بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

JOURNAL PRESENTATION

DR. FAEZEH NAJI

ALZAHRA HOSPITAL

Journal of the Endocrine Society, 2025, 9, bvaf020
https://doi.org/10.1210/jendso/bvaf02 0
Advance access publication 28 January 2025
Clinical Research Article

ENDOCRINE SOCIETY
OXFORD

GLYCEMIA, INSULIN SENSITIVITY, AND SECRETION IMPROVE 3 MONTHS POST-SLEEVE GASTRECTOMY IN YOUTH WITH TYPE 2 DIABETES

- **Obesity** remains a **major health problem** affecting **20.6% of youth** , with rates of youth-onset type 2 diabetes and associated complications projected to increase **700% by 2060** .
- **Youth-onset type 2 diabetes** has many unique features distinguishing it from adult onset and appears **more severe than in adults**, with youth having markedly **lower insulin sensitivity (SI); fasting and stimulated insulin and C-peptide secretion** that is approximately **twice as high**; **lower stimulated glucagon and glucagon-like peptide-1 (GLP-1) secretion**; **less response to diabetes medications** and **lifestyle interventions regarding weight loss; β-cell function and glycemic control**; **and more rapid onset of pancreatic β-cell failure, cardiovascular, and kidney disease .**

The recent American Academy of Pediatrics guidelines **recommend nutritional, physical activity, behavioral, and obesity pharmacotherapy for adolescents ≥12 years** old with **obesity** [**body mass index (BMI) ≥95th percentile**]

and **evaluation for metabolic bariatric surgery (MBS) for adolescents ≥13 years old with class II obesity (BMI ≥120% of the 95th percentile) plus a major comorbidity or with class III obesity (BMI >140% of the 95th percentile) either with or without a documented comorbidity.**

MBS results in significant and durable **weight loss of nearly 30% after 7 years in adults** , **with short- and medium-term metabolic effects** that appear independent of weight loss, including **improvements in glycemia, hypertension, and hyperlipidemia and diabetes remission** in most adults .

However, **applying these data to youth** is challenging given the **severe insulin resistance of puberty**, marked **compensatory hyperinsulinemia**, and early and rapid **β-cell failure**.

Roux-en-Y gastric bypass (RYGB) in adolescents results in **similar weight loss as in adults,** with about **27% absolute weight loss at 5 years** in both the Adolescent Morbid Obesity Surgery study and the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study, but **few adolescent data exist on the impact of MBS on glycemic control, SI, or insulin secretion.**

The **limited data** in **youth with type 2 diabetes** from the Teen-LABS study support the **benefits of MBS in adolescents regarding glycemic control, with 95% experiencing diabetes remission at 3 years post-MBS.**

Vertical sleeve gastrectomy (VSG) is now the **most common MBS procedure** performed in youth and adults due at least in part to its improved safety profile.

Moreover, **most MBS studies lack short-term outcomes**, missing valuable opportunities to examine the **early effect of MBS before full weight loss is achieved on the glycemic, metabolic, and hormonal response to feeding, including potential weight loss independent improvements in health.**

Given the well-established phenotypic differences between youth and adults with type 2 diabetes, such as **more severe hyperinsulinemia** and **poorer response to medical treatments in youth**, it is reasonable to hypothesize that **youth with type 2 diabetes may respond differently to MBS.**

Therefore, **the aim of the Impact of Metabolic surgery on Pancreatic, Renal, and cardiOVascular health in youth with type 2 diabetes (IMPROVE-T2D) study** was to determine the **early effect of VSG on glycemia (primary outcome), SI, insulin secretion,,diabetes medication use, substrate oxidation, and the incretin response to feeding in youth-onset type 2 diabetes before and 3 months after undergoing VSG.**

Materials and Methods

Participants

Fourteen adolescents ages 14 to 19 years with confirmed **antibody-negative youth-onset type 2 diabetes (negative for insulin, glutamic acid decarboxylase, islet-cell, and zinc transporter antibodies)** and **severe obesity,** scheduled for VSG were recruited from the pediatric MBS clinic at Children's Hospital Colorado.

Screening included a medical history and physical exam including **pubertal Tanner staging by the study physician.**

Exclusion criteria included **diabetes diagnosis after age 18, prepubertal status, anemia, pregnancy or breastfeeding, or recent diabetic ketoacidosis.**

Participants were asked to **refrain from strenuous physical activity for 3 days prior to study visits** to limit the impact of the last bout of acute exercise on SI and metabolism.

Metformin and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) were discontinued 72 hours, **GLP-1 receptor analogs (GLP-1RA) 1 week**, and **long-acting insulin 24 hours prior to their study visit if applicable**.

Three participants were on **GLP-1RA agents (1 on daily liraglutide, half-life approximately 13 hours, and 2 on daily semaglutide oral tablets, half-life approximately 1 week)**

- After VSG, our adolescent MBS clinic follows a **standard diet** stage progression to address nutrient needs, beginning with **sugar-free clear liquids postoperatively on days 1 to 2,** followed by **full high protein liquids for the following 2 weeks.**
- **Soft protein foods** are then introduced by **weeks 3 and 4.**
- By **2 to 3 months postoperatively**, patients **typically return to a high-protein, solid-food diet.**

Mixed-meal Tolerance Test and Indirect Calorimetry

- A **modified mixed-meal tolerance test (MMTT)** with indirect calorimetry was performed using **Boost +** (Nestle Corp., Switzerland, **45 g glucose, 14 g fat, 14 g protein).**
- To prevent potential gastrointestinal distress in a **smaller-volume** stomach postoperatively, we modified the MMTT at both pre- and postsurgical visits by dividing the Boost + into 7 1.1 oz aliquots consumed **every 5 minutes for 30 minutes,** starting at time 0.
- Blood was collected for **glucose and insulin** at time points −10, 0, 10, 20, 30, 45, 60, 90, 120, 150,180, and 240 minutes; **C-peptide** at −10, 0, 10, 20, 30, 60, 90, 120,180, and 240 minutes; **GLP-1 and glucagon** at −10, 0, 10, 30, 45, 60, 120, and 240 minutes; **free-fatty acids (FFA)** and **peptide YY(PYY)** at −10, 0, 30, 60, 120, 180, and 240 minutes.

- **Indirect calorimetry via a metabolic cart** (CareFusion, CA) was used to measure **resting energy expenditure (REE), carbohydrate and fat oxidation, and metabolic flexibility with feeding.**
- The cart was **calibrated** to manufacturer specifications prior to each measurement and indirect calorimetry measured just **prior to the MMTT start and again 60 minutes after beginning Boost + consumption.**
- **Oxygen consumption (VO_2)** and **carbon dioxide production (VCO_2)** in both **absolute (L/min)** and **relative (mL/kg/min)** amounts were collected to determine **REE** using the Weir equation , **respiratory quotient (RQ)** **(CO_2 produced/O_2 consumed)**, and **rates of carbohydrate vs fat oxidation** using previously established methods .

- Identical measures were taken **at baseline and 60 minutes after the MMTT** start to calculate change in **carbohydrate and fat oxidation and metabolic flexibility.**
- Participants were **laid supine in a dimly lit and quiet room and respiratory gas exchange measured within a canopy hood circuit for at least 20 minutes until steady state was achieved.**

- **Measures of Insulin Sensitivity and Secretion**
- The **Homeostasis Model of Insulin Sensitivity (HOMA-IR)** was used to assess **fasting SI** the **Matsuda Index** to assess **SI,** and the **disposition index** to assess **β-cell function** (the product of **Matsuda Index and insulinogenic index**) during the MMTT.
- The **Oral Minimal Model (OMM)** was also used to model **glucose dynamics and estimate SI during the MMTT,** after modification for use in adolescents with insulin resistance and in the MMTT setting.

Participant clinical characteristics pre- and postsurgery

Variable	Presurgery	Postsurgery	P (unadjusted)	P (adjusted)
Age (years)	16.8 ± 1.4			
Sex (M/F)	7/7			
Race/ethnicity [n (%)]				
Hispanic or Latino	11 (78.6)			
Non-Hispanic Black	2 (14.3)			
Non-Hispanic White	1 (7.2)			
Diabetes duration (months)	17.6 ± 13.8			
Age at diagnosis of diabetes (yr)	15.9 ± 1.4			
Height (cm)	169.5 ± 7	169.5 ± 7.3	.747	.747
Weight (kg)	134.4 ± 5.6	109.2 ± 5.6	<.001	
BMI (kg/m^2)	46.7 ± 2	38 ± 2	<.001	
BMI percentile	161.3 ± 29	130.4 ± 21.1	<.001	
Waist circumference (cm)	133.6 ± 3.1	117.3 ± 3.1	<.001	<.001
Hip circumference (cm)	129.2 ± 2	117.4 ± 4	.001	.001
Body fat (%)	50.4 ± 1.4	45.9 ± 1.5	.012	.014
Fat mass (kg)	66.6 ± 5.1	52.5 ± 5.4	.005	.006
Fat-free mass (kg)	64.5 ± 3.5	60 ± 3.7	.034	.037
HbA1c (%)	6.6 ± 0.2	5.7 ± 0.2	.003	.003
Metformin use [n (%)]	14 (100%)	2 (14.3%)	n/a	
SGLT-2i use [n (%)]	5 (35.7%)	0 (0%)		
GLP-1RA use [n (%)]	3 (21.4%)	0 (0%)		
Insulin use [n (%)]	2 (14.3%)	0 (0%)		
Resting heart rate (bpm)	94 ± 5	74 ± 5	.018	.024
SBP (mmHg)	129 ± 4	123 ± 4	.087	.09
DBP (mmHg)	75 ± 2	68 ± 2	.075	.083
Total cholesterol (mg/dL)	180 ± 7	144 ± 7	<.001	<.001
LDL-C (mg/dL)	119 ± 8	97 ± 8	.002	.002
HDL-C (mg/dL)	34 ± 2	34 ± 2	.872	.872
Triglycerides (mg/dL)	271 ± 47	123 ± 47	.024	.024
ALT (U/L)	65 ± 7	29 ± 8	.002	.002

Results

Demographics of Cohort and Clinical Outcomes Before and After Surgery

- The 14 participants had a **mean age of 16.8 ± 1.4 years** and were **50% female**; a majority were **Hispanic White** (78.6%) (Table 2).
- The **average age at diagnosis of diabetes** was **15.9 ± 1.4 years** and average **diabetes duration** was **17.6 ± 13.8 months**.

- VSG induced **significant reductions** in **weight (25.2 kg, or a 19% decrease** from presurgery), **BMI, and BMI percentile** (all $P < .001$).
- **Body composition was improved** after surgery with a 4.5% reduction in body fat ($P = .012$), resulting in an absolute reduction of **14.1 kg of fat mass** ($P = .005$) and **4.5 kg of FFM** ($P = .034$).
- Both **waist and hip circumference** were also significantly reduced after surgery ($P < .001$ and $P = .001$, respectively).

- **HbA1c decreased** from **6.6%±0.2 to 5.7%±0.2** (*P* = .003).
- Notably, **all participants were on at least 1 diabetes medication** at baseline, **with 70% of participants requiring multiple agents (6 participants on 1 medication, 6 on 2 medications, and 2 on 3 medications).**
- Of these, **all were on metformin**, **5 (35.7%) were on an SGLT-2i, 3 (21.4%) were on a GLP-1RA, and 2 (14.3%) were on glargine insulin.**
- After surgery, **12 participants (85.7%) no longer required diabetes medication**, with a mean HbA1c in this subset of **5.5%** (range 5.0-6.0%).

Only **2 participants remained on diabetes medication**, both on only **metformin** with an HbA1c of **6.3% and 6.6%,** respectively.

At baseline, these **2 participants (who continued to need diabetes medications at 3 months)** were **on metformin plus a SGLT-2i and metformin plus insulin; 1 participant was an African American male with a preoperative BMI of 60 kg/m^2 and the other was a 19-year-old Hispanic female with a diabetes duration of 50 months.**

Although we were **not powered to detect sex differences**, there were **no significant differences by sex in the primary outcomes of weight loss or HbA1c** (data not shown).

- Resting heart rate was significantly reduced from 94 ± 5 to 74 ± 5 bpm (*P* = .018).

- **Significant improvements were observed** in **total cholesterol** (*P* < .001), **low-density lipoprotein cholesterol** (*P* = .002), **triglycerides** (*P* = .024), **alanine aminotransferase** (*P* = .002), and **aspartate aminotransferase** (*P* = .046), with **no difference in high-density lipoprotein cholesterol.**

- **Systolic and diastolic blood pressure also tended to decrease but were not statistically significant** (*P* = .087 and .075, respectively).

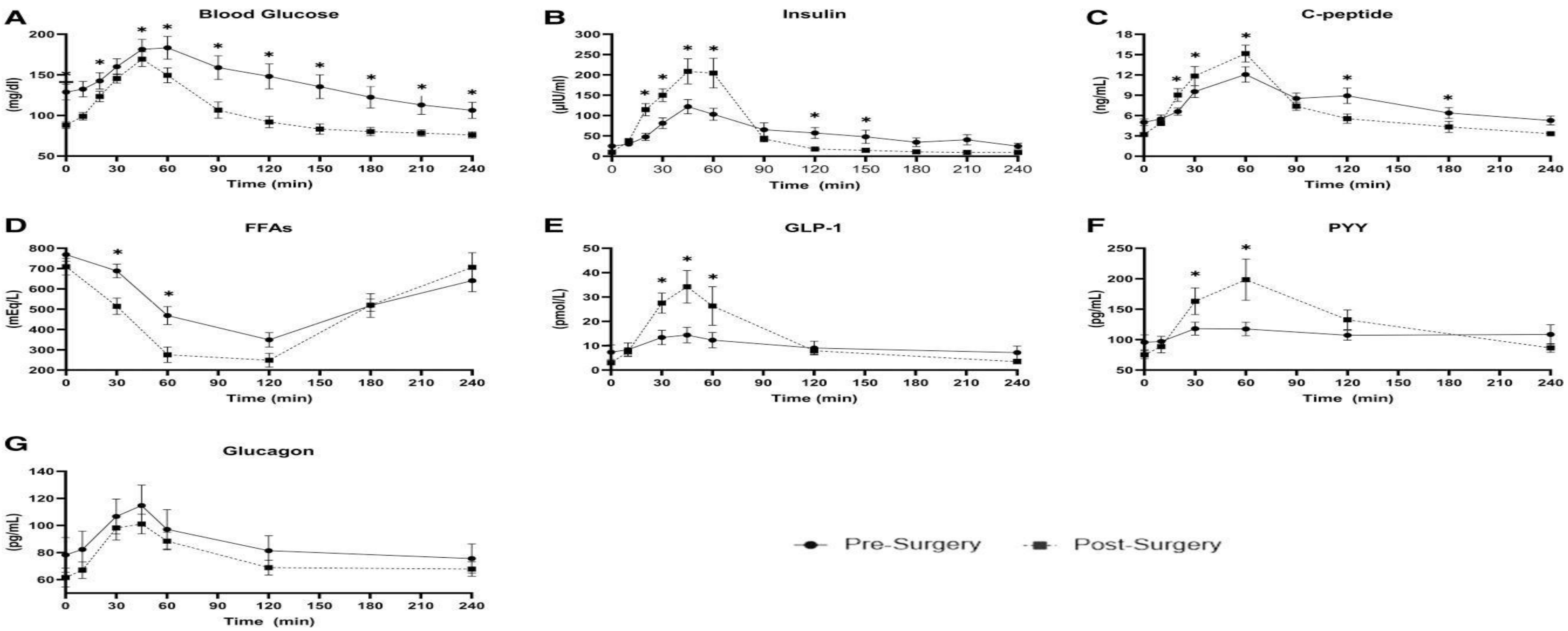

Figure 1. MMTT labs. MMTT results pre- and postmetabolic bariatric surgery shown as mean ± SE. Estimated marginal means were calculated for each time point of the MMTT, and pairwise comparisons were used to test whether each time point differed across visits. Significant differences at each time point are indicated by *P < .05 for comparison between pre- and post-time points in each respective lab measure. Solid circles represent presurgery and dashed squares represent postsurgery.
Abbreviations: FFA, free-fatty acid; GLP-1, glucagon-like peptide 1; MMTT, mixed-meal tolerance test; PYY, peptide YY.

- **Metabolic Response to MMTT**
  - As **measured by the MMTT, glucose, insulin, C-peptide, FFA, GLP-1, PYY, and glucagon excursions all changed significantly after surgery** (Fig. 1).
  - **Fasting and postprandial blood glucose** was **lower across the entire MMTT** study following surgery and was **significantly lower at time points 0, 10, 45, 60, 90, 120, 150, 180, 210, and 240 minutes** ($P < .01$ for all).
  - **Insulin secretion was significantly higher at 20, 30, 45, and 60 minutes** ($P < .001$ for all) and was **significantly lower at 120 and 150 minutes** ($P < .05$ for both).
  - Similar to insulin, **C-peptide** was **significantly higher** at **20, 30, and 60 minutes** ($P < .05$ for all) and **significantly lower** at **120 and 180 minutes** ($P < .05$ for both).

- **FFAs** were **significantly lower** at **30 and 60 minutes** (*P* < .05 for both).

- The incretins **GLP-1 and PYY** were both **significantly higher** at **30, 45, and 60 minutes** (*P* < .005 for both).

- **Fasting fat oxidation increased** (*P* = .042) with a parallel trend in **reduced fasting carbohydrate oxidation (*P* = .083) and fasting RQ** (*P* = .079).

- **REE** was **significantly lower** postsurgery (*P* < .001) (Table 3).

- There were **no significant differences in glucagon, indirect calorimetry-assessed metabolic flexibility at this early 3-month postoperative time point.**

Insulin Sensitivity and Secretion Dynamics

- **Fasting SI** measured by **HOMA-IR** **significantly improved** from **8.3 ± 1.5 to 2.2 ± 1.5** (*P* = .009), as did **SI by** Matsuda Index during the MMTT (*P* = .048).
- **Static and dynamic SI** and **efficiency** were **unchanged** when assessed by OMM (Table 4).
- **Insulin secretion** measured showed **no change in timing of the peak** (43.9 vs 41.9 minutes, *P* = .841), but the **ISR peak heights increased by 2.5-fold during the first 30 minutes** (*P* < .001), **doubled during the first 60 minutes** (*P* < .001) of the MMTT, and **tended to increase over the entire 4-hour MMTT (*P* = .09).**
- **Thirtyminute β-cell responsivity** was **unchanged,** as was **60 minute**, but **4-hour significantly improved** (data not shown).
- **Disposition index** **significantly improved** from 0.14 ± 0.1 to 0.39 ± 0.1
- (*P* = .027).

Table 3. Indirect calorimetry

	Presurgery	Postsurgery	P (unadjusted)	P (adjusted)
Time 0 VO_2 (mL/kg/min)	2.4 ± 0.2	2.5 ± 0.2	.356	.356
Time 60 VO_2 (mL/kg/min)	2.5 ± 0.2	2.8 ± 0.2	.251	.249
Time 0 RQ	0.84 ± 0.01	0.81 ± 0.02	.079	.076
Time 60 RQ	0.86 ± 0.01	0.85 ± 0.01	.499	.494
Time 0 REE	2199 ± 119	1733 ± 123	<.001	<.001
Time 60 REE	2262 ± 117	1882 ± 118	<.001	<.001
Time 0 Fat oxidation	0.61 ± 0.06	0.74 ± 0.06	.042	.041
Time 60 Fat oxidation	0.55 ± 0.07	0.63 ± 0.07	.305	.306
Time 0 carbohydrate oxidation	1.48 ± 0.17	1.09 ± 0.18	.083	.079
Time 60 carbohydrate oxidation	1.77 ± 0.17	1.67 ± 0.18	.604	.602
Metabolic flexibility (+60 minutes RQ—0 minutes RQ)	0.02 ± 0.01	0.04 ± 0.01	.284	.269

Table 4. Measures of insulin sensitivity and secretion				
Variable	Presurgery	Postsurgery	P (unadjusted)	P (adjusted)
HOMA-IR	8.3 ± 1.5	2.2 ± 1.5	.009	.009
Matsuda Index	2.7 ± 0.4	3.5 ± 0.4	.048	.048
DI	0.14 ± 0.1	0.39 ± 0.1	.027	.027
Model-based variables Static SI	6.01×10^{-4}	4.14×10^{-4}	.099	.099
Dynamic SI	1.32×10^{-4}	1.14×10^{-4}	.45	.45
Efficiency	0.262	0.296	.293	.293
ISR 30 minutes AUC	2747	6809	<.001	<.001
ISR 60 minutes AUC	8078	16867	<.001	<.001
ISR 4 hours AUC	15439	20259	.09	.09
ISR time to peak	43.9	41.9	.841	.841
30-minute β-cell responsivity	8.58	9.59	.532	.532

Discussion

- To our knowledge, **IMPROVE-T2D** is the **first study to examine glucose and insulin homeostasis, body composition, cardiovascular risk markers, REE and nutrient oxidation, or incretin response in youth with type 2 diabetes undergoing VSG,** and to do so in a prospective design.

- We observed **notable improvements** in **body weight, body composition, liver transaminases as a marker of metabolic dysfunction-associated steatotic liver disease, glycemic control, fasting glucose, SI, fat oxidation, heart rate, and fasting lipid profile.**

- Moreover, we observed **markedly higher early incretin, insulin, and C-peptide secretion during the MMTT**, leading to **notably improved glucose tolerance and FFA suppression**, and **faster recovery of glucose, insulin, and C-peptide secretion back to fasting values**.

- **These changes remained significant even when statistically controlling for weight loss, implying early, weight loss independent effects of VSG in youth-onset type 2 diabetes.**

- Importantly, **these metabolic improvements occurred despite the discontinuation of diabetes medications in most participants.**

- **MBS significantly reduces weight in youth up to 10 years postoperatively, but less is known about MBS's earlier effects,** and specifically regarding effects of VSG, now the most common MBS procedure worldwide .

- The **~19% weight loss** in our cohort is **slightly more than the 1% to 17% previously reported** in youth at 3 months , however, **prior studies were retrospective**, and **all included RYGB.**

- While we observed **significant body fat reductions** (14.1 kg), we also saw **reductions in metabolically active FFM** (4.5 kg) and thus **REE, potentially increasing the risk for weight regain.**

- In a **recent meta-analysis, Nuijten et al** reported **>8 kg of FFM loss within 1-year post-MBS** in adults, with about **55%** (4.4 kg) lost within **the first 3 months**. While nearly identical to our findings at 3 months, the meta- analysis included adults without diabetes , emphasizing the importance of **longer-term follow-up in youth** and interventions to reduce FFM loss with MBS.

- Indeed, we show **significant increases in insulin secretion, fasting and Matsuda Index-calculated SI, and GLP-1 and PYY following food ingestion**.
- **Peak ISR was 2 to 2.5-fold higher and peak GLP-1 and PYY secretion nearly 2.5 and 2-fold higher, respectively, postsurgery, resulting in marked reductions in blood glucose throughout the MMTT, with a return to fasting glucose levels nearly 2 hours earlier postoperatively.**
- Although **insulin secretion was significantly higher from minutes 20 to 60 postoperatively,** it **returned to basal levels approximately 2 hours earlier**, **limiting systemic exposure to hyperinsulinemia and hyperglycemia.**

- **Post-VSG,** we saw a clear **improvement in fasting SI as indicated by HOMA-IR and combined fasting and postprandial SI assessed by the Matsuda Index;** however, there was **no improvement in SI as estimated using OMM.** This could be attributed to an **interaction between changes in SI and insulin secretion,** to **Matsuda** being **more strongly influenced by fasting values**, thus aligning more with **HOMA-IR**.

- We also documented **improvements in other hormones and metabolites** that **play important roles in individuals with type 2 diabetes**.
- **FFA elevations correlate with muscle insulin resistance and vascular dysfunction** .
- **FFA suppression improved postsurgery, suggesting improved adipose tissue SI and/or a response to the increased first-phase insulin secretion.**
- The **incretins GLP-1 and PYY** both **increased postoperatively**. PYY and GLP-1 **both induce satiety** and may explain the **weight loss** we observed with VSG.
- In addition, PYY may **also improve islet secretory function post-MBS** , and GLP-1 is known to **increase glucose-dependent insulin secretion and suppress glucagon during hyperglycemia** , **all factors that likely contribute to the metabolic improvements seen in participants of IMPROVE-T2D.**

- **Some adult studies** have shown **short-term improvements following MBS** in as little as **2 weeks postoperatively** including **fasting glucose, insulin, and GLP-1 and improved SI in people without diabetes**.

- However, **few adult studies have investigated the response to a MMTT 3 months post-MBS.**

- **Peterli et al** studied **27 adults** (13 RYGB and 14 VSG) **3 months post-MBS and, similar to our study, found improvements in MMTT-assessed glucose homeostasis and significantly increased postprandial insulin, GLP-1, and PYY, with improvements in HOMA-IR.** However, **only 3 of the 14 participants who underwent VSG had type 2 diabetes.**

- The **strengths of IMPROVE-T2D** include our understudied but **severely affected and growing population of youth-onset type 2 diabetes** and novel data on **short-term hormonal effects that occur prior to full weight loss from VSG in this population.**

- **Study weaknesses** include the **small sample size**, which **was not powered to look at sex differences, and lack of a control group without diabetes,** which may affect the generalizability to other cohorts and the ability to detect differences in some hormones

- The **MMTT protocol in our study**, consumed over 30 minutes, **may not be directly comparable to other studies using different beverages or protocols.**

- Further, our **short- term outcomes may not reflect long-term improvements**, thus we are **continuing to follow this cohort to prospectively study longer-term outcomes and durability.**

- In summary, we present the **first study showing early MMTT outcomes in youth-onset type 2 diabetes undergoing VSG.**

- **VSG was well-tolerated in this age group**, and within 3 months, VSG induced notable **improvements in weight, body composition, SI and insulin secretion, glucose tolerance, FFA suppression and fat oxidation, glycemic control, and cardiometabolic health,** including **diabetes remission in the majority,** supporting consideration of VSG for weight and metabolic management in this high-risk population.

- Future studies will evaluate **longer-term durability of these improvements at 1 year,** which will allow for further analyses to **compare this early time point with the 1-year mark** and identify potential predictors of longer-term outcomes that could indicate who is at risk for failure, needing earlier additional intervention.


THANKS FOR YOUR ATTENTION