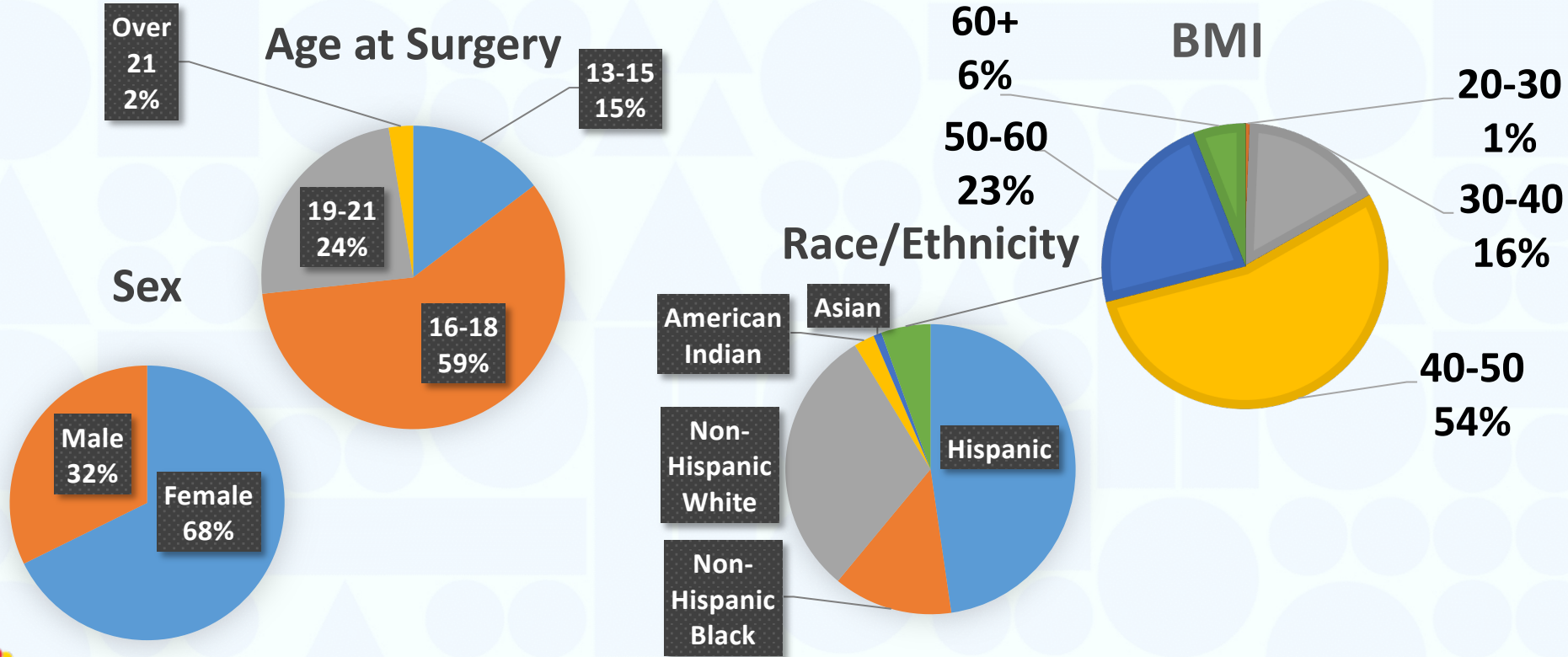
Surgical Management: Outcomes

- Compared to adults with T2D in the ADOPT/US DOD/UKPDS studies, youth in the TODAY study had:
 - More glycemic failure
 - Less improvement in insulin sensitivity
 - More β -cell failure in response to single or dual drug therapy

- Over 2 years, HbA1c fell from 6.8% on medication to 5.5% off medication in Teen-LABS (Bariatric Surgery – mainly Roux-en-Y gastric bypass) but increased from 6.2% to 7.8% on medication in TODAY (Medical Management)



CHCO Bariatric Surgery Clinic Statistics



*n (% of total). Data are expressed as mean (SD) unless otherwise specified.

CONCLUSIONS

- Higher BMI is associated with increased insulin resistance and a worse CV profile in youth with T1D and nearly approximates the phenotype of youth with T2D
- Closer attention to lifestyle management and maintenance of a normal weight is needed to help reduce long term microvascular and macrovascular risk in youth with T1D and T2D



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