Presence of Liver Steatosis Is Associated With Greater Diabetes Remission After Gastric Bypass Surgery

Roman Vangoitsenhoven,[1,2] Rickesha L. Wilson,[1] Deepa V. Cherla,[1] Chao Tu,[3] Sangeeta R. Kashyap,[4] David E. Cummings,[5] Philip R. Schauer,[6] and Ali Aminian[1]

Diabetes Care 2021;44:321–325 | https://doi.org/10.2337/dc20-0150

OBJECTIVE

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance (IR) and β-cell dysfunction. Ectopic fat accumulation in liver and muscle causes IR. Since bariatric and metabolic surgery significantly improves fatty liver disease, we hypothesized that coexistence of liver steatosis (i.e., when hepatic IR contributes in T2DM) would be associated with greater diabetes improvement after surgery.

RESEARCH DESIGN AND METHODS

A total of 519 patients with T2DM who underwent Roux-en-Y gastric bypass and simultaneous liver biopsy and had a minimum 5-year follow-up were analyzed to assess the independent association between biopsy-proven liver steatosis and postoperative long-term diabetes remission (glycated hemoglobin <6.5% [48 mmol/mol] off medications).

RESULTS

Of the 407 patients with biopsy-proven liver steatosis, long-term diabetes remission was achieved in 211 (52%) patients compared with remission in 44 out of 112 (39%) patients without steatosis ($P = 0.027$). In multivariable analysis, presence of liver steatosis was an independent predictor of long-term diabetes remission (odds ratio 1.96 [95% CI 1.04–3.72]; $P = 0.038$). Hepatocyte ballooning, lobular inflammation, or fibrosis at baseline did not predict diabetes remission.

CONCLUSIONS

This study, for the first time, suggests that in patients with T2DM who are considering bariatric and metabolic surgery, coexistence of liver steatosis is associated with better long-term glycemic outcomes. Furthermore, our data suggest that there are distinct variants of T2DM in which metabolic responses to surgical weight loss are different. A subgroup of patients whose T2DM is characterized by the presence of hepatic steatosis (presumably associated with worse IR) experience better postoperative metabolic outcomes.

The pathophysiology of type 2 diabetes mellitus (T2DM) is characterized by insulin resistance (IR) and β-cell failure. A widely accepted paradigm states that IR originates in large measure from the ectopic fat accumulation and subsequent inflammation in liver, muscle, and other key tissues (1,2). An alternative model, however, suggests that hepatic IR due to dietary fructose overload causes primary hepatic fat accumulation, with subsequent whole-body hyperinsulinism, adiposity, and low-grade inflammation

[1]Bariatric and Metabolic Institute, Department of General Surgery, Cleveland Clinic, Cleveland, OH
[2]Department of Endocrinology, UZ Leuven, Leuven, Belgium
[3]Department of Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH
[4]Department of Endocrinology, Endocrinology and Metabolism Institute, Cleveland Clinic, Cleveland, OH
[5]VA Puget Sound Health Care System and UW Medicine Diabetes Institute, University of Washington, Seattle, WA
[6]Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA

Corresponding author: Ali Aminian, aminiaa@ccf.org

Received 22 January 2020 and accepted 29 October 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.13166255.

(3,4). Both cascades result in stressed β-cells and loss of functional β-cell mass, leading to hyperglycemia, the hallmark of the diabetes diagnosis.

In parallel with the pandemics of obesity and T2DM, the prevalence of nonalcoholic fatty liver disease (NAFLD) has soared to affect more than a third of the general U.S. population and 80% of people living with obesity (5). NAFLD can progress to nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and ultimately hepatocellular carcinoma. To date, there is no highly effective, specific treatment for NAFLD/NASH, but observational studies suggest that bariatric/metabolic surgery in patients with NAFLD and NASH is safe and significantly improves steatosis and NASH-related liver disease, including fibrosis (6).

The relationship between T2DM and NAFLD is complex and bidirectional, with IR as a shared common pathway. Each disease has the potential to exacerbate the other. However, metabolic surgery is a powerful tool to treat both T2DM and NAFLD as major comorbidities of obesity (7,8). We hypothesized that coexistence of liver steatosis and T2DM would be associated with greater diabetes improvement after metabolic surgery.

RESEARCH DESIGN AND METHODS

A retrospective review of electronic medical records (EMR) was conducted after obtaining approval from our Institutional Review Board. We identified all patients with obesity and T2DM undergoing primary Roux-en-Y gastric bypass (RYGB) at a single academic institution between the years 2004 and 2012. Our analysis included only patients who had intraoperative core needle liver biopsy at the time of metabolic surgery and had a minimum 5-year glycemic follow-up. Per our management protocol, intraoperative liver biopsy was routinely performed in all patients undergoing metabolic surgery, via percutaneous passing of a Tru-Cut needle in the left hepatic lobe, under direct laparoscopic visualization.

We recorded baseline characteristics including sex, age at surgery, BMI before surgery, duration of T2DM before surgery, preoperative insulin use, number of preoperative antidiabetes medications, preoperative glycated hemoglobin (HbA_{1c}; with poor glycemic control defined as an $HbA_{1c} \geq 7.0\%$ [53 mmol/mol] irrespective of diabetes medication), and liver histopathologic findings, including presence of liver steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis. Additionally, we checked whether baseline insulin or C-peptide measurements were available in the EMR. Since these evaluations were not performed in routine care, we did not include them in the multivariate analyses. Remission of T2DM was defined as $HbA_{1c} < 6.5\%$ (48 mmol/mol) off diabetes medications at ≥5 years after RYGB.

Liver histology was evaluated according to the NASH Clinical Research Network definitions (9). Liver steatosis was graded on a scale of 0–3, with 0 corresponding to <5% steatosis, 1 corresponding to 5–33% steatosis, 2 corresponding to 34–66% steatosis, and 3 corresponding to >66% steatosis. NAFLD was defined as presence of liver steatosis grade 1, 2, or 3. Hepatocyte ballooning was graded on a scale of 0–2, with 0 corresponding to none, 1 corresponding to few (mild), and 2 corresponding to many (moderate/marked). Lobular inflammation was graded on a scale of 0–3, with 0 corresponding to no foci, 1 corresponding to <2 foci/high-power field (hpf), 2 corresponding to 2–4 foci/hpf, and 3 corresponding to >4 foci/hpf. Fibrosis was scored on a scale of 0–4, with 0 corresponding to none, 1 corresponding to either perisinusoidal or periportal fibrosis, 2 corresponding to perisinusoidal with portal/periportal fibrosis, 3 corresponding to bridging fibrosis, and 4 corresponding to cirrhosis.

Categorical and continuous variables were presented as frequencies (%) and median (25th; 75th percentile), respectively. Remission of diabetes was compared on variables of interest using χ^2, Fisher exact, and Wilcoxon rank-sum tests. Multivariate logistic regression models were built to assess the association between steatosis and remission of diabetes, adjusting for other variables. To further quantify the relative importance of each predictor, we calculated the *z* value for all variables by dividing the absolute value of the regression coefficient by its SE (a larger *z* value corresponds to a larger effect of the variable on the outcome). All tests were two-tailed, with $P < 0.05$ deemed statistically significant. Odds ratios (OR) and 95% CIs were used as measures of the magnitude of associations. R software (version 3.5.1, 2018-07-02; Vienna, Austria) was used for all analyses.

RESULTS

During the 9-year study period, 644 patients with T2DM and obesity underwent primary RYGB at our center. Of these, 519 patients met the inclusion criteria of available intraoperative liver biopsy and at least 5-year postoperative glycemic follow-up. The median postoperative follow-up time was 8 years (range 5–14).

Demographic details and relevant histologic characteristics of the included patients are summarized in Table 1. Among these individuals, 348 (67.1%) were female. Preoperatively, the median BMI was 45.2 kg/m^2 (40.3; 50.6), and the median age was 52 years (45; 58). On average, the patients had T2DM for 6.0 years (2.5; 11.0) and used 2 (1; 3) diabetes medications, including insulin in 188 (36.2%) patients, to attain a median HbA_{1c} of 7.3% (6.4; 8.5) or 56 mmol/mol (46; 69). There were 304 patients (58.6%) with poor baseline glycemic control.

The intraoperative liver biopsy showed at least some degree of steatosis (grades 1–3) in 407 patients (78.4%). Signs of lobular inflammation were present in 359 patients (69.2%), and 184 patients (35.5%) displayed hepatocyte ballooning. A total of 211 patients (40.7%) had fibrosis, but only 56 (10.8%) scored F3 or F4.

Among 519 patients in the total cohort, 255 (49.1%) experienced long-term remission of T2DM after RYGB. In univariate analysis, patients with remission had shorter diabetes duration (3.0 [1.0; 6.0] vs. 10 [6.0; 15.0] years; $P < 0.001$), better glycemic control (HbA_{1c} 6.7% [6.0; 7.70] vs. 7.9% [7.0; 9.2] or 50 [42; 61] vs. 63 [53; 77] mmol/mol; $P < 0.001$), with fewer diabetes medications used (1 [1; 2] vs. 2 [2; 3]; $P < 0.001$), especially less insulin usage (13.7% vs. 58%; $P < 0.001$). Moreover, remission occurred in patients who were heavier (BMI 46.2 [41.3; 52.0] vs. 43.9 [39.1; 49.2] kg/m^2; $P < 0.001$), younger (50 [45; 55] vs. 54 [47; 60] years; $P < 0.001$), and more likely to be female (71.8% vs. 62.5%; $P = 0.035$).

Of the 407 patients with NAFLD (steatosis grades 1–3), 211 (52%) experienced diabetes remission, compared with 44 out of 112 (39%) patients without steatosis ($P = 0.027$ for comparison of binary variables). Long-term diabetes remission rates in patients with steatosis grade 0, 1, 2, and 3 were 39%, 50%, 55%, and 57%, respectively ($P = 0.079$ for comparison of ordinal variables). There were no significant differences in preoperative presence

Table 1—Descriptive summary and univariate analysis

	All patients (n = 519)	Remission of diabetes		P value
		No (n = 264)	Yes (n = 255)	
Sex				**0.035**
Female	348 (67.1)	165 (62.5)	183 (71.8)	
Male	171 (32.9)	99 (37.5)	72 (28.2)	
Age at time of surgery (years)	52 (45; 58)	54 (47; 60)	50 (42; 55)	**<0.001**
BMI before surgery (kg/m^2)	45.2 (40.3; 50.6)	43.9 (39.1; 49.2)	46.2 (41.3; 52.0)	**<0.001**
Duration of diabetes (years)	6.0 (2.5; 11.0)	10.0 (6.0; 15.0)	3.0 (1.00; 6.00)	**<0.001**
Preoperative insulin use				**<0.001**
No	331 (63.8)	111 (42.0)	220 (86.3)	
Yes	188 (36.2)	153 (58.0)	35 (13.7)	
Diabetes medications	2.0 (1.0; 3.0)	2.0 (2.0; 3.0)	1.0 (1.0; 2.0)	**<0.001**
Preoperative HbA_{1c}				**<0.001**
%	7.3 (6.4; 8.5)	7.9 (7.0; 9.2)	6.7 (6.0; 7.7)	
mmol/mol	56 (46; 69)	63 (53; 77)	50 (42; 61)	
Poor glycemic control (HbA_{1c} ≥7%)				**<0.001**
No	215 (41.4)	68 (25.8)	148 (58.0)	
Yes	304 (58.6)	196 (74.2)	107 (42.0)	
Liver steatosis score				0.079
0	112 (21.6)	68 (25.8)	44 (17.3)	
1	272 (52.4)	136 (51.5)	136 (53.3)	
2	107 (20.6)	48 (18.2)	59 (23.1)	
3	28 (5.4)	12 (4.5)	16 (6.3)	
Lobular inflammation score				0.128
0	160 (31.2)	80 (30.3)	80 (31.4)	
1	254 (48.9)	140 (53.0)	114 (44.7)	
2	99 (18.8)	41 (15.5)	58 (22.7)	
3	6 (1.14)	3 (1.1)	3 (1.2)	
Hepatocyte ballooning score				0.539
0	335 (64.5)	165 (62.5)	170 (66.7)	
1	159 (30.6)	84 (31.8)	75 (29.4)	
2	25 (4.8)	15 (5.7)	10 (3.9)	
Liver fibrosis score				0.145
0	308 (59.3)	156 (59.1)	152 (59.6)	
1	107 (20.6)	56 (21.2)	51 (20.0)	
2	48 (9.2)	19 (7.2)	29 (11.4)	
3	42 (8.1)	22 (8.3)	20 (7.8)	
4	14 (2.7)	11 (4.2)	3 (1.2)	

Data are n (%) or median (interquartile range). Liver histology was scored according to the NASH Clinical Research Network definitions (9). Significant P values ($P < 0.05$) are presented in bold.

of lobular inflammation, hepatocyte ballooning, or fibrosis between patients who achieved diabetes remission or not after surgery.

Multivariate logistic regression analysis showed that longer duration of diabetes (OR 0.87 [95% CI 0.82–0.92]; $P < 0.001$), preoperative insulin use (OR 0.33 [95% CI 0.19–0.56]; $P < 0.001$), higher number of diabetes medications (OR 0.50 [95% CI 0.37–0.67]; $P < 0.001$), and poor preoperative glycemic control (OR 0.53 [95% CI 0.32–0.86]; $P = 0.01$) were baseline independent factors that predicted less likely remission of diabetes after RYGB surgery. Presence of liver steatosis before surgery predicted postoperative remission of diabetes (OR 1.96, [95% CI 1.04–3.72]; $P = 0.038$) (Table 2). The absolute z value for steatosis was 2.07, which was relatively similar to the z value for poor glycemic control (2.58), but relatively less than the z values for duration of diabetes (4.96), preoperative insulin use (4.00), or preoperative number of diabetes medications (4.64).

Compared with patients without liver steatosis, those with steatosis more frequently had lobular inflammation (307 out of 407 [75%] vs. 52 out of 112 [46%]; $P < 0.001$), hepatocyte ballooning (177 out of 407 [43%] vs. 7 out of 112 [6%]; $P < 0.001$), and fibrosis (192 out of 407 [47%] vs. 19 out of 112 [17%]; $P < 0.0001$) (Supplementary Table 1). Weight loss was similar in patients with and without baseline steatosis: 34.3% versus 35% at last follow-up, respectively. Presence of steatosis remained a significant predictor of diabetes remission when multivariate logistic regression was executed, including total body weight loss data (Table 3). Again, the z value for steatosis was lower than z values for diabetes duration, insulin use, and preoperative diabetes medication, but in a similar order of magnitude as poor glycemic control.

We could retrieve at least one serum insulin measurement among 223 patients during the year before surgery and 36 C-peptide measurements, but only 173 measurements had a traceable simultaneous glucose recording. Because 83 of the available insulin measurements were in patients who used exogenous insulin according to their EMR, and because it was impossible to ascertain retrospectively that the insulin or C-peptide measurements were done in fasting conditions, we decided that these data could not be used retrospectively to approximate IR in the study population.

CONCLUSIONS

Metabolic surgery has proven to be a powerful tool to treat obesity and T2DM. This study, based on clinical and histopathology data from a large cohort of patients with long-term follow-up after RYGB, suggests for the first time that presence of biopsy-proven hepatic steatosis at baseline is associated with an increased likelihood of diabetes remission after surgery.

Although bariatric surgery was initially designed as a pure weight-loss strategy, several of these operations have now been shown to induce remission of T2DM (7,10). Due to the improvement in glucose homeostasis typically occurring very soon after surgery, even before significant weight loss, numerous weight-independent antidiabetes mechanisms have been shown to play an important role in diabetes remission, along with expected secondary consequences of weight loss. These mechanisms include favorable changes in gut hormones, bile acid signaling, gut microbiota, intestinal glucose transport and utilization, proximal intestinal nutrient sensing, iron metabolism, and others (11).

Currently, <1% of patients who are eligible for bariatric/metabolic surgery actually undergo surgery. Given the increasing prevalence of obesity, however,

Table 2—Multivariate logistic regression model for long-term diabetes remission after RYGB considering baseline variables only

Baseline variables	OR	95% CI	*P* value	*z* value
Sex (male vs. female)	1.11	0.67–1.83	0.683	0.409
Age at surgery	0.98	0.96–1.00	0.098	1.653
BMI before surgery	1.03	1.00–1.06	**0.037**	**2.087**
Duration of diabetes	0.87	0.82–0.92	**<0.001**	**4.964**
Preoperative insulin use (yes vs. no)	0.33	0.19–0.56	**<0.001**	**3.997**
Preoperative number of diabetes medications	0.50	0.37–0.67	**<0.001**	**4.640**
Poor glycemic control (HbA_{1c} ≥7%)	0.53	0.32–0.86	**0.010**	**2.579**
Liver steatosis (yes vs. no)	1.96	1.04–3.72	**0.038**	**2.074**
Lobular inflammation (yes vs. no)	1.02	0.59–1.78	0.933	0.084
Hepatocyte ballooning (yes vs. no)	0.74	0.39–1.39	0.350	0.934
Hepatic fibrosis (yes vs. no)	1.07	0.60–1.92	0.814	0.235

z value is the absolute value of regression coefficient divided by its SE. A larger *z* value indicates a stronger statistical relation of factor on outcome. As a rule of thumb, if the absolute value of the *z* value is larger than cutoff value of 2.0, the variable is significant. Significant *P* values ($P < 0.05$) and *z* values ($z > 2.0$) are presented in bold.

and given the increasing numbers of metabolic operations performed, it will become more important in the future to delineate subgroups of patients who will benefit the most from surgical interventions. Until now, prediction models for diabetes remission after metabolic surgery were based almost entirely on parameters directly related to β-cell status, such as age, diabetes duration, HbA_{1c}, insulin treatment, and number of antidiabetes drugs used (e.g., DiaRem [12], ABCD [13], and Individualized Metabolic Surgery [IMS] Score [14]). Specifically, the IMS Score was developed based on four independent predictors of long-term remission, including preoperative number of diabetes medications, insulin use, preoperative duration of T2DM, and glycemic control, which can assist in classification of diabetes severity before metabolic surgery. The current analysis, which shares some patients who were included in the original IMS Score study, confirms the major importance of β-cell capacity before surgery, as longer diabetes duration, preoperative use of exogenous insulin, higher number of diabetes medications, and poor preoperative glycemic control have significantly lowered the likelihood of postoperative diabetes remission.

Additionally, this study revealed that liver steatosis at the time of surgery predicts a higher chance of diabetes remission after RYGB. Our analysis is based on histological scoring of liver biopsy specimens, which remains the gold standard method to evaluate NAFLD and NASH to date. This finding fits the notion that intrahepatic fat is of primordial importance to metabolic complications of obesity compared with visceral or peripheral adiposity (15,16), and it is consistent with recently published findings of the DiRECT trial, in which remission of T2DM after weight loss intervention coincided with a decrease in liver fat (17). In the DiRECT trial, an increase in first-phase insulin secretion in the subgroup of patients who responded to weight loss suggested improvement of β-cell function, and the investigators noted that the capacity for β-cell recovery remains the permissible factor for diabetes remission (17). In our multivariate analysis, the indirect surrogate markers of functional β-cell capacity were of major significance, confirmed by large *z* values. But the preoperative presence of hepatic steatosis seemed to have an important additional predictive role.

Patients with preoperative liver steatosis might have been a subgroup with a major contribution of IR to their T2DM, perhaps with relatively preserved β-cell function. Although we hypothesized that coexistence of liver steatosis would be associated with greater diabetes improvement after metabolic surgery due to improvement of hepatic IR following surgery, the presence of liver steatosis might be a surrogate marker for reversible β-cell dysfunction. It could be possible that the liver steatosis in this study is a reflection of pancreatic steatosis, which is known to be negatively correlated with β-cell function (18). We tried to collect insulin and C-peptide measurements to estimate the relative contribution of IR and β-cell function, but in this retrospective analysis, we could not retrieve sufficient insulin or C-peptide measurements for reliable analysis. In any case, Ahlqvist et al. (19) have recently highlighted the importance of identifying subgroups of diabetes to tailor and target early treatment to patients who would benefit most, thereby representing a first step toward precision medicine in diabetes.

Surprisingly, the actual presence of lobular inflammation, hepatocyte ballooning, or hepatic fibrosis was not independently associated with remission of diabetes. This seemed to be in contrast with the notion that it is hepatic inflammation and not steatosis per se that causes IR (20). In contrast, earlier mechanistic

Table 3—Multivariate logistic regression model for long-term diabetes remission after RYGB considering baseline variables and postoperative weight loss data

Variables	OR	95% CI	*P* value	*z* value
Sex (male vs. female)	1.22	0.72–2.06	0.465	0.730
Age at surgery	0.98	0.95–1.00	0.088	1.707
BMI before surgery	1.01	0.98–1.04	0.550	0.597
Percent total weight loss in long term	1.05	1.03–1.08	**<0.001**	**4.317**
Duration of diabetes	0.86	0.81–0.91	**<0.001**	**5.093**
Preoperative insulin use (yes vs. no)	0.32	0.18–0.57	**<0.001**	**3.825**
Preoperative number of diabetes medications	0.49	0.36–0.67	**<0.001**	**4.526**
Poor glycemic control (HbA_{1c} >7%) (yes vs. no)	0.45	0.26–0.76	**0.003**	**2.978**
Steatosis (yes vs. no)	2.21	1.14–4.31	**0.020**	**2.335**
Lobular inflammation (yes vs. no)	1.19	0.66–2.11	0.565	0.576
Hepatocyte ballooning (yes vs. no)	0.67	0.35–1.31	0.244	1.165
Fibrosis (yes vs. no)	0.97	0.53–1.77	0.910	0.113

$N = 505$, as long-term weight loss data could not be retrieved for 14 patients. *z* value is the absolute value of regression coefficient divided by its SE. A larger *z* value indicates a stronger statistical relation of factor on outcome. As a rule of thumb, if the absolute value of the *z* value is larger than cutoff value of 2.0, the variable is significant. Significant *P* values ($P < 0.05$) and *z* values ($z > 2.0$) are presented in bold.

studies did report that hepatic steatosis leads to hepatic IR by stimulating gluconeogenesis and activating protein kinase C-ε and JNK1, thereby interfering with tyrosine phosphorylation of insulin receptor substrate 1 and 2 (21). Previous clamp studies have shown that hepatic IR is lowered shortly after metabolic surgery (22). Moreover, the fact that more serious liver conditions such as hepatocyte ballooning, inflammation, and fibrosis do not predict diabetes outcomes after RYGB, but mere hepatic steatosis does, might be another argument in favor of considering metabolic surgery earlier in the progression of NAFLD/NASH/cirrhosis.

This study has several important limitations. First, because it was a single-center retrospective analysis, the findings should be considered as hypothesis-generating and should be validated in prospective mechanistic studies, with more thorough evaluation of β-cell function, IR, and liver status. Second, the current analysis was performed on patients who underwent RYGB only, and the results can therefore not be extrapolated to other types of metabolic surgery, such as sleeve gastrectomy. Third, while RYGB is contraindicated in patients with significant alcohol use, patients with occult or sporadic alcohol use (with alcoholic hepatic steatosis) might have been included and influenced our findings. Fourth, reliable data on waist circumference were not available to be included in the multivariate logistic regression model. The strength of this study was that we used histological scoring of liver biopsy specimens, which remains the gold standard method to evaluate NAFLD/NASH to date. Future studies can be extended to include clinically practical and noninvasive methods for preoperative liver assessment in order to determine if findings of this study are replicable. Doing so, predictive models can be updated to assist in patient selection and risk-benefit assessment of metabolic surgery.

Conclusion

This study suggests that in patients with T2DM who are considering metabolic surgery, coexistence of liver steatosis is associated with better long-term glycemic outcomes, although it has a smaller predictive value than the known clinical markers of residual β-cell function at the time of surgery (e.g., duration of diabetes or number of diabetes medications). Furthermore, our data suggest that there are probably different variants of T2DM in which glycemic responses to metabolic surgery are different. A subgroup of patients whose T2DM is characterized by the presence of hepatic steatosis experience better postoperative glycemic outcomes, possibly due to reduced hepatic IR. Given the nature of this study, these data should be considered hypothesis-generating. Future mechanistic studies are warranted to further clarify the effects of baseline β-cell function, IR, and liver steatosis on glycemic responses after metabolic surgery.

Funding. R.V. was supported by a Fellowship of the Fulbright Commission and a Fellowship of the Belgian American Educational Foundation.
Duality of Interest. D.E.C. is a principal investigator on the Comparison of Surgery and Medicine on the Impact of Diverticulitis (COSMID) trial, which is funded by Johnson & Johnson. P.R.S. reports receiving grants from Medtronic, Ethicon Inc., and Pacira Pharmaceuticals Inc. and receiving personal fees from Medtronic, GI Dynamics, W.L. Gore and Associates, Becton Dickinson Surgical Instruments, and Global Academy for Medical Education. A.A. reports receiving research grants from Medtronic outside the scope of this study. No other potential conflicts of interest relevant to this article were reported.
Author Contributions. R.V., R.L.W., D.V.C., and A.A. gathered the data. R.V. and C.T. analyzed the data. R.V. and A.A. interpreted the findings. R.V. and R.L.W. drafted the manuscript. A.A. designed the study. All authors reviewed the manuscript, edited it for intellectual content, and gave final approval for this version to be published. A.A. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Prior Presentation. This study was presented at the ObesityWeek 2019 Congress, Las Vegas, NV, 3–7 November 2019.

References

1. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006;444:840–846
2. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 2010;72:219–246
3. Kim SP, Ellmerer M, Van Citters GW, Bergman RN. Primacy of hepatic insulin resistance in the development of the metabolic syndrome induced by an isocaloric moderate-fat diet in the dog. Diabetes 2003;52:2453–2460
4. Lim JS, Mietus-Snyder M, Valente A, Schwarz J-M, Lustig RH. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. Nat Rev Gastroenterol Hepatol 2010;7:251–264
5. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11–20
6. Lassailly G, Caiazzo R, Buob D, et al. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. Gastroenterology 2015;149:379–388; quiz e15–e16
7. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. N Engl J Med 2017;376:641–651
8. Hatoum IJ, Blackstone R, Hunter TD, et al. Clinical factors associated with remission of obesity-related comorbidities after bariatric surgery. JAMA Surg 2016;151:130
9. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005; 41:1313–1321
10. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med 2012;366:1577–1585
11. Batterham RL, Cummings DE. Mechanisms of diabetes improvement following bariatric/metabolic surgery. Diabetes Care 2016;39:893–901
12. Still CD, Wood GC, Benotti P, et al. Preoperative prediction of type 2 diabetes remission after Roux-en-Y gastric bypass surgery: a retrospective cohort study. Lancet Diabetes Endocrinol 2014;2:38–45
13. Lee W-J, Chong K, Chen S-C, et al. Preoperative prediction of type 2 diabetes remission after gastric bypass surgery: a comparison of DiaRem Scores and ABCD Scores. Obes Surg 2016;26:2418–2424
14. Aminian A, Brethauer SA, Andalib A, et al. Individualized metabolic surgery score: procedure selection based on diabetes severity. Ann Surg 2017;266:650–657
15. Fabbrini E, Magkos F, Mohammed BS, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Proc Natl Acad Sci U S A 2009;106:15430–15435
16. Perry RJ, Kim T, Zhang X-M, et al. Reversal of hypertriglyceridemia, fatty liver disease, and insulin resistance by a liver-targeted mitochondrial uncoupler. Cell Metab 2013;18:740–748
17. Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, et al. Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for β cell recovery. Cell Metab 2018;28:547–556.e3
18. Tushuizen ME, Bunck MC, Pouwels PJ, et al. Pancreatic fat content and β-cell function in men with and without type 2 diabetes. Diabetes Care 2007;30:2916–2921
19. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol 2018;6:361–369
20. Amaro A, Fabbrini E, Kars M, et al. Dissociation between intrahepatic triglyceride content and insulin resistance in familial hypobetalipoproteinemia. Gastroenterology 2010;139:149–153
21. Samuel VT, Liu Z-X, Qu X, et al. Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. J Biol Chem 2004;279:32345–32353
22. Camastra S, Gastaldelli A, Mari A, et al. Early and longer term effects of gastric bypass surgery on tissue-specific insulin sensitivity and beta cell function in morbidly obese patients with and without type 2 diabetes. Diabetologia 2011;54:2093–2102