The Effects of Gastric Bypass on the Brain-Liver Inflammatory Axis and Cognition

Yasamin Taghikhan, DO[1]; Dingning Liu, BS, MA[2]; Emmanuel Zamora, PsyD[1]; Sean Romeo, BS[3]; Zilan Zheng, BS[1]; Quyen Tran, PhD[4]; Kevin Chung, PhD[4]; Shuai Chen, PhD[2]; Karen Matsukuma, MD, PhD[5]; Michael Corwin, MD[4]; Valentina Medici, MD, MAS, FAASLD[6]; Ramsey Badawi, PhD[4]; Guobao Wang, PhD[4]; Souvik Sarkar, MD, PhD[6]; Mohamed Ali, MD[1]; Victoria Lyo, MD, MTM, FACS[1]

[1]UC Davis Department of Surgery; [2]UC Davis Department of Biostatistics; [3]UC Davis Department of PM&R; [4]UC Davis Department of Radiology; [5]UC Davis Department of Pathology; [6]UC Davis Department of GI & Hepatology

Purpose

This pilot study investigated the impact of Roux-en-Y gastric bypass (RYGB) on the liver-brain axis using total-body, dynamic ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET).

Obesity is associated with neuroinflammation and metabolic dysfunction associated steatohepatitis (MASH). Formerly known as NASH, MASH is a form of nonalcoholic liver disease, which describes a spectrum of conditions marked by fat buildup in the liver not caused by alcohol use. Studies have known RYGB improves MASH and obesity-related cognitive impairment. However, the response of the liver-brain inflammatory axis to RYGB is understudied.

Currently there are few ways to study end-organ inflammation. Inflammation can alter glucose transport and metabolism. we previously showed that the rate of glucose transport out of the liver (K1, delivery rate from blood-to liver) using total-body, dynamic PET imaging directly correlated with the severity of inflammation in MASH, as confirmed by biopsy. Therefore, the goal of our study was to develop non-invasive assessment tools to study the effect of weight loss from RYGB on MASLD disease severity and the liver-brain axis, namely MASH severity & neuroinflammation

We hypothesized that post-RYGB changes in weight, adiposity, and MASH severity as measured by hepatic K1 and glucose metabolism (Ki, net influx rate) may correlate with alterations in 1) cerebral glucose transport and metabolism as measured by kinetic modeling of FDG-PET and 2) postoperative cognitive improvements.

Methods

Ten patients underwent RYGB with intraoperative liver biopsy and completed pre-and 6-month post-operative labs, total-body FDG-PET, MRI evaluation of steatosis and fibrosis, and cognitive testing for attention, executive function, memory, and language. Tracer kinetic modeling provided quantitative measures of K1 and Ki. Wilcoxon signed-rank tests were used to compare pre/post-operative mean values and Spearman's correlation coefficients between imaging parameters and cognitive results were calculated.

Results

Of 10 patients (80% female), 6 had steatosis, 3 MASH, and 5 fibrosis on pathology scoring. Postoperatively, significant improvements occurred in weight, visceral adiposity, glycemic dysfunction, dyslipidemia, AST, ALT, and hepatic steatosis and fibrosis by MRI. Hepatic glucose transport (K1) and SUV/SUV ratio decreased significantly. Worse baseline fibrosis by biopsy and patients with greater improvements in insulin resistance correlated with greater improvements in steatosis and fibrosis by MRI. AST-Platelet ratio index (APRI), a fibrosis score indicator, detected significant improvement. (Table 1, 2)

There were no significant changes in brain glucose transport or glucose metabolism. However, brain standardized uptake value (SUV), a surrogate of metabolic activity, significantly decreased. (Table 3).

Improved memory and learning correlated with greater % total weight loss, reductions in MRI steatosis and fibrosis but decreased hepatic glucose transport, brain glucose transport and metabolism. Lastly, language improvement was associated with increased brain glucose transport.

Conclusion

We demonstrate that multi-modal, non-invasive imaging can measure RYGB-induced improvements in steatotic liver disease severity, cognition, and alterations in glucose transport and metabolism. Postoperative alterations in hepatic and neuroinflammation may be reflected in glucose alterations, which correlate with cognitive improvements.

Table 1. Changes in Clinical Variables after Roux-en-Y Gastric Bypass

Variable	Preoperative	Postoperative	Change	P Value
	Mean (±SD) for n=10			
Age at Surgery (years)	48.1 (±15.39)	-	-	
Total MASLD Activity Score	2.2 (± 2.2)	-	-	
Weight (kg)	119.8 (±17.7)	95.1(±14.2)	- 20.5% (±3.3%)	**0.006**
BMI (kg/m^2)	41.7 (±3.9)	33.2 (±3.4)	-8.6 (±1.5)	**0.006**
Waist Circumference (cm)	125.9 (±6.76)	106.3 (±6.57)	-19.6 (±6.57)	**0.006**

Table 2. Changes in Imaging Variables after Roux-en-Y Gastric Bypass

Variable	Preoperative	Postoperative	Change	P Value
	Mean (±SD) for n=10			
Visceral Adipose volume (cm2)	229.1 (±67.9)	124.2 (±54.2)	-104.9 (± 50.7)	**0.006**
Subcutaneous Adipose volume (cm2)	615.7 (±84.1)	406.1 (±84.3)	-209.6 (±76.2)	**0.006**
Visceral Adipose Tissue %	27.1 (±7.4)	23.1 (±7.6)	-4.0 (±5.2)	**0.083**
MRI Elastography: Fibrosis (kPa)	2.7 (±0.4)	2.4 (±0.3)	-0.3 (±0.3)	**0.036**
MRI PDFF: Steatosis (%)	11.9 (±9.5)	4.1 (±3.7)	-7.7 (±6.3)	**0.006**
Liver K1 (blood-tissue glucose transport; mL/min/cm3)	1.20 (±0.36)	0.97 (±0.11)	-0.23 (±0.34)	**0.067**
Liver Ki (net influx, glucose , metabolism; mL/min/cm3)	0.01 (±0.00)	0.01 (±0.00)	-0.00 (±0.01)	0.838
Liver SUV	2.96 (±0.29)	2.66 (±0.23)	-0.29 (±0.33)	**0.025**
Liver SUVR	0.74 (±0.14)	0.61 (±0.12)	-0.13 (±0.13)	**0.014**
APRI	0.44 (±0.35)	0.25 (±0.14)	-0.19 (±0.26)	**0.036**

Table 3. Changes in Brain Variables after Roux-en-Y Gastric Bypass

Variable	Preoperative	Postoperative	Change	P Value
	Mean (±SD) for n=10			
Brain K_1 (mL/min/cm^3)	0.15 (±0.03)	0.15 (±0.03)	0.00 (±0.02)	1.000
Brain Ki (mL/min/cm^3)	0.06 (±0.01)	0.06 (±0.01)	0.00 (±0.01)	0.333
Brain SUV	10.08 (±1.61)	9.21 (±1.64)	-0.87 (±1.24)	**0.053**
Brain SUVR	4.19 (±0.58)	4.22 (±0.74)	0.03 (±0.44)	0.683
Brain Volume (cm3)	1318.52 (±133.02)	1317.71 (±133.44)	-0.81 (±3.24)	0.610