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Letters

Cardiovascular Biomarkers After Metabolic Surgery Versus Medical Therapy for Diabetes

Metabolic surgery has emerged as an important therapeutic option for the treatment of type 2 diabetes mellitus, particularly in patients who are obese (1). Although observational data had suggested the efficacy of metabolic surgery in promoting improved glycemic, blood pressure, and lipid control, until the STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) trial, randomized data were lacking (2-4). STAMPEDE randomized 150 patients with type 2 diabetes and a body mass index of 27 to 43 kg/m^2 to intensive medical therapy (IMT) alone or IMT plus Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) and then followed them for ≤5 years. RYGB and SG were each superior to IMT alone in improving glycemic control, weight, triglycerides, high-density lipoprotein cholesterol, and quality-of-life parameters. Additionally, medications for diabetes, hyperlipidemia, and hypertension were significantly reduced. The present study reports 5-year changes in cardiometabolic biomarkers after surgical versus medical treatment of diabetes.

Paired samples of 12 biomarkers (lipoprotein related, inflammatory related, thrombosis related, and endocrine related) were available in 100 patients (IMT, n = 25; RYGB, n = 39; SG, n = 36) at baseline and 5 years after randomization. Percentage changes from baseline were compared between the study groups using the Mann-Whitney *U* test for nonparametric distributions. Biomarkers associated with cardiovascular risk, including apolipoprotein A-I, high-sensitivity C-reactive protein, and plasminogen activator inhibitor-1, were favorably influenced in both surgical groups at 5 years compared with the IMT group (**Table 1**). Myeloperoxidase, interleukin-6, leptin, adiponectin, and uric acid were significantly improved after RYGB compared with IMT. Leptin was reduced after RYGB compared with SG. Changes in apolipoprotein B, lipoprotein(a), homocysteine, and pro-B-type natriuretic peptide were not statistically significant. No significant differences in low-density lipoprotein cholesterol or apolipoprotein B levels were noted among the 3 groups, although the number of patients on lipid-lowering therapy at the end of the study was significantly lower in the surgical groups than in the IMT group.

In the overall STAMPEDE trial, weight loss 5 years after RYGB (−23.2 ± 9.6 kg) was greater than after SG (−18.6 ± 7.5 kg) or IMT (−5.3 ± 10.8 kg). Parallel to loss of weight, favorable changes were seen in adipokines produced by adipocytes, with decreases in leptin and increases in adiponectin. Obesity results in a chronic inflammatory state that may in part contribute to its association with cardiovascular disease. Significant reduction in biomarkers reflecting arterial inflammation—C-reactive protein, interleukin-6, and myeloperoxidase—were observed. As a causal role of inflammation in atherosclerosis and its adverse events has now been affirmed, these changes in biomarkers due to metabolic surgery may be predictive of beneficial effects on the risk for future ischemic events.

The findings of this study indicate that in patients with type 2 diabetes, compared with IMT, metabolic surgery is associated with long-term favorable changes in various cardiometabolic biomarkers related to lipids, inflammation, thrombosis, and obesity. These types of changes in biomarkers, when previously observed in the context of trials of evidence-based medications, have been associated with substantial reductions in cardiovascular events. Potentially, these "pleiotropic" effects of metabolic surgery may provide similar or even synergistic benefits to what had been observed with medical therapy, without the challenge of long-term adherence to medical therapy (5).

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TABLE 1 Percentage Changes From Baseline in Cardiovascular and Cardiometabolic Biomarkers and Status of Medications 5 Years After Randomization

	IMT (n = 25)	RYGB (n = 39)	SG (n = 36)	RYGB vs. IMT	SG vs. IMT	RYGB vs. SG
Lipoprotein related						
Apolipoprotein A-I	0 (−9.0 to 17.0)	15.7 (5.7 to 25.5)	16.6 (7.6 to 21.1)	0.007	0.02	0.74
Apolipoprotein B	11.3 (−14.3 to 38.8)	1.2 (−24.4 to 28.6)	−0.6 (−21.4 to 22.0)	0.51	0.38	0.86
Lipoprotein(a)	0 (−5.9 to 15.0)	0 (−20.1 to 9.7)	0 (−3.0 to 30.5)	0.20	0.72	0.09
LDL cholesterol*	7.6 ± 61.9	16.4 ± 54.4	17.8 ± 46.9	0.56	0.47	0.91
HDL cholesterol*	1.0 ± 21.19	32.1 ± 31.10	31.8 ± 31.27	<0.001	<0.001	0.97
Triglycerides	−10.6 (−41.7 to 22.0)	−39.8 (−57.3 to −1.2)	−32.3 (−52.7 to −0.6)	0.03	0.06	0.56
Any lipid medications†	21 (84.0)	16 (41.0)	19 (52.8)	0.001	0.01	0.31
Inflammatory related						
C-reactive protein	−25 (−47 to 25)	−75 (−93 to −35)	−69 (−83 to −34)	<0.001	0.002	0.14
Myeloperoxidase	−4 (−18 to 9)	−17 (−30 to −0.7)	−19 (−26 to −0.6)	0.04	0.07	0.89
Interleukin-6	−9.5 (−29.5 to 45.5)	−37.4 (−58.8 to −18.9)	−32.1 (−53.9 to 14.7)	0.009	0.09	0.38
Thrombosis related						
Plasminogen activator inhibitor-1	−26 (−56.3 to 75.0)	−57 (−78.0 to −9.2)	−48 (−71.4 to −22.2)	0.01	0.03	0.37
Homocysteine	22 (5.0 to 47.3)	16 (−9.5 to 53.5)	23 (−5.5 to 45.6)	0.44	0.90	0.63
Endocrine related						
HbA_{1c}*	−6.4 ± 21.7	−23.5 ± 17.1	−22.6 ± 21.8	0.001	0.006	0.84
Leptin	7.1 (−20.1 to 60.0)	−50.0 (−70.3 to −0.6)	−12.5 (−38.6 to 9.8)	0.002	0.11	0.03
Adiponectin	19.2 (−6.1 to 68.3)	100.4 (17.8 to 206.6)	50.7 (11.1 to 111.9)	0.03	0.19	0.17
Uric acid	11.6 (−10.4 to 35.3)	−4.9 (−18.4 to 14.3)	−2.9 (−15.6 to 21.8)	0.05	0.10	0.61
Any diabetes medications†	24 (96)	19 (49)	27 (75)	<0.001	0.04	0.02
Hemodynamic related						
Pro-B-type natriuretic peptide	54.3 (−6.0 to 179.3)	121 (30.9 to 295.9)	105 (27.6 to 163.8)	0.25	0.59	0.29
Systolic blood pressure*	−2.7 ± 15.2	−2.4 ± 17.0	−6.3 ± 14.2	0.94	0.35	0.28
Diastolic blood pressure*	−5.0 ± 13.9	−8.9 ± 13.3	−10.9 ± 15.9	0.26	0.14	0.56
Any antihypertensive medications†	14 (56)	18 (46.2)	12 (33.3)	0.44	0.08	0.26

Except where indicated, values are median (interquartile range) for percentage changes between baseline and 5 years after randomization. *Values are mean ± SD. †Values are n (%) taking the medications at the end of the trial.

HbA_{1c} = glycated hemoglobin; HDL = high-density lipoprotein; IMT = intensive medical therapy; LDL = low-density lipoprotein; RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy.

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