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Original article

Long-term outcomes comparing metabolic surgery to no surgery in patients with type 2 diabetes and body mass index 30–35

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Abstract

Background: We previously conducted a randomized study comparing metabolic surgery with medical weight management in patients with type 2 diabetes (T2D) and body mass index (BMI) 30 to 35 kg/m^2. At 3-year follow-up, surgery was very effective in T2D remission; furthermore, in the surgical group, those with a higher baseline soluble receptor for advanced glycation end products had a lower postoperative BMI.

Objectives: To provide long-term follow-up of this initial patient cohort.

Setting: University Hospital.

Methods: Retrospective chart review was performed of the initial patient cohort. Patients lost to follow-up were systematically contacted to return to clinic for a follow-up visit. Data were compared using 2-sample *t* test, Fisher's exact test, or analysis of variance when applicable.

Results: Originally, 57 patients with T2D and BMI 30 to 35 kg/m^2 were randomized to metabolic surgery (n = 29) or medical weight management (n = 28). Ten patients in the medical weight management group crossed over to surgery. Five-year follow-up data were available in 43 of 57 (75%) patients. Baseline mean BMI and glycated hemoglobin were 32.6 kg/m^2 and 7.8%, respectively. Median follow-up was 79 and 88 months in the surgical group and nonsurgical group, respectively. Compared with the nonsurgical group, the surgical patients had significantly lower rate of T2D (62% versus 100%; $P = .008$), lower insulin use (10% versus 50%; $P = .0072$), lower glycated hemoglobin (6.93% versus 8.26%; $P = .012$), lower BMI (25.8 versus 28.6 kg/m^2; $P = .007$), and higher percent weight loss (21.4% versus 10.3%; $P = .025$). Baseline soluble receptor for advanced glycation end products was not associated with long-term outcomes.

Conclusions: Metabolic surgery in T2D patients with BMI 30 to 35 kg/m^2 remains effective long term. Baseline soluble receptor for advanced glycation end products are most likely predictive of early outcomes only. (Surg Obes Relat Dis 2020;■:1–6.) © 2020 American Society for Bariatric Surgery. Published by Elsevier Inc. All rights reserved.

Key words: Metabolic surgery; Bariatric surgery; Body mass index <35; Obesity; sRAGE; Biomarker; Gastric bypass; Sleeve; Band

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Currently, patients with type 2 diabetes (T2D) and body mass index (BMI) <35 kg/m^2 are not traditionally eligible for insurance approval for bariatric/metabolic surgery, based on original 1991 National Institutes of Health (NIH) guidelines [1]. Although there is increasing evidence regarding the efficacy of metabolic surgery in this patient population, these patients are usually offered medical therapy only.

We previously conducted a pilot randomized controlled trial comparing metabolic surgery and medical weight management (MWM) in patients with T2D and BMI 30 to 35 kg/m^2 demonstrating the efficacy of surgery at 6-months follow-up [2]. Three-year follow-up data of the same cohort revealed surgery remained effective in remission of diabetes, compared with the patients who underwent routine medical care [3].

In the previous studies, the soluble form of the receptor for advanced glycation end products (sRAGE) was also found to be a potential biomarker for early surgical outcomes. RAGE binds numerous ligands linked to hyperglycemia and chronic inflammation, common in both obesity and T2D complications, especially vascular complications [4]. sRAGE, which naturally circulates in the plasma, acts as a decoy to prevent interaction between advanced glycation end products and RAGE, thereby blocking subsequent RAGE ligand-mediated effects relevant to obesity and T2D complications [5]. Therefore, sRAGE levels have been hypothesized to be innate biomarkers of vulnerability to obesity and T2D [6].

The purpose of this study was to provide longer-term follow-up data of the original cohort of patients with T2D and BMI 30 to 35 kg/m^2 randomized to surgery versus MWM and to determine if baseline sRAGE levels continue to predict long-term outcomes.

Methods

In the original study, 57 patients with T2D and BMI 30 to 35 kg/m^2 who were otherwise eligible for bariatric surgery according to NIH consensus criteria were randomly assigned to MWM (n = 28) over 6 months or metabolic surgery (n = 29) [2]. Patients assigned to MWM underwent 6 months of MWM as part of the initial study, then usual medical care thereafter. For this study, these patients (excluding crossovers) were considered the nonsurgical group. Patients assigned to surgery underwent laparoscopic Roux-en-Y gastric bypass (LRYGB), laparoscopic sleeve gastrectomy (LSG), or laparoscopic adjustable gastric banding (LAGB) based on patient preference, as described previously. All patients underwent thorough evaluation by a surgeon, medical physician, nutritionist, and psychologist.

Baseline data included demographic data, glycated hemoglobin (HbA1C), weight, BMI, and sRAGE levels. Chart review was conducted to collect longer-term data on the initial patient cohort. Patients lost to follow-up were systematically contacted to return to clinic for a follow-up visit.

Data were compared using 2-sample *t* test, Fisher's exact test, or analysis of variance when applicable. Scatter plots and Pearson's correlation tests were used to evaluate the sRAGE biomarker as a predictor of outcomes. The original trial was registered at clinicaltrials.gov (ID: NCT01423877). Institutional review board approval was obtained for the initial study as well as this retrospective review.

Results

There were 57 patients in the initial study (28 MWM and 29 Surgery). Ten patients in the initial MWM group subsequently crossed over to surgery, resulting in 18 patients in the nonsurgical group and 39 surgery patients. Long-term follow-up data were available in 43 of 57 original patients (75%), including 14 of 18 (77%) nonsurgical patients and 29 of 39 (74%) surgery patients (Fig. 1).

Table 1 shows the demographic data of 43 patients. The 29 surgical patients consisted of 18 LSG, 8 RYGB, and 3 LAGB. Baseline HbA1C was 7.5% and approximately one-third of the patients were on insulin at baseline. Remaining characteristics were similar except the surgical group was slightly younger age (49 versus 55 yr; $P = .034$).

Median follow-up based on time of enrollment to last available lab data was 88 months for the nonsurgical patients and 79 months for the surgical patients. The surgery patients had a significantly lower rate of diabetes, significantly lower insulin use, lower HbA1C, lower triglyceride level, and more weight loss compared with the nonsurgical patients (Table 2). The overall diabetes resolution rate was

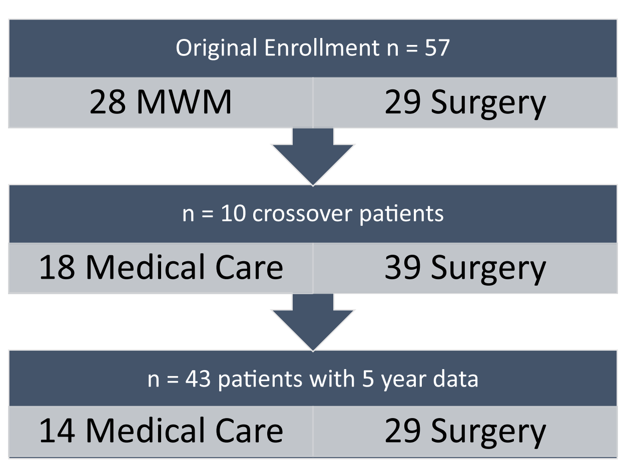

Fig. 1. Forty-three patients with 5-year data.

Table 1
Description of the study population (n = 43)

	No surgery n = 14	Surgery n = 29	*P* value
Age	55.3 (10.6)	49.1 (7.5)	.034*
Female	71% (n = 10)	86% (n = 25)	.404†
Race			
Latino	86% (n = 12)	93% (n = 27)	.497†
Asian	7% (n = 1)	7% (n = 2)	
White	7% (n = 1)	0% (n = 0)	
Height, in	63.9 (3.7)	62.3 (3.2)	.163*
Weight, lbs	185.2 (25.5)	181.9 (19.0)	.633*
Body mass index, kg/m^2	32.0 (2.2)	32.8 (1.5)	.161*
Waist circumference, cm	106.3 (8.7)	107.0 (8.6)	.796*
Glucose	143.4 (48.3)	146.2 (45.6)	.855*
Insulin	10.5 (8.3)	12.3 (9.4)	.547*
HOMA-IR	3.8 (2.9)	4.4 (3.6)	.552*
HbA1C	7.5 (.9)	7.5 (1.2)	.914*
Triglycerides	139.5 (60.5)	173.8 (92.6)	.215*
HDL	45.1 (14.9)	49.6 (15.9)	.379*
LDL	117.6 (60.3)	106.6 (34.5)	.458*
CHOL	190.5 (71.1)	190.7 (46.1)	.990*
Systolic BP	128.9 (23.2)	123.4 (28.0)	.530*
Diastolic BP	72.9 (6.2)	76.0 (18.9)	.550*
Diabetes medication type			
None	14% (n = 2)	5% (n = 2)	
Metformin only	14% (n = 2)	28% (n = 8)	.748†
Other meds without insulin	36% (n = 5)	34% (n = 10)	
Any insulin	36% (n = 5)	31% (n = 9)	
Type of surgery			
None	100% (n = 14)	-	
LAGB	-	10% (n = 3)	NA
LSG	-	62% (n = 18)	
RYGB	-	28% (n = 8)	

HOMA-IR = homeostatic model assessment of insulin resistance; HbA1C = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CHOL = cholesterol; BP = blood pressure; LAGB = laparoscopic adjustable gastric banding; NA = not applicable; LSG = laparoscopic sleeve gastrectomy; RYGB = Roux-en-Y gastric bypass.

* Two-sample *t* test.

† Fisher's exact test.

38% in the surgery group versus 0% in the nonsurgical group.

Outcome measures were stratified by surgery type (Table 3). At over 5-year follow-up, differences in outcomes between surgery groups were significant for change in BMI and percent weight loss (higher for RYGB/LAGB and lower for LSG). Differences in diabetes, HbA1C, and other metabolic outcomes were not significant.

sRAGE data were available in 34 of 43 (79%) patients. Baseline sRAGE was not associated with long-term outcomes (Table 4). After repeating the analysis excluding the 10 patients that crossed over, the results changed slightly but were weak and remained nonsignificant for HbA1C change ($r = -.026$; $P = .938$), change in BMI ($r = -.157$; $P = .626$), and weight loss ($r = -.186$; $P = .563$).

There were no mortalities. In the nonsurgical group, 4 of 14 patients (29%) were subsequently diagnosed with diabetic retinopathy compared with none in the surgery group, and 6 of 14 patients (43%) were subsequently diagnosed with peripheral neuropathy compared with none in the surgery group. In the nonsurgical group, 10 of 14 (71%) were either readmitted or underwent operation for various reasons including liver fibrosis, chronic kidney disease/hyperkalemia (n = 2), stroke, congestive heart failure, foot debridement, leg amputation, incisional hernia, peripheral vascular disease requiring intervention, and cholecystectomy. In the surgery group, 11 of 29 (38%) were either readmitted or underwent reoperation for various reasons, including cholecystectomy (n = 4), endoscopy (n = 2), dehydration, B12 deficiency, small bowel obstruction, pancreatitis, and right hemicolectomy for incidentally diagnosed cancer. When looking

Table 2
Five-year outcomes in 43 patients with T2D and BMI 30–35 kg/m^2

	No surgery n = 14	Surgery n = 29	*P* value
Diabetes, % (n)	100 (14)	62 (18)	.0081*
Insulin use, % (n)	50 (7)	10 (3)	.0072*
HbA1C, N	14	27	
Pre	7.46 (.94)	7.50 (1.17)	.914†
Post	8.26 (1.80)	6.93 (1.37)	.012†
Change	+.81 (1.47)	−.57 (1.40)	.0058[2]
BMI, N	14	29	
Pre	32.0 (2.2)	32.8 (1.5)	.161†
Post	28.6 (3.6)	25.8 (3.1)	.013†
Change	−3.4 (2.6)	−7.0 (3.2)	.0007†
%WL, mean (SD)	10.3 (8.1)	21.4 (9.4)	.025†
Triglycerides, N	14	29	
Pre	139.5 (60.5)	173.8 (92.6)	.215†
Post	153.6 (82.6)	132.4 (58.4)	.336†
Change	14.1 (66.3)	−41.4 (90.3)	.047†
HDL, N	14	29	
Pre	45.1 (14.9)	49.6 (15.9)	.379†
Post	50.9 (18.2)	59.2 (18.8)	.174†
Change	5.8 (10.2)	9.6 (11.3)	.283†
LDL, N	14	28	
Pre	117.6 (60.4)	106.6 (34.5)	.458†
Post	88.7 (29.6)	111.0 (41.5)	.081†
Change	−28.9 (50.8)	4.36 (51.4)	.054†
CHOL, N	14	29	
Pre	190.5 (71.1)	190.7 (46.1)	.990†
Post	164.1 (45.0)	197.4 (46.6)	.032†
Change	−26.3 (43.7)	6.7 (60.2)	.074†
Systolic BP, N	14	28	
Pre	128.9 (23.2)	129.1 (15.5)	.976†
Post	135.6 (17.5)	132.8 (20.2)	.663†
Change	6.7 (25.3)	3.75 (23.8)	.711†
Diastolic BP, N	14	28	
Pre	72.9 (6.2)	79.2 (12.6)	.034†
Post	74.4 (10.3)	76.7 (10.6)	.516†
Change	1.6 (13.4)	−2.5 (14.9)	.391†
Median follow-up	88 mo	79 mo	NA

T2D = type 2 diabetes; BMI = body mass index; HbA1C = glycated hemoglobin; %WL = percent weight loss; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CHOL = cholesterol; BP = blood pressure; NA = not applicable.

N for continuous data is the number of nonmissing values within each group.

* Fisher's exact test.

† Two-sample *t* test.

specifically at diabetes-related cardiovascular complications, including acute myocardial infarction, stroke, and hospitalization for heart failure, 2 of 14 (14%) of patients in the nonsurgical group developed complications (1 stroke, 1 heart failure requiring admission), compared with none in the surgery group [7].

Discussion

There is increasing focus on surgical treatment for patients with T2D and BMI 30 to 35 kg/m^2. There is also very little data on Hispanics and nonHispanic blacks with T2D, who are disproportionately affected by diabetes and diabetes-related complications. The Agency for Healthcare Research and Quality has recognized this area has a critical research gap [8].

Our data add to the growing body of evidence supporting the long-term efficacy of surgery in patients with T2D and BMI 30 to 35 kg/m^2. Schauer et al. [9] randomized 150 patients with BMI 27 to 42 kg/m^2 and T2D to surgery versus MWM and reported 5-year outcome data showing that surgery was more effective [9]. Ikramuddin et al. [10] reported extended follow-up of 120 patients with BMI 30 to 39 kg/m^2 and T2D randomized to surgery versus MWM and found significantly better outcomes in the surgery group at 5 years. Kular et al. [11] reported excellent long-term control of T2D in 128 patients with BMI 30 to 35 kg/m^2 after 1-anastomosis gastric bypass. Lakdawala et al. [12] reported significant improvement in 52 patients with T2D and BMI 30 to 35 kg/m^2 5 years after RYGB.

A previously conducted systematic review and meta-analysis of the literature regarding surgery in 1389 patients with T2D and BMI <35 kg/m^2 revealed a 55% remission rate at 12 months [13]. The 2016 joint statement by the international diabetes organizations, including the American Diabetes Association, stated metabolic surgery "may be considered as an option for adults with T2D and BMI 30 to 35 kg/m^2 who do not achieve durable weight loss with reasonable nonsurgical methods" [14]. Despite these recommendations, larger data sets with long-term follow-up, or meta-analyses incorporating these data, will be required for insurance companies to formally modify current coverage policies.

Our initial studies found that higher baseline sRAGE was associated with better outcomes in terms of weight loss and metabolic recovery. However, this was no longer seen long term. This suggests the predictive factors are the most predictive early (6 mo to 3 yr). Over time, other factors (age, other co-morbidities, environmental factors) in these aging patients might have significantly affected their body mass and state of insulin resistance and HbA1C. Furthermore, the inability to rephenotype all of the patients from the original cohort, and the fact that 10 of the original patients in the initial cohort crossed over to surgery, may have also led to an underpowered analysis.

The patients who did not undergo surgery had a significant incidence of diabetes-related complications, including peripheral neuropathy (n = 6), retinopathy (n = 4), stroke (n = 1), and hospitalization for heart failure (n = 1), compared with none in the surgery group. This supports other long-term studies in obese (BMI >35 kg/m^2) patients demonstrating bariatric surgery is associated with more frequent diabetes remission than usual care, as

Table 3
Five-year outcomes in 43 patients with T2D and BMI 30–35 kg/m^2, stratified by surgery type

	LSG n = 18	RYGB n = 8	LAGB n = 3	*P* value
Diabetes, % (n)	61 (11)	50 (4)	100 (3)	.388*
Insulin use, % (n)	11 (2)	0% (8)	33 (1)	.304*
HbA1C, N	17	7	3	
Pre	7.39 (1.33)	7.66 (.93)	7.73 (.80)	.830†
Post	6.91 (1.25)	6.67 (1.60)	7.63 (1.82)	.613†
Change	−.48 (1.48)	−.99 (1.28)	−.10 (1.51)	.618†
Any HTN meds, % (n)	61 (11)	50 (4)	67 (2)	.585*
>1 HTN meds, % (n)	33 (6)	13 (1)	33 (1)	.480*
BMI, N	18	8	3	
Pre	32.8 (1.7)	32.8 (1.2)	33.0 (.8)	.975†
Post	27.0 (2.4)	24.3 (2.7)	23.1 (5.4)	.030†
Change	−5.9 (1.9)	−8.6 (3.4)	−9.9 (5.8)	.027†
%WL, mean (SD)	18.0 (6.0)	26.0 (10.0)	29.9 (16.9)	.028†
Triglycerides, N	18	8	3	
Pre	193.7 (103.9)	142.9 (63.6)	137.0 (68.6)	.345†
Post	131.9 (63.0)	128.9 (45.1)	145.0 (81.1)	.924†
Change	−61.8 (94.6)	−14.0 (68.1)	8.0 (107.4)	.288†
HDL, N	18	8	3	
Pre	46.3 (11.0)	57.9 (23.5)	47.3 (14.2)	.228†
Post	56.2 (18.5)	63.9 (21.3)	14.7 (8.5)	.544†
Change	9.9 (11.8)	6.0 (10.6)	18.0 (6.9)	.296†
LDL, N	17	8	3	
Pre	109.4 (32.5)	109.8 (41.4)	83.0 (26.2)	.471†
Post	115.6 (41.3)	94.1 (44.3)	130.0 (30.1)	.353†
Change	6.2 (54.1)	−15.6 (47.0)	47 (12.8)	.196†
CHOL, N	18	8	3	
Pre	194.1 (37.7)	196.4 (62.4)	155.3 (44.1)	.385†
Post	199.1 (45.4)	183.8 (48.0)	224.0 (54.3)	.445†
Change	5.0 (60.2)	−12.6 (59.8)	68.7 (10.2)	.134†
Systolic BP, N	17	8	3	
Pre	133.0 (15.3)	124.1 (15.5)	120.3 (14.7)	.248†
Post	143.8 (14.8)	111.4 (8.8)	128.0 (26.3)	.000†
Change	10.8 (20.6)	−12.7 (20.4)	7.7 (35.5)	.060†
Diastolic BP, N	17	8	3	
Pre	81.4 (13.3)	76.8 (9.4)	73.3 (18.0)	.497†
Post	79.7 (10.5)	73.1 (10.1)	68.7 (6.0)	.130†
Change	−1.7 (14.1)	−3.6 (17.0)	−4.7 (20.1)	.927†

T2D = type 2 diabetes; BMI = body mass index; HbA1C = glycated hemoglobin; HTN = hypertension; %WL = percent weight loss; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CHOL = cholesterol; BP = blood pressure.

N for continuous data is the number of nonmissing values within each group.

* Fisher's exact test.

† Analysis of variance.

well as fewer microvascular and macrovascular complications [15].

Limitations of this study are related to the small sample size, the fact that aging and other unrecognized comorbidities might have affected weight and insulin resistance/T2D, and the retrospective nature of this study. Our sample size was too small for adequately powered analysis comparing LSG, RYGB, and LAGB. Another limitation is the comparator arm was usual medical care, not "intensive diabetes management." Nevertheless, previous randomized control trial, including intensive diabetes management, have demonstrated similar superior results with surgery as seen in this study [9,10].

Conclusion

Long-term, metabolic surgery remains very effective in patients with T2D and BMI 30 to 35 kg/m^2. Baseline sRAGE levels are most likely predictive of early outcomes only.

Table 4
sRAGE not associated with long-term outcomes

	No surgery n = 14		Surgery n = 20	
	r	*P* value	*r*	*P* value
Change in HbA1C	.172	.557	.018	.944
Change in BMI	.261	.367	.172	.626
%WL	−.255	.379	−.182	.443

sRAGE = soluble receptor for advanced glycation end products; HbA1C = glycated hemoglobin; BMI = body mass index; %WL = percent weight loss.

Disclosure statement

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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