Bariatric Surgery–Induced Cardiac and Lipidomic Changes in Obesity-Related Heart Failure with Preserved Ejection Fraction

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Objective: To determine the effects of gastric bypass on myocardial lipid deposition and function and the plasma lipidome in women with obesity and heart failure with preserved ejection fraction (HFpEF).

Methods: A primary cohort (N = 12) with HFpEF and obesity underwent echocardiography and magnetic resonance spectroscopy both before and 3 months and 6 months after bariatric surgery. Plasma lipidomic analysis was performed before surgery and 3 months after surgery in the primary cohort and were confirmed in a validation cohort (N = 22).

Results: After surgery-induced weight loss, Minnesota Living with Heart Failure questionnaire scores, cardiac mass, and liver fat decreased (P < 0.02, P < 0.001, and P = 0.007, respectively); echo-derived e' increased (P = 0.03), but cardiac fat was unchanged. Although weight loss was associated with decreases in many plasma ceramide and sphingolipid species, plasma lipid and cardiac function changes did not correlate.

Conclusions: Surgery-induced weight loss in women with HFpEF and obesity was associated with improved symptoms, reverse cardiac remodeling, and improved relaxation. Although weight loss was associated with plasma sphingolipidome changes, cardiac function improvement was not associated with lipidomic or myocardial triglyceride changes. The results of this study suggest that gastric bypass ameliorates obesity-related HFpEF and that cardiac fat deposition and lipidomic changes may not be critical to its pathogenesis.

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Introduction

Obesity is a major risk factor for developing heart failure (HF), especially HF with preserved ejection fraction (HFpEF) (1). Women are particularly at risk for developing HFpEF (1). Unlike HF with reduced ejection fraction, obesity-related HFpEF is increasing in prevalence in the United States. Because the pathophysiology of HFpEF and HF with reduced ejection fraction may be different, these diseases may require distinct therapeutic approaches. Currently, no therapies improve survival in cases of HFpEF (1).

Studies in animal models of obesity show that the dysfunction of organs, such as the heart and liver, is pathophysiologically linked to excessive fat uptake and storage, and specific waxy lipids such as “ceramides,” via a process known as “lipotoxicity” (2). Although there are likely multiple mechanisms underlying obesity-related HFpEF, myocardial total ceramides and toxic lipid species may play a role (3). Obesity in humans without HF is associated with cardiac dysfunction, elevated plasma ceramide levels, and myocardial fat uptake and storage (4-6). In contrast, weight loss in patients without...
HF is associated with decreased plasma triglyceride and ceramide levels (6), decreased myocardial fat utilization (7) and storage (8), left ventricular (LV) mass, and improved cardiac function (7). Furthermore, gastric bypass–induced weight loss is associated with decreased cardiovascular death rates (9). However, in HF patients, obesity has been purported to have a protective effect because patients with obesity and HF live longer than lean patients with HF (10,11). Thus, it is not clear whether patients with obesity-related HFpEF should, in fact, lose weight. Recent data show that in animals with obesity and HF, myocardial triglycerides and LV mass were increased and diastolic function was impaired; furthermore, these data show that these abnormalities improved with weight loss, suggesting that weight loss is beneficial even in the presence of HF (12). Whether the same is true in humans with HFpEF is not clear. It is also not clear whether weight loss in patients with HFpEF decreases plasma ceramide levels and sphingolipids.

The aim of this study was to determine the effect of gastric bypass–induced weight loss on HF symptoms, on myocardial fat deposition, and on the plasma lipidomic profile in women with obesity. We also analyzed plasma lipidomic changes in a validation cohort of patients who underwent gastric bypass surgery. To this end, we prospectively studied women with HFpEF both before and 3 months and 6 months after gastric bypass surgery by using HF questionnaires, magnetic resonance spectroscopy, echocardiography, and mass spectrometry. We hypothesized that weight loss in women with obesity and HFpEF would improve HF symptoms and diastolic function, decrease myocardial fat deposition, and alter plasma levels of ceramides and sphingolipids.

Methods
Subjects: primary cohort
The study was approved by the Washington University School of Medicine Human Research Protection Office. All patients gave written informed consent before participating. The primary cohort was recruited from the bariatric surgery center at the Washington University School of Medicine. Inclusion criteria required participants to be women between 35 and 65 years of age with BMI > 35 kg/m² and a diagnosis of HFpEF (as determined by 2 physicians who confirmed the diagnosis by using the patient’s medical history, a physical examination, echocardiography, and the diagnostic criteria outlined by Eggebeen et al., which are based on the American College of Cardiology and American Heart Association guidelines) (13). Exclusion criteria included current tobacco use, an inability to be ambulatory or to lie flat for procedures, pregnancy or lactation, cardiac conditions that interfered with assessment of diastolic function (e.g., constrictive pericarditis or atrial fibrillation/flutter), contraindication to magnetic resonance spectroscopy, other major systemic disease except for type 2 diabetes, ejection fraction < 50%, uncontrolled hypertension, significant pulmonary hypertension by history and/or echocardiography, and/or evidence of ischemia on screening stress echocardiogram.

Twenty-four patients were in the primary cohort. Eleven dropped out or were screen failures: nine for personal or financial reasons, one because of Crohn disease activation, and one because of a positive stress test. Of the remaining 13 patients, 1 was not included in the final analysis because of uninterpretable echocardiographic data.

Experimental procedures
Primary cohort patients were extensively screened and phenotyped before surgery for evaluation of HF symptoms and signs and determination of New York Heart Association (NYHA) HF class. Patients underwent phlebotomy while fasting for a comprehensive metabolic panel, complete blood count, cholesterol profiles, glucose levels, and sphingolipid and ceramide measurement both before surgery and 3 months and 6 months after surgery. All subjects were in energy balance when their presurgery measurements were taken. A Minnesota Living with HF (MNLFH) questionnaire was administered to assess symptomatic limitations from HF. The MNLFH 100-point scale questionnaire is a well-validated tool used in many HF clinical trials (14). A higher score indicates worse HF symptoms and a score of “0” indicates no symptoms. As a reference, prior validating studies have correlated HFpEF patients with scores of 15 to 48 with NYHA class II and scores of 32 to 67 with NYHA class III (14,15). All patients underwent dual-energy x-ray absorptiometry (Lunar iDXA, General Electric, Fairfield, Connecticut) for fat mass and fat-free mass measurement. All subjects underwent a rest and stress echocardiogram.

Echocardiography. Resting echocardiograms before surgery were used to evaluate cardiac structure and function. LV mass was measured by using the area-length method. Relative wall thickness was calculated as (2 × posterior wall thickness)/LV end-diastolic diameter. LV ejection fraction was calculated by using the modified Simpson method. The mitral valve inflow E wave was measured by using spectral Doppler, and tissue Doppler was used to quantify early relaxation e’ at both the septal and lateral mitral valve annuli. These were averaged to obtain an average E/e’ value. A measure of left atrial pressure, was calculated. Echocardiography was repeated at 3 months and 6 months after surgery. (The validation cohort also had E and e’ average measured at baseline.)

1H-magnetic resonance spectroscopy. The validation and reproducibility of 1H-magnetic resonance spectroscopy technique have been published previously by our group and others (5,16). Magnetic resonance spectroscopy was used to measure myocardial and hepatic tissue lipid levels, as described previously by our research group (17). Cardiac spectra were acquired from the interventricular septum at end-systole and at end-respiration. Liver spectra were obtained from a region of interest in the right lobe of the liver that did not include visible vasculature. The spectra were analyzed by using AMARES fitting programs and jMRUI software (http://www.jmrui.eu/). 1H-magnetic resonance spectroscopy was performed both before and 3 months and 6 months after surgery in the primary cohort. The regions of interest in subsequent scans were placed as close to the original regions as possible.

Roux-en-Y gastric bypass surgery. The same surgeon (JCE) performed all of the gastric bypass surgeries for the primary cohort. In brief, stapling across the stomach created a small gastric pouch. A Roux-en-Y limb was then constructed by cutting across the jejunalum distal to the ligament of Treitz and creating a jejunojejunos- tomy distal to the transection.

Lipidomics. Liquid chromatography-tandem mass spectrometry was used to analyze presurgery and 3-months-post surgery plasma samples for long-chain and very-long-chain ceramides and sphingomyelins at the Washington University Metabolomics Facility. The
reagents, sample preparation, instrumentation, internal standards, and quantification methods were previously described in detail in Fan et al. (18). Analyses were carried out blinded to subject treatment phase on samples from the initial Washington University cohort and on samples from a validation cohort of women undergoing gastric bypass at the University of Texas-Houston. Eight subjects in the primary cohort and twenty-two in the validation cohort had plasma samples at the presurgery and 3-months-postsurgery time points. The validation cohort was added because the primary cohort was relatively small and because this is one of the first studies of lipidomic effects of weight loss. The validation cohort had significant obesity, but the members of the cohort were not evaluated for signs and symptoms of HFpEF preoperatively. Validation analysis focused on lipid species that were significantly different after weight loss in the primary cohort and had a coefficient of variation less than 10% (Supporting Information Table S1).

Statistical analysis. Data were analyzed by using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina). Data are presented as mean ± SE. A repeated-measures analysis based on a mixed model approach was conducted to examine the change in patient characteristics and heart function measures over time (before and 3 months and 6 months after gastric bypass surgery). Mean estimates were obtained from the model results. All pair-wise comparisons were made, and a Bonferroni adjustment was applied when reporting P values. The Houston data contained 2 measurements per subject per time point. A repeated-measures analysis based on a mixed model approach was used to account for correlated data within each subject at each time point and across time points (before surgery and 3 months after surgery). Mean estimates and comparisons between time points were obtained from model results. Pearson correlations were created to describe the linear relationship between the change in heart function and the change in lipidomic species. Comparisons of the baseline characteristics of both cohorts were achieved with unpaired t tests. Statistical significance was set at P < 0.05.

Results

Baseline characteristics

The primary cohort data are shown in Table 1. The average age of the women was 47 years, all had at least class II obesity, and on average, ~44% of their body mass was fat mass. Patients scored relatively poorly on the MLWHF quality of life questionnaire (27 ± 6), which objectifies the symptoms of HF (Figure 1). Eight subjects had type 2 diabetes and most were taking insulin or hypoglycemic agents (Table 2). Similarly, although the subjects’ hemodynamics were in the normal range, most were taking at least one vasoactive and/or diuretic medication.

| TABLE 1 Whole-body and cardiac parameters before and after surgery (primary cohort) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Number                          | 12              | 12              | 10              | 10              | 10              |
| Weight parameters               |                 |                 |                 |                 |                 |
| Weight (kg)                     | 120 ± 4         | 96 ± 4          | < 0.001         | 83 ± 4          | < 0.001         | < 0.001         |
| BMI (kg/m²)                     | 43.9 ± 1.2      | 35.3 ± 1.2      | < 0.001         | 30.7 ± 1.3      | < 0.001         | < 0.001         |
| Fat mass (kg)                   | 53 ± 3          | 39 ± 3          | < 0.001         | 29 ± 3          | < 0.001         | < 0.001         |
| Fat-free mass (kg)              | 62 ± 2          | 55 ± 2          | < 0.001         | 54 ± 2          | < 0.001         | < 0.001         |
| Hemodynamic parameters          |                 |                 |                 |                 |                 |
| Heart rate (beats/min)          | 81 ± 3          | 68 ± 3          | 0.01            | 69 ± 3          | 0.04            | 0.009           |
| SBP (mm Hg)                     | 127 ± 4         | 120 ± 4         | 0.53            | 122 ± 4         | 0.97            | 0.37            |
| DBP (mm Hg)                     | 72 ± 3          | 75 ± 3          | 1.00            | 77 ± 3          | 0.88            | 0.56            |
| Echocardiography                |                 |                 |                 |                 |                 |                 |
| Ejection fraction (%)           | 63 ± 2          | 62 ± 2          | 1.000           | 61 ± 2          | 1.000           | 0.63            |
| E' (cm/s)                       | 9.5 ± 0.6       | 10.8 ± 0.6      | 0.03            | 10.5 ± 0.6      | 0.19            | 0.03            |
| E/e'                            | 8.2 ± 0.5       | 7.6 ± 0.5       | 0.73            | 7.0 ± 0.5       | 0.13            | 0.12            |
| Relative wall thickness         | 0.44 ± 0.02     | 0.40 ± 0.02     | 0.21            | 0.39 ± 0.02     | 0.046           | 0.04            |
| 1H-magnetic resonance spectroscopy (fat/water %) |                 |                 |                 |                 |                 |
| Hepatic fat (%)                 | 18.97 ± 3.37    | 7.02 ± 3.37     | 0.05            | 2.85 ± 3.70     | 0.009           | 0.007           |
| Cardiac fat (%)                 | 1.18 ± 0.16     | 1.29 ± 0.18     | 1.000           | 1.06 ± 0.18     | 1.000           | 0.49            |
| Metabolic parameters            |                 |                 |                 |                 |                 |                 |
| Fasting glucose (mg/dL)         | 120 ± 12        | 103 ± 12        | 0.88            | 94 ± 13         | 0.42            | 0.31            |
| Total cholesterol (mg/dL)       | 169 ± 10        | 154 ± 10        | 0.32            | 150 ± 11        | 0.18            | 0.11            |
| HDL (mg/dL)                     | 46 ± 5          | 45 ± 5          | 1.00            | 55 ± 5          | 0.08            | 0.04            |
| LDL (mg/dL)                     | 90 ± 8          | 87 ± 8          | 1.00            | 76 ± 9          | 0.44            | 0.32            |

Data are mean ± SE. Repeated-measures analyses conducted by using mixed model approach. All pair-wise comparisons made by using Bonferroni adjustment. Text in bold font indicates significant P value.

DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
There were several echocardiographic abnormalities at baseline. Although all subjects had normal ejection fractions, their LV mass was severely increased (Figure 2) (19-21). The normal range of LV mass in women is 66 to 150 g with severe hypertrophy >193 g. This, in combination with increased relative wall thickness, is consistent with concentric LV hypertrophy (LVH) (19,21). The subjects’ average early cardiac relaxation (average septal and lateral e’ of 9.5 ± 0.6) was abnormal for women in their 40s (normal: 14.2 ± 2.3) (20), though E/e’ was borderline normal (8.2 ± 0.5, normal <8; Table 1).

Weight loss and metabolism, hemodynamics, and medications

At 3 and 6 months after gastric bypass surgery, there was progressive weight loss accompanied by significant improvements in resting heart rate (Table 1), despite fewer subjects taking beta-blocker medications (Table 2). Although there was no significant difference in plasma glucose level or blood pressure, fewer subjects took antihypertensive and glucose-lowering medications after weight loss. The validation cohort also experienced metabolic improvements (Table 3): namely, lower total cholesterol, lower fasting glucose levels, and lower insulin levels. High-density lipoprotein levels also decreased.

**Weight loss and HF symptoms**

 Patients also experienced fewer HF symptoms, as evidenced by the decrease in the MNLHF score (Figure 1) and NYHA class (Figure 3), suggesting that they were able to perform more activities with fewer HF symptoms.

**Weight loss and LV structure/function**

LV mass regressed significantly, although it was still above normal 6 months after surgery (Figure 2). Relative wall thickness also decreased (Table 1). The abnormally low LV relaxation, (e’), improved with weight loss (Table 1). The borderline normal baseline left atrial filling pressure (E/e’) trended toward an improvement (Table 1).

**Weight loss and steatosis**

Patients in this study had a high baseline hepatic fat content of 18.97 ± 3.37%, which is well above the upper limit of normal

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**TABLE 2 Vasoactive, diabetes, and lipid medications before and after gastric bypass surgery in the primary cohort**

| Medication                        | Baseline | 3 mo after surgery | 6 mo after surgery |
|-----------------------------------|----------|--------------------|--------------------|
| Vasoactive/diuretic medication    |          |                    |                    |
| ACE inhibitors/ARBs               | 7/12     | 3/10               | 2/10               |
| Beta-blockers                     | 3/12     | 3/10               | 1/10               |
| Loop/thiazide diuretic            | 4/12     | 1/10               | 1/10               |
| Diabetes medication               |          |                    |                    |
| Oral hypoglycemic                 | 6/12     | 1/10               | 0/10               |
| Insulin                           | 3/12     | 1/10               | 0/10               |
| Lipid management                  |          |                    |                    |
| Statins                           | 5/12     | 4/10               | 1/10               |
| Other lipid medication            | 1/12     | 1/10               | 3/10               |

Values expressed as number taking a medication/total patients.

ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

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**TABLE 3 Metabolic profile of the University of Texas-Houston patients at baseline and after 3 mo of weight loss**

| Metabolic Profile                          | Presurgery | 3 mo after surgery | P     |
|--------------------------------------------|------------|--------------------|-------|
| Total cholesterol (mg/dL)                  | 176 ± 6    | 150 ± 6            | <0.001|
| High-density lipoprotein (mg/dL)           | 41 ± 2     | 37 ± 2             | <0.001|
| Triglycerides                              | 155 ± 45   | 98 ± 9             | 0.22  |
| Free fatty acids (mmol/L)                  | 0.90 ± 0.05| 0.93 ± 0.06        | 0.67  |
| Fasting glucose (mg/dL)                    | 105.1 ± 9.9| 79.4 ± 2.2         | 0.02  |
| Fasting insulin (IU/L)                     | 20.63 ± 3.85| 9.93 ± 0.90      | 0.01  |

Data are mean ± SE. N = 19. Text in bold font indicates significant P value.
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(5.56%) (Table 1) (5,22,23). Hepatic fat decreased with weight loss (Table 1). Six months after surgery, hepatic fat was within normal levels. In contrast, cardiac fat content was much lower than hepatic fat at baseline and did not change after the surgery.

Weight loss and lipidomic results

Four ceramides and twelve sphingomyelins in the primary cohort decreased after 3 months of weight loss. Four sphingomyelins and one ceramide (18:0) increased after 3 months. All species that changed significantly in both cohorts and that had the prerequisite coefficient of variation of less than 10% are shown in Table 4. Other ceramides and sphingolipids are listed in Supporting Information Table S1. The validation cohort had a higher baseline BMI of 50.4 ± 9.7 kg/m² (P = 0.02) but was not different in age, sex, blood pressure, or fasting glucose. Ejection fraction, e', and E/e' were also not different at baseline from the primary cohort (data not shown). The validation cohort’s metabolic profile improved 3 months after surgery, like the primary cohort (Table 3). Again, most of the ceramide and sphingolipids species tested decreased after 3 months of weight loss. Three of the four sphingomyelins that increased in the primary cohort (SM18:0, SM24:1, SM24:2) also increased in the validation cohort. The only lipid species that did not change in the same direction in the validation cohort and the primary cohort was the odd-chain SM23:1, which decreased in the primary cohort and increased in the validation cohort. None of these lipidomic changes correlated with improvement in diastolic function as assessed by e’.

Discussion

In this study, we showed that gastric bypass–induced weight loss ameliorated the symptoms of obesity-related HFpEF, reversed adverse LV remodeling, improved diastolic function, and was associated with alterations in the plasma lipidome in women. Surgery-induced weight loss also improved symptoms and quality of life as assessed by the MNLWHF and NYHA scores. Weight loss improved cardiac structure, specifically LV mass and relative wall thickness, and LV relaxation as assessed by e’. Moreover, weight loss decreased liver fat and plasma levels of several sphingolipids, which have generally been implicated in lipotoxicity in animal models (2,24). The changes in plasma sphingolipids were largely replicated in a validation cohort. However, the lipidomic changes in the primary cohort did not correlate with the diastolic function improvements. Weight loss did not alter cardiac but did decrease hepatic triglyceride content. Thus, it appears that triglyceride deposition may not be critical to the pathogenesis of human obesity-related HFpEF.

Currently, few therapies have been shown to improve symptoms for HFpEF (25), which is why the results after gastric bypass–induced weight loss shown in our study are so striking. The baseline MHLHF score was 27 ± 6, which decreased to 7 ± 6 after weight loss, and weight loss improved the average NYHA class. Our results are also in line with a recent finding of reduced emergency room visits and HF hospitalizations after bariatric surgery in patients with obesity-related HFpEF (26). Importantly, gastric bypass-induced weight loss improves symptoms and quality of life without increasing heart rate or other cardiac markers of increased mortality, unlike other treatments of HF, such as adrenergic agonists.

Our study showed improved hemodynamics, LV structure, and LV function after weight loss in patients with obesity-related HFpEF. It is already well known that these parameters improve with weight loss in obesity without HFpEF (6). Decreased resting heart rate is an especially important finding because high resting heart rate is a well-known marker of poor outcomes (27) and because the decrease in heart rate occurred despite fewer patients taking beta-blockers after weight loss. In addition, subjects needed less antihypertensive medication to maintain a normal pressure (Table 2). Recent data from a study in animals with obesity with HF show that weight loss improved LVH and diastolic function (12). Our data in humans are similar, showing that there was a significant reduction in LV mass...
and relative wall thickness. However, though mean relative wall thickness normalized, LV mass did not. A longer follow-up and greater weight loss may be required for both parameters to normalize. Reduction in LVH is an especially important end point in women because it has been linked to a higher risk of cardiovascular fatal outcomes when compared to men (28). LVH regression is also linked with reduced HF hospitalizations and improved diastolic function (29,30). Active relaxation (e') in diastole also improved (Table 1). This is a notoriously difficult parameter to influence with any therapy. For example, in the VALIDD study, aggressive blood pressure control with valsartan resulted in only a 0.6-cm/s change from baseline but was not different from the placebo-treated group (31). Interestingly, the improved LV relaxation and decrease in heart size in patients with HFpEF occurred without a change in blood pressure and in spite of fewer patients taking antihypertensive medications after weight loss. The improvements in markers of poor prognostic (increased LV mass and resting heart rate) after weight loss appear to contradict the complex, and likely multifactorial, “obesity paradox,” in which subjects with HF and obesity have a better prognosis than those without obesity. However, our findings of the beneficial effect of weight loss on survival rates are supported by 2 large studies (N > 13,000) of gastric bypass (9,32).

Despite the change in LV mass, as well as marked weight loss and marked decreases of hepatic lipids (Table 1), the myocardial lipid levels did not change. In our study, baseline cardiac lipid levels were ~1.18%, which was higher than reported values in normal subjects (~0.4 ± 0.2%) (16). This is in contrast to several studies in animal models of obesity that suggest excessive fat deposition is a key element in the development of toxic lipid species (such as some ceramides), lipotoxicity, and cardiac dysfunction (2). This is also in contrast to a study of diet-induced weight loss in patients with type 2 diabetes, which showed a decrease in myocardial lipid content, although this decrease did not correlate with the improvement in diastolic function (7). Our findings suggest that although myocardial triglyceride stores reflect the altered metabolic environment of obesity, the triglyceride itself may not be a major mediator of cardiac dysfunction, a notion supported by findings in cultured cells (33) and rodent models of lipotoxic cardiomyopathy (34). The precise nature of lipotoxic species in the heart affected by obesity remains to be determined, but changes in the plasma sphingolipids suggest these could include some ceramides and sphingomyelins. A decrease in hepatic triglycerides, but not cardiac triglycerides, 6 months following bariatric surgery may reflect a more dynamic pool of lipids in the liver. The liver also moves less than the heart and is therefore easier to image than the heart. It is also likely to be easier to detect a difference in the liver fat of our subjects after weight loss, given that liver fat content was 18-fold higher than cardiac fat at baseline. Thus, it appears that myocardial oxidation (7) and/or processing of fatty acids, which can yield reactive oxygen species (24) and/or toxic lipid species (such as some ceramides (2,3)), may play a more important role in obesity-related cardiac dysfunction than lipid deposition.

In the current study, we found that the plasma ceramides and sphingolipid levels change after gastric bypass–induced weight loss in HFpEF patients. The majority of sphingolipids and ceramides decreased, but a few increased after 3 months. Our findings were replicated in a validation cohort of patients from the University of Texas-Houston who also underwent gastric bypass. We did not find a correlation between the plasma lipidomic changes and the improvements in LV mass or function. A few other studies evaluated specific lipid changes after bariatric surgery, though none in HFpEF patients, and no studies evaluated their possible relationship with cardiac indices (6,35). Generally, a decrease was found in ceramides after gastric bypass surgery (6), although changes in specific ceramide species vary somewhat among the studies. For example, in the study by Huang et al., ceramides 14:0, 16:0, 20:0, and 24:0 were decreased at 3 and 6 months following surgery (6), whereas we found decreases in ceramides 22:0, 23:0, 24:0, and 25:0. There are some indications that certain ceramides, and possibly sphingomyelins, may be associated with favorable outcomes and that others may be associated with adverse outcomes in patients referred for cardiac catheterization (36). However, more long-term research on the prognostic role of ceramides/sphingomyelins in patients with obesity, patients with HFpEF, patients who have lost weight, and in population studies is required. The lipidome during short-term weight loss may also be different from the lipidome after weight stabilization for years.

Our study is limited by small numbers and by the relatively short duration of follow-up. Although the University of Texas-Houston cohort was similar to the primary cohort in several baseline characteristics and had very similar lipidomic changes, the former was not rigorously evaluated for signs and symptoms of HFpEF. Thus, the comparison of the 2 groups is not perfect. The results of our study cannot automatically be extended to men or other subjects who do not fit our entry criteria. We limited our study to women because they make up the vast majority of subjects who undergo gastric bypass surgery and because of the known myocardial metabolic differences between men and women with obesity (37). Magnetic resonance spectroscopy evaluation of steatosis is generally validated for measuring triglyceride accumulation and does not yield information regarding the deposition of other lipid species, such as ceramides.

Conclusion
Gastric bypass surgery–induced weight loss in women with obesity-related HFpEF results in improvement of HF symptoms and diastolic function. Surgery-induced weight loss also decreases LV mass and resting heart rate, which are associated with increased mortality. These data suggest that gastric bypass may alleviate HFpEF in patients with obesity. Moreover, there are intriguing alterations in the plasma lipidome in HFpEF after gastric bypass surgery. Future studies are needed to clarify the pathogenesis of these changes and whether they have potential to serve as biomarkers of cardiac and whole-body function or whether they may impact function themselves.

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