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Dramatic Reversal of Derangements in Muscle Metabolism and Diastolic Left Ventricular Function after Bariatric Surgery

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Abstract

Objective—To define muscle metabolic and cardiovascular changes following surgical intervention in clinically severe obese patients.

Background—Obesity is a state of metabolic dysregulation which may lead to maladaptive changes in heart and skeletal muscle, including insulin resistance and heart failure. In a prospective longitudinal study 43 consecutive patients were subjected to metabolic profiling, skeletal muscle biopsies and resting echocardiograms at baseline as well as three and nine months after bariatric surgery.

Results—Body mass index (BMI) decreased [mean changes (95% CI): 7.7 kg/m² (6.70–8.89) at 3 months and 5.6 kg/m² (4.45–6.80), $p < 0.0001$ at 9 months after surgery], with restoration of insulin sensitivity and decreases in plasma leptin at the same time points. Concurrent with these changes were dramatic decreases in skeletal muscle transcript levels of stearoyl CoA desaturase (SCD) and pyruvate dehydrogenase kinase-4 (PDK4) at three and nine months ($p < 0.0001$, for both), and a significant decrease in peroxisome proliferation activated receptor alpha (PPAR- α) regulated genes at nine months. Left ventricular relaxation impairment, assessed by tissue Doppler imaging, normalized nine months after surgery.

Conclusions—Weight loss results in the reversal of systemic and muscle metabolic derangements and is accompanied by a normalization of left ventricular diastolic function.

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Keywords

obesity; metabolism; bariatric surgery; leptin; stearoyl Co-A desaturase; pyruvate dehydrogenase kinase-4; echocardiography

Introduction

Obesity is a state of metabolic dysregulation with an increased risk for premature death and disability.¹ The maladaptive response of obesity has been attributed to metabolic changes caused by either increased energy substrate supply or decreased energy substrate utilization, or both. The body's initial response is to store the energy excess in adipose tissue, to increase cardiac mass in response to the hemodynamic load associated with obesity, and to upregulate gene expression to account for changing metabolic demands. It has been suggested that, when the storage capacity of the adipocyte is exhausted there is "spillover" to other organs of the body.² Lipid accumulation in non-adipose tissue is a hallmark of dysregulated local and systemic metabolism,^{3, 4} of insulin resistance,⁵ and possibly also of the development of heart failure.^{6, 7}

Obesity has reached epidemic proportions and obesity-related illness consumes billions of dollars in health care.⁸ In addition to premature heart disease, obesity is linked to cancer, sleep apnea and birth defects. Treatment of obesity should therefore be an important determinant for a normal life expectancy and quality of life. Weight reduction can ameliorate many of the comorbid conditions associated with obesity.⁹ Indeed, bariatric surgery for severe obesity is associated with survival benefits.^{10–12} The metabolic changes that accompany significant weight loss are paramount for these improved outcomes. Here we proposed that there is a potential for reversal of the maladaptive processes of obesity with sustained weight loss after bariatric surgery.

Material and Methods

Subject Selection

We offered participation to patients of any race/ethnicity from the University of Texas Houston Bariatric Surgery Center (UTHBSC), who met the inclusion criteria for bariatric surgery outlined previously.¹³ Exclusion criteria were coronary artery disease, ischemic cardiomyopathy, severe peripheral vascular disease, a current history of smoking, pregnancy, or an age of less than 18 years. The study was approved by the Committee for the Protection Human Subjects at The University of Texas Health Science Center – Houston. All patients signed an informed consent form prior to enrollment in the study.

Study Protocol

We prospectively enrolled 43 consecutive patients. The study protocol has been published previously.¹³ Briefly, patients underwent a physical examination, anthropometric measurements, a 12-lead electrocardiogram, and resting echocardiogram. At the time of surgery a skeletal muscle biopsy was performed. All studies were repeated at three and nine months post-operatively.

Surgery

Patients were offered two types of bariatric surgery. The patients chose which surgery they preferred to have, as this is the current standard practice in the United States.¹⁴ The majority (n=30) chose laparoscopic small pouch gastric bypass (SPGB) with a Roux-en Y procedure;

the others (n=13) chose a laparoscopic adjustable gastric banding (LAGB) procedure. Both procedures are well described in the literature.^{15, 16}

Patient Enrollment and Follow-up

Of the 43 patients enrolled six were lost to follow-up at nine months. Reasons for the loss to follow-up were either inability to contact the patients or the patients' stated unwillingness to continue with the study. Of the 6 patients who were lost to follow-up, 5 underwent SPGB and 1 underwent LAGB. Of the remaining 37 patients (86%) there were six individuals with inadequate baseline echocardiograms and four other patients who had limited studies because of technical difficulties due to body habitus. All patients had skeletal muscle biopsies at baseline but only 25 completed the follow-up at three and nine months. Reasons for the lower completion rate of the skeletal muscle biopsies were fear of pain, a stated discomfort during the procedure, or (in two instances) our inability to obtain an adequate sample for analysis.

Biopsies

At the time of surgery, and at three and nine months after surgery, a percutaneous biopsy of the vastus lateralis was obtained using a 6 G × 4.75-inch biopsy needle (Popper and Sons, New Hyde Park, NY). Tissue samples were immediately placed in liquid nitrogen and stored at -80° C until analyzed.

Histology

Oil-red-O staining was performed on skeletal muscle sections by the Department of Pathology at The University of Texas Medical School at Houston using standard procedures. Photomicrographs of (10x) stained sections were taken on a Zeiss Axiophoto microscope using a Leitz Microlumina digital camera. Oil-red-O staining was quantified using Image Pro Plus software with color cube-based selection criteria to ensure that only stained regions were counted as described previously.⁶ We examined four sections for each patient at each of the time points. Results are expressed as a percentage of stained area [arbitrary units (AU)].

Quantitative RT-PCR

RNA was extracted from skeletal muscle biopsies by standard methods, and RNA concentrations were measured spectrophotometrically.¹⁷ Transcript levels were measured by reverse transcription followed by real-time quantitative PCR as described before.¹⁷ We focused on enzymes of fatty acid metabolism, especially those regulated by the peroxisome proliferation activated receptor alpha (PPAR- α), including: carnityl palmitoyl transferase 1 (CPT-1), medium chain acetyl CoA dehydrogenase (MCAD), uncoupling protein 3 (UCP3), pyruvate dehydrogenase kinase 4 (PDK4). We also analyzed gene transcript levels for human stearoyl CoA desaturase (SCD). The nucleotide sequences for probes as well as forward and reverse primers for the quantitative PCR assays have been published previously¹⁸ with the exceptions of SCD (forward primer, 5'-TGGTGATGTTCCAGAGGAGGTACT-3'; reverse primer, 5'-AACGAACACACTGTTTTGAAAAGTTT-3'; and probe, 5'-FAMCCTGGCTTGCTGATGATGTGCTTCA-TAMRA3). Transcript levels were normalized to two internal controls and referenced to total RNA content.

Statistical Analyses

Statistical analyses were performed with SPSS 14.0 (SPSS Inc., Chicago, IL). Significance levels were set at $\alpha=0.05$. We evaluated all of the study variables for conformation to normality using Q-Q plots, skewness and kurtosis statistics. Significantly nonnormal variables were transformed prior to analysis. Independent sample t-tests were performed to evaluate differences in outcomes between the patients who underwent laparoscopic adjustable gastric banding and those patients who underwent laparoscopic small pound gastric bypass. Repeated

measures ANOVA were performed to evaluate the effects at three and nine months post-operatively. Effect of surgery was assessed as a variable between subjects with the repeated measures ANOVA. Data are expressed as mean values plus or minus the standard error of the mean and as the change in mean values from baseline to three months post-operatively and from three months to nine months post-operatively with 95% confidence intervals. Pearson correlation coefficients were prepared to evaluate the univariate relationships.

Results

Pre-operative Findings

Table 1 lists the baseline characteristics of all patients, for the patients undergoing small pouch gastric bypass and for the patients undergoing laparoscopic adjustable gastric banding. There were no significant differences in the baseline characteristics between the two surgical groups for any of the variables measured. Patients had more fat mass than lean body mass at baseline, as measured by bioelectrical impedance analysis (Table 1). Mean blood pressure and heart rates were in the normal range. Almost all of the patients met criteria for insulin resistance, but only 35% of the patients had frank diabetes mellitus. Fasting plasma free fatty acid levels were elevated, and leptin levels were almost three times higher than the reference range.

Post-operative Changes

Weight and Hemodynamic Parameters—For practical purposes we chose to analyze patients who underwent laparoscopic small pouch gastric bypass and those who selected laparoscopic adjustable gastric banding as one group. Table 2 shows parameters at three and nine months after surgery. Weight, BMI, waist circumference and fat mass decreased at a faster rate during the first three months than during the subsequent six months. Fat mass changed to a greater extent than lean mass (Table 2). Lean mass decreased to a greater extent during the first three months compared to the subsequent six months (0.73 kg/month in the first three months vs 0.16 kg/month during the last six months).

Hemodynamics and Systemic Metabolism—Table 2 also lists the changes in hemodynamic measurements and metabolism after surgery. Concurrent with the decrease in blood pressure was a 33% reduction in the use of anti-hypertensive drugs at three and nine months compared to baseline. A decrease in glucose, insulin, and leptin concentrations was observed early in the weight loss period, whereas the decrease in plasma FFA was apparent only at nine months after surgery. The decrease in leptin correlated with the loss of weight from baseline to three months and three months to nine months post-operatively ($r=0.3$, $p=0.03$ and $r=0.64$, $p<0.0001$, respectively). Despite the greater decreases in leptin and fat mass early on, the correlation between the changes in leptin and fat mass was stronger later on ($r=0.53$, $p=0.001$). Glucose and insulin concentrations rapidly decreased after surgery and thus insulin sensitivity (HOMA-S) began to normalize at three months or earlier (three months was the first time point we assessed). HOMA-S continued to improve and was in the normal range by nine months post-operatively (Table 2). This improvement in insulin sensitivity occurred despite the relatively small decreases in glucose and insulin concentrations at nine months. It is a function of the non-linear nature of the HOMA model.¹⁹

Echocardiography—Left ventricular mass was increased compared to normal²⁰ and decreased after three months of weight loss (Table 3). At baseline, i.e. before surgery, 42% of the cohort exhibited left ventricular relaxation impairment based on tissue Doppler imaging (Ems)²¹ with a mean velocity of 8.3 cm/sec (data not shown). There were no significant differences in any other baseline characteristics between those with diastolic dysfunction and those without (data not shown). Compared to baseline velocities Ems increased at three months and nine months after surgery [Mean change (CI 95%): 1.9 cm/sec (0.52 – 3.4), $p=0.011$ and

1.2 cm/sec (0.32–2.1)]. Similar trends were seen with more load dependent variables of diastolic function such as early mitral inflow (E) and deceleration time (DecT) in the diastolic dysfunction group (Table 3).

Histology—Figure 1 shows oil-red-O stains of vastus latralis biopsy samples at 0, 3, and 9 months after surgery. There was a significant decrease in oil-red-O staining at nine months. [4.2 AU (–2.4 – 10.9), $p < 0.2$, and 8.7 AU (2.4 – 15.1), $p < 0.009$, comparing baseline to three months, and three months to nine months, respectively]. The decrease in oil-red-O staining between three and nine months correlated significantly with a decrease in weight and fat mass ($r = 0.57$, $p < 0.004$; and $r = 0.44$, $p < 0.03$, respectively). There was also a borderline association between oil-red-O intensity and plasma free fatty acid levels ($r = 0.39$, $p < 0.059$).

Skeletal Muscle Gene Expression—Transcript levels for metabolic enzymes are shown in Figure 2. SCD transcript levels decreased dramatically at three months after surgery (Figure 2A) and remained so at nine months. PDK4 transcript levels also decreased rapidly and significantly at three months after surgery and continued to decrease at nine months after surgery (Figure 2B). The expression of the PPAR- α regulated genes (with the exception of PDK4) only decreased nine months post-operatively (Figure 2C), and the changes in the PPAR- α regulated genes were highly correlative with each other (data not shown). These changes were concurrent with the decrease in the plasma FFA concentrations between three and nine months post-operatively.

Impact of the Type of Surgery on Outcomes—The two types of surgery, laparoscopic small pound gastric bypass and laparoscopic adjustable gastric banding, included in this study produce weight loss by different mechanisms; laparoscopic small pound gastric bypass is a restrictive and malabsorptive process whereas laparoscopic adjustable gastric banding is a restrictive process. We analyzed the outcomes for each group in this study in order to ascertain whether there was an effect produced by the surgery type. Not surprisingly there was a significant difference in the rate of weight loss between the two groups at both three and nine months [Mean weight loss at three and nine months (SEM): laparoscopic small pound gastric bypass 23 kg (1.9) and 20 kg (1.8), laparoscopic adjustable gastric banding 15 kg (2.0) and 9 kg (2.8), $p = 0.01$ and 0.003, respectively for three and nine months]. However there was no significant contribution of the type of surgery to the overall improvement in weight by analysis of variance. Furthermore, there was no overall effect of the type of surgery on other outcomes measured, such as systemic metabolism, cardiac function, hemodynamics or skeletal muscle gene expression (data not shown). These results suggest that outcomes in the early phase of weight loss are independent of the type of surgery.

Discussion

The main findings of our study are that weight loss induced by surgery is accompanied by a reversal of insulin resistance and dramatic changes in skeletal muscle metabolism. The former findings were expected but the latter findings are new. Adipose tissue is an active endocrine organ and an increased adipose mass is associated with insulin resistance and alterations of fatty acid oxidation by complex mechanisms.^{22, 23} These effects are mediated by adipose derived hormones and cytokines (e.g. leptin and TNF- α) which exert control over skeletal muscle metabolic gene expression. We speculate that the decrease in fat mass led to a decrease in leptin concentrations and to improvements in systemic insulin sensitivity. The most surprising findings were profound changes in skeletal muscle metabolic gene expression. Expression of SCD and PDK4 decreased very early in the weight loss process, while the PPAR- α regulated gene expression decreased later in weight loss, at the same time plasma FFA concentrations decreased. The changes may be responsible for the reversal of the maladaptive processes associated with obesity.

Skeletal muscle histology

Oil-red-O stains intra-myocellular triglycerides and increased intensity suggests increased lipid storage in non-adipose tissue, most likely as the result of increased fatty acid supply, decreased rates of triglyceride export or hydrolysis, and/or decreased rates of fatty acid oxidation. The decrease in oil-red-O staining is associated with a normalization of substrate and hormone levels in the circulation as well as transcript levels in the tissue, suggesting a concerted program of reversed lipotoxicity.

Skeletal muscle gene expression

Other surprising findings were profound changes in skeletal muscle metabolic gene expression. Expression of SCD and PDK4 decreased very early in the weight loss process, while the PPAR- α regulated gene expression decreased later in weight loss, at the same time plasma FFA concentrations decreased. This is the first demonstration of gene expression changes early after bariatric surgery. These changes have important implications for the possible mechanisms for the reversal of the maladaptive processes in non-adipose tissue.

The dramatic changes in transcript levels of steroyl-CoA desaturase (SCD) are especially relevant because SCD is the rate limiting enzyme responsible for converting saturated fatty acids into monounsaturated fatty acids, the main precursors of triglycerides.²⁴ SCD is known to be increased in the skeletal muscle of obese individuals and may lead to abnormal lipid partitioning.²⁵ The marked decrease in SCD gene expression post-operatively suggests a change in the flux of fatty acid metabolism, moving from esterification towards beta-oxidation. This result is supported by a sustained expression of the key genes responsible for fatty acid oxidation, the PPAR- α regulated genes and the increased concentrations of plasma FFA. Leptin mediates lipid oxidation through the inhibition of SCD,²⁶ which may result in an increase in saturated fatty acids and their oxidation.

Systemic glucose and insulin concentrations also decreased resulting in improved systemic insulin sensitivity early in weight loss. As weight loss continued at nine months after surgery insulin sensitivity normalized in a majority of the cohort. Skeletal muscle gene expression of pyruvate dehydrogenase kinase-4 (PDK-4) decreased by 83% from the baseline expression at three months and 92% at nine months. PDK-4 phosphorylates the pyruvate dehydrogenase complex, and is an important inhibitory regulator of glucose oxidation.²⁷ PDK-4 is regulated by several factors including insulin and fatty acid concentrations.^{28, 29}

These findings are interesting because in the state increased FFA concentrations or insulin resistance, PDK-4 expression is generally increased, limiting glucose oxidation. Our data at three months suggest a mechanism independent of systemic concentrations of FFA or insulin, as the cause for the decreased expression of PDK-4. We suspect that the change is linked to improved insulin signaling, because there was no change in PPAR- α gene expression at this time point and PDK-4 expression has been shown to act independently of PPAR- α expression.³⁰ Our findings are corroborated with another study demonstrating a decrease in PDK-4 expression three years after bilio-pancreatic diversion for weight loss.³¹

Left ventricular diastolic function

We speculate that the improvement in dysregulation of skeletal muscle metabolism may also have a correlate in improved function of cardiac muscle. Obesity is associated with derangements in left ventricular diastolic function.³² More importantly, diastolic dysfunction is an independent risk for increased morbidity and mortality.^{33, 34} We demonstrated an improvement in a load independent measure of diastology, the septal mitral annular velocity, as measured by tissue Doppler imaging. Although we have previously demonstrated an inverse relationship between plasma FFA and diastolic function in obese individuals,³⁵ in this study

we were not able to demonstrate any significant correlations between the change in Ems and other measured outcomes. The inability to detect a relationship may be due to the small number of subjects in this cohort.

However, there are experimental data to suggest a role in FFA metabolism affecting left ventricular contractile function. Animal models of PPAR- α over-expression³⁶ as well as animals treated with PPAR agonists^{37, 38} show evidence of cardiomyopathy and worsening heart failure. Furthermore, animal models of PPAR- α knockout demonstrate a cardioprotective phenotype compared to overexpression of PPAR- α .³⁹ Diastolic function in our cohort shows an early and sustained improvement in those with dysfunction and it is tempting to speculate that this change may be influenced by the improved FFA metabolism, influenced by leptin, SCD, and PPAR- α gene expression.

Limitations

We are excited about the findings but we are also aware of the following limitations. First, this is a small prospective, longitudinal observational study and we can only infer a relationship between the outcomes, but not prove a causal relationship. Larger studies using external controls need to be done to help define true relationships between gene skeletal gene expression, systemic metabolism, and contractile function of the heart. Secondly, gene expression does not necessarily reflect protein content or activity. This is a shortcoming encountered in all gene expression studies and further work is needed to establish metabolic, structural and functional correlates.

Conclusions

Non-pharmacologic weight loss induced by bariatric surgery results in an early reversal of the maladaptive responses to obesity. Leptin resistance and insulin resistance reverse, leading to improved systemic metabolism as well as skeletal muscle gene expression. It is possible that these mechanisms may also exert a positive effect on left ventricular diastolic function. The implications of these findings for freedom from co-morbidities of obesity remain to be substantiated by the long-term follow-up of the post-surgical patients.

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REFERENCES

1. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* 2006;355:763–778. [PubMed: 16926275]
2. Friedman JJ. Fat in all the wrong places. *Nature* 2002;415:268–269. [PubMed: 11796987]
3. Unger R, Zhou Y, Orci L. Regulation of fatty acid homeostasis in cells: novel role of leptin. *Proc Natl Acad Sci U S A* 1999;96:2327–2332. [PubMed: 10051641]
4. Young ME, Guthrie PH, Razeghi P, et al. Impaired long-chain fatty acid oxidation and contractile dysfunction in the obese Zucker rat heart. *Diabetes* 2002;51:2587–2595. [PubMed: 12145175]
5. Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest* 2000;106:171–176. [PubMed: 10903330]
6. Sharma S, Adroge JV, Golfman L, et al. Intramyocardial lipid accumulation in the failing human heart resembles the lipotoxic rat heart. *FASEB J* 2004;18:1692–1700. [PubMed: 15522914]

7. Kencanaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med* 2002;347:305–313. [PubMed: 12151467]
8. Finkelstein EA, Fiebelkorn IC, Wang G. National medical spending attributable to overweight and obesity: how much, and who's paying? *Health Aff (Millwood)*. 2003Suppl Web Exclusives:W3-219-226.
9. Sjostrom L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;351:2683–2693. [PubMed: 15616203]
10. Sjostrom L, Narbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007;357:741–752. [PubMed: 17715408]
11. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007;357:753–761. [PubMed: 17715409]
12. Bray GA. The missing link - lose weight, live longer. *N Engl J Med* 2007;357:818–820. [PubMed: 17715415]
13. Leichman JG, Aguilar D, King TM, et al. Improvements in systemic metabolism, anthropometrics, and left ventricular geometry 3 months after bariatric surgery. *Surg Obes Relat Dis* 2006;2:592–599. [PubMed: 17138229]
14. Buchwald H. Bariatric surgery for morbid obesity: health implications for patients, health professionals, and third-party payers. *J Am Coll Surg* 2005;200:593–604. [PubMed: 15804474]
15. Higa KD, Boone KB, Ho T, Davies OG. Laparoscopic Roux-en-Y gastric bypass for morbid obesity: technique and preliminary results of our first 400 patients. *Arch Surg* 2000;135:1029–1033. [PubMed: 10982506]discussion 1033-1024.
16. Fielding GA, Allen JW. A step-by-step guide to placement of the LAP-BAND adjustable gastric banding system. *Am J Surg* 2002;184:26S–30S. [PubMed: 12527347]
17. Razeghi P, Young ME, Alcorn JL, Moravec CS, Frazier OH, Taegtmeier H. Metabolic gene expression in fetal and failing human heart. *Circulation* 2001;104:2923–2931. [PubMed: 11739307]
18. Razeghi P, Sharma S, Ying J, et al. Atrophic remodeling of the heart in vivo simultaneously activates pathways of protein synthesis and degradation. *Circulation* 2003;108:2536–2541. [PubMed: 14610007]
19. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care* 1998;21:2191–2192. [PubMed: 9839117]
20. Liu JE, Roman MJ, Pini R, Schwartz JE, Pickering TG, Devereux RB. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. *Ann Intern Med* 1999;131:564–572. [PubMed: 10523216]
21. Munagala VK, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Association of newer diastolic function parameters with age in healthy subjects: a population-based study. *J Am Soc Echocardiogr* 2003;16:1049–1056. [PubMed: 14566298]
22. Kahn BB, Flier JS. Obesity and insulin resistance. *J Clin Invest* 2000;106:473–481. [PubMed: 10953022]
23. Lelliott C, Vidal-Puig AJ. Lipotoxicity, an imbalance between lipogenesis de novo and fatty acid oxidation. *Int J Obes Relat Metab Disord* 2004;28:S22–S28. [PubMed: 15592482]
24. Enoch HG, Strittmatter P. Role of tyrosyl and arginyl residues in rat liver microsomal stearylcoenzyme A desaturase. *Biochemistry* 1978;17:4927–4932. [PubMed: 31169]
25. Hulver MW, Berggren JR, Carper MJ, et al. Elevated stearyl-CoA desaturase-1 expression in skeletal muscle contributes to abnormal fatty acid partitioning in obese humans. *Cell Metab* 2005;2:251–261. [PubMed: 16213227]
26. Cohen P, Miyazaki M, Succi ND, et al. Role for stearyl-CoA desaturase-1 in leptin-mediated weight loss. *Science* 2002;297:240–243. [PubMed: 12114623]
27. Bowker-Kinley MM, Davis WI, Wu P, Harris RA, Popov KM. Evidence for existence of tissue-specific regulation of the mammalian pyruvate dehydrogenase complex. *Biochem J* 1983;329(Pt 1): 191–196. [PubMed: 9405293]
28. Wu P, Sato J, Zhao Y, Jaskiewicz J, Popov KM, Harris RA. Starvation and diabetes increase the amount of pyruvate dehydrogenase kinase isoenzyme 4 in rat heart. *Biochem J* 1998;329:197–201. [PubMed: 9405294]

29. Fuller SJ, Randle PJ. Reversible phosphorylation of pyruvate dehydrogenase in rat skeletal-muscle mitochondria. Effects of starvation and diabetes. *Biochem J* 1984;219:635–646. [PubMed: 6331393]
30. Holness MJ, Smith ND, Bulmer K, Hopkins T, Gibbons GF, Sugden MC. Evaluation of the role of peroxisome-proliferator-activated receptor alpha in the regulation of cardiac pyruvate dehydrogenase kinase 4 protein expression in response to starvation, high-fat feeding and hyperthyroidism. *Biochem J* 2002;364:687–694. [PubMed: 12049632]
31. Rosa G, Di Rocco P, Manco M, et al. Reduced PDK4 expression associates with increased insulin sensitivity in postobese patients. *Obes Res* 2003;11:176–182. [PubMed: 12582211]
32. Peterson LR, Waggoner AD, Schechtman KB, et al. Alterations in left ventricular structure and function in young healthy obese women: assessment by echocardiography and tissue Doppler imaging. *J Am Coll Cardiol* 2004;43:1399–1404. [PubMed: 15093874]
33. Bella JN, Palmieri V, Roman MJ, et al. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. *Circulation* 2002;105:1928–1933. [PubMed: 11997279]
34. Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. *J Am Coll Cardiol* 2003;41:1510–1518. [PubMed: 12742291]
35. Leichman JG, Aguilar D, King TM, Vlada A, Reyes M, Taegtmeier H. Association of plasma free fatty acids and left ventricular diastolic function in patients with clinically severe obesity. *Am J Clin Nutr* 2006;84:336–341. [PubMed: 16895880]
36. Finck BN, Han X, Courtois M, et al. A critical role for PPARalpha-mediated lipotoxicity in the pathogenesis of diabetic cardiomyopathy: modulation by dietary fat content. *Proc Natl Acad Sci U.S.A* 2003;100:1226–1231.
37. Young ME, Laws FA, Goodwin GW, Taegtmeier H. Reactivation of peroxisome proliferator-activated receptor alpha is associated with contractile dysfunction in hypertrophied rat heart. *J Biol Chem* 2001;276:44390–44395. [PubMed: 11574533]
38. Vikramadithyan RK, Hirata K, Yagyu H, et al. Peroxisome proliferator-activated receptor agonists modulate heart function in transgenic mice with lipotoxic cardiomyopathy. *J Pharmacol Exp Ther* 2005;313:586–593. [PubMed: 15671204]
39. Sambandam N, Morabito D, Wagg C, Finck BN, Kelly DP, Lopaschuk GD. Chronic activation of PPARalpha is detrimental to cardiac recovery after ischemia. *Am J Physiol Heart Circ Physiol* 2006;290:H87–H95. [PubMed: 16155108]

Figure 1.

Oil-red-O stain of muscle biopsies. Samples were obtained at baseline, 3 and 9 months after surgery. The slides are representative of four sections for each patient at each of the time points (baseline, 3 and 9 months). Baseline vs 3 months 4.2 AU (−2.4–10.9), $p<0.2$. Three months vs 9 months 8.7 AU (2.4–15.1), $p<0.009$. See text for further details.

Figure 2.

Transcript Levels of Metabolically Relevant Enzymes.

2A. mRNA levels of pyruvate dehydrogenase kinase 4 (PDK4). * $p < 0.0001$ time point vs baseline; ** $p < 0.001$, 3 months vs 9 months. 2B. mRNA levels of Stearoyl CoA Desaturase (SCD1). * $p < 0.0001$, time point vs baseline. 2C. mRNA levels of PPAR- α Regulated Genes. * $p < 0.05$, baseline vs 9 months; ** $p < 0.05$, 3 months vs 9 months.

PPAR- α -- Peroxisome Proliferator Activating Receptor- α ; CPT1, -- Carnitine Phosphotidyl Transferase 1; MCAD -- Medium Chain Acetyl-CoA Dehydrogenase. See text for further details.

Table 1

Baseline Characteristics

	All (n=43)	SPGB* (n=30)	LAGB* (n=13)
Age (years)	45 (1.6)	43 (2.0)	49 (2.5)
Female (%)	86%	83%	92%
Ethnic Data			
Caucasian	72%	67%	84%
African-American	21%	26%	8%
Hispanic	7%	7%	8%
Clinical Data			
Weight (kg)	142 (6.2)	140 (7.9)	147 (10.5)
BMI (kg/m ²)	51 (1.7)	50 (2.2)	53 (2.9)
Waist Circ. (cm)	136 (3.1)	134 (3.8)	139 (5.6)
Fat Mass (kg) [†]	40 (2.6)	40 (3.5)	39 (3.0)
Lean Mass (kg) [†]	35 (2.6)	36 (3.5)	30 (2.6)
Hemodynamic Data			
SBP (mmHg)	133 (2.9)	134 (3.7)	130 (4.0)
DBP (mm Hg)	74 (2.0)	74 (2.5)	74 (3.4)
HR (bpm)	78 (1.7)	79 (2.3)	78 (2.2)
Metabolic Data			
Glucose (mg/dL)	114 (9.6)	121 (13.4)	98 (6.0)
Insulin (μU/mL)	22 (2.5)	21 (2.6)	24 (5.7)
FFA (mmol/L)	0.84 (0.03)	0.83 (0.04)	0.84 (0.06)
Triglycerides (mg/L)	142 (20)	149 (28)	126 (14)
Leptin (ng/mL)	58 (4.3)	58 (5.3)	58 (7.3)
Co-Morbidities			
Insulin Resistance	95%	93%	100%
Diabetes	35%	36%	30%
Hypertension	53%	56%	46%
Dyslipidemia	26%	30%	15%
Medication Usage			
Antihypertensive Drugs	48%	53%	38%
Oral Hypoglycemic Drugs	23%	23%	23%
Lipid Lowering Drugs	23%	26%	15%

All values are the mean ± SE (standard error, given in parentheses).

Abbreviations: BMI – body mass index; Waist Circ. – waist circumference; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; FFA – plasma free fatty acids.

* Independent Samples t-tests for Small Pouch Gastric Bypass (SPGB) vs. Laparoscopic Adjustable Gastric Band (LAGB) showed no significant differences for all parameters.

[†] Body mass as measured by bioelectrical impedance analysis (see Methods).

Table 2
Clinical, Hemodynamic and Metabolic Changes after Surgery

	Months 0 to 3 Mean Difference*	Significance (p value) [†]	Months 3 to 9 Mean Difference*	Significance (p value) [†]
Clinical Data				
Weight (kg)	21.5 (18.1–25.0)	<0.0001	16.4 (12.8–20.1)	<0.0001
BMI (kg/m ²)	7.7 (6.7–8.9)	<0.0001	5.6 (4.4–6.8)	<0.0001
Waist Circ. (cm)	9.7 (–1.5–21.0)	NS	16.0 (5.6–26.3)	<0.005
Fat Mass (kg)	8.3 (6.2–10.5)	<0.0001	6.1 (4.8–7.5)	<0.0001
Lean Mass (kg)	2.2 (1.4–3.1)	<0.0001	1.0 (0.7–1.5)	<0.0001
Hemodynamics Data				
SBP (mmHg) [‡]	1.3 (–6.2–9.0)	NS	4.4 (–1.3–10.2)	NS
DBP (mmHg)	3.9 (–1.1–9.0)	NS	1.7 (–3.5–6.8)	NS
HR (bpm)	10.0 (5.5–14.5)	<0.0001	2.4 (–3.1–8.0)	NS
Metabolic Data				
Glucose (mg/dL)	19.1 (5.0–33.2)	<0.01	2.0 (–7.2–11.2)	NS
Insulin (μU/mL)	11.2 (5.6–16.8)	<0.0001	–0.5 (–3.2–3.1)	NS
HOMA-S (%)	–31.2 (–46.6 – –15.8)	<0.0001	–45.2 (–77.7 – –12.7)	<0.0001
FFA (mmol/L)	–0.03 (–0.15–0.09)	NS	0.2 (0.1–0.3)	<0.001
Triglycerides (mg/dL)	43.9 (5.9–93.7)	NS	18.7 (7.2–30.3)	<0.005
Leptin (mg/mL)	27.2 (20.8–33.5)	<0.0001	7.7 (2.7–12.7)	<0.005

All values are the mean differences (95% CI in parentheses) of 36 patients.

Abbreviations: CI 95% - Confidence Interval for difference; BMI – body mass index; Waist Circ. – waist circumference; SBP – systolic blood pressure; DBP – diastolic blood pressure; HOMA-S – Homeostatic Model of Assessment for insulin sensitivity; HR – Heart Rate; FFA – plasma free fatty acids; NS – not significant.

* Mean difference is a decrease in the outcome value unless indicated by a negative value.

[†] Significance for a difference at alpha <0.05.

[‡] There was a significant decrease in SBP from baseline to 9 months.

Table 3

Echocardiographic Parameters

	Baseline (SEM)	Months 0 to 3 Mean Difference*	Significance (p value) [†]	Months to 3 to 9 Mean Difference	Significance (p value) [†]
LV Size					
LVM/ht ^{2.7} (g/m ^{2.7})	49 (2.3)	3.0 (-0.1-6.1)	NS	6.3 (2.4-10.2)	<0.005
RWT (mm)	42 (0.9)	0.3 (-1.8-2.4)	NS	-0.2 (-2.1-1.7)	NS
Systolic Function					
LVEF (%)	63 (1.4)	1.2 (-2.2-4.6)	NS	-2.1 (-5.9-1.7)	NS
FS (%)	33 (1.1)	0.4 (-1.8-2.7)	NS	-1.3 (-4.4-1.9)	NS
Sms (cm/sec)	9.1 (0.2)	-0.1 (-0.8-0.6)	NS	0.4 (-0.3-1.1)	NS
Diastolic Function					
E (cm/sec)	79 (2.5)	-16.0 (-23.6--8.4)	<0.0001	-11.0 (-18.7--3.3)	<0.01
A (cm/sec)	75 (3.1)	-3.2 (-11.1-4.7)	NS	0.8 (-6.5-8.0)	NS
Dec time (msec)	222 (7.1)	23.8 (5.4-42.1)	<0.05	19.1 (-6.5-44.7)	NS
Ems	10 (0.3)	-0.4 (-1.3-0.6)	NS	0.4 (-0.4-1.1)	NS

Abbreviations: LV – left ventricle; LVEF – left ventricular ejection fraction; FS – fractional shortening; Sms – tissue Doppler systolic velocity; E – early mitral inflow velocity; Dec Time – deceleration time; Ems – tissue Doppler diastolic velocity; LVM/ht^{2.7} – left ventricular mass/height^{2.7}; RWT – relative wall thickness; NS – not significant.

* Mean Difference is a decrease in the outcome value unless indicated by a negative value.

[†] Significance for a difference at alpha <0.05.