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Elevated plasma endothelin-1 is associated with reduced weight loss post vertical sleeve gastrectomy

Haley N. Jenkins, B.S.^a, London J. Williams, M.S.^a, Adam Dungey, M.B.A.^b, Kenneth D. Vick, M.D.^b, Bernadette E. Grayson, Ph.D.^c, Joshua S. Speed, Ph.D.^{a,*}

^aDepartment of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi

^bDepartment of Surgery, University of Mississippi Medical Center, Jackson, Mississippi

^cDepartment of Neurobiology and Anatomical Sciences, University of Mississippi Medical Center, Jackson, Mississippi

Abstract

Background: Obesity and insulin resistance are positively correlated with plasma endothelin-1 (ET-1) levels; however, the mechanisms leading to increased ET-1 are not understood. Similarly, the full physiological complexity of ET-1 has yet to be described, especially in obesity. To date, one of the best treatments available for morbid obesity is bariatric surgery to quickly reduce body fat and the factors associated with obesity-related disease; however, the effects of vertical sleeve gastrectomy (SG) on plasma ET-1 have not been described.

Objectives: To determine if SG will reduce plasma ET-1 levels and to determine if plasma ET-1 concentration is associated with weight loss after surgery.

Setting: The studies were undertaken at a University Hospital.

Methods: This was tested by measuring plasma ET-1 levels from 12 obese patients before and after SG. All data were collected from clinic visits before SG, 6 weeks after SG, and 6 months after surgery.

Results: At 6 weeks after SG, plasma ET-1 levels increased by 24%; however, after 6 months, there was a 27% decrease compared with presurgery. Average weight loss in this cohort was $11.3\% \pm 2.4\%$ body weight after 6 weeks and $21.4\% \pm 5.7\%$ body weight after 6 months. Interestingly, we observed an inverse relationship between baseline plasma ET-1 and percent body weight loss ($R^2 = .49$, $P = .01$) and change in body mass index 6 months ($R^2 = .45$, $P = .011$) post bariatric surgery.

Conclusions: Our results indicate that SG reduces plasma ET-1 levels, a possible mechanism for improved metabolic risk in these patients. These data also suggest that ET-1 may serve as a predictor of weight loss after bariatric surgery.

*Correspondence: Joshua S. Speed, Ph.D., Department of Physiology and Biophysics, Division of Nephrology, Department of Medicine, University of Mississippi Medical Center, 2500 North State St., Guyton 558, Jackson, MS 39216. jspeed@umc.edu (J.S. Speed).

Disclosures

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Keywords

Bariatric surgery; ET-1; Inflammation

Obesity and metabolic syndrome are among the leading causes of morbidity and mortality in Western countries. Various treatments have been implemented to better the health outcomes of those affected. Among the most invasive, yet most effective, long-term approaches is bariatric surgery. Vertical sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are the 2 most common bariatric procedures in use [1]. Both procedures have similar mortality rates and exhibit no statistical differences between weight loss at 1 and 3 years postsurgery, with the percent estimated excess weight loss at 3 years being 62% for RYGB versus 68% for SG in one study [1,2]. An advantage of SG over RYGB is that vitamin B12 deficiencies are much less common in SG because the duodenum remains intact and functional; other nutritional deficiencies are similar between the 2 procedures and are ameliorated with supplementation [1]. Aside from weight loss, other noted benefits are an almost immediate improvement in insulin sensitivity [2,3], more rapid clearance of postprandial serum glucose [3], and a long-term reduction in serum lipids and leptin hormone [2]. Given the high degree of variability in excess weight loss after gastric bypass [4], more work is required to understand the factors involved in weight loss post SG and to understand the physiological changes seen in patients after surgery.

A major hormonal factor that is typically elevated in obese patients is endothelin-1 (ET-1). In several studies, a positive correlation has been shown between endothelin levels and obesity, yet a true mechanism for this rise in serum concentration and increased activity has yet to be established [5]. ET-1 is the most prevalent endothelin hormone synthesized mainly by endothelial cells; however, other tissues, including adipose cells, also produce detectable levels of ET-1. ET-1 binds to ET_A and ET_B receptors, which are both Gq protein-coupled receptors [6]. Activation of this subtype of G protein-coupled receptor results in activation of the phospholipase C/diacylglycerol pathway, leading to protein kinase C activation, increased intracellular calcium, and mitogen-activated protein kinase activation [6,7]. Both receptors have been identified on several tissue types, including vascular smooth muscle, cardiomyocytes, and adipocytes. The positive inotropic and mitogenic effects on vascular smooth muscle and cardiomyocytes are thought to contribute to hypertension, coronary and peripheral artery disease, and renal dysfunction in many obese patients [5–7]. Endothelin receptors have been identified and characterized on adipocytes as well, with ET_A stimulation leading to increased lipolysis and ET_B activation resulting in inhibition of the antilipolytic effects of insulin in visceral adipose tissue [8]. Interestingly, protein levels of ET_A are significantly elevated in the adipose tissue of obese versus lean patients. This is speculated to arise from a post-transcriptional regulatory mechanism [8]. The obese state is known to correlate with increased free fatty acid levels and increased basal lipolysis, possibly mediated by increased stimulation of ET_A receptors secondary to increased ET-1 levels [8,9]. This increase in free fatty acid levels leads to decreased clearance of glucose by skeletal muscles and altered hepatic lipogenesis, worsening or even leading to obesity-associated insulin resistance, serum lipid derangements, and atherosclerosis [8,10]. In addition, ET-1 has been shown to increase messenger RNA (mRNA) and protein levels of

several proinflammatory markers, including tumor necrosis factor α , interleukin (IL) 1 β , and IL-6, in both human and rat tissue types [11,12] Monocyte chemoattractant peptide-1 (MCP-1) is a potent inflammatory mediator and macrophage attractant that is also upregulated by ET-1 [13]. Recent studies have shown that MCP-1 results in vascular inflammation and subsequent atherosclerosis secondary to macrophage infiltration of the vessel wall and fibroblast proliferation [14,15]. ET-1 is therefore associated with a proinflammatory state combined with insulin resistance, hypertension, and elevated serum lipids, a health profile shared by many obese patients.

Given the current knowledge of ET-1 in obese patients and its effects on lipid metabolism, the hypothesis of the current study is that SG will reduce plasma ET-1 levels. We also hypothesized that plasma ET-1 may predict weight loss following SG. The major implications of this study are that ET-1 may either be a direct inhibitor of weight loss in obese patients or it may serve as a marker of weight loss success after bariatric surgery.

Materials and Methods

Cohort

Samples from 12 random patients that entered the bariatric weight loss program at our institution were used in this study. Patients consented to the use of blood samples and tissues for ancillary studies. Patients on blood pressure medications were excluded from this study. All samples were de-identified upon collection. The Institutional Review Board approved all procedures.

All patient data were collected at office visits. Clinic blood pressure was measured by cuff. Ideal body weight was calculated as 45.4 kg for the first 60 inches of height plus 2.3 kg per inch above 60 inches of height for women and 2.7 kg per inch above 60 inches for men. Excess body weight (EBW) was calculated as body weight – ideal body weight. Excess weight loss (EWL) was calculated as (presurgery EBW) – (EBW at given time point).

Enzyme-linked immunosorbent assay (ELISA)

Plasma ET-1 was measured using Human ET-1 Quanti-Glo ELISA (R&D Systems, Minneapolis, MN). Insulin was measured with the Human Insulin ELISA (Crystal Chem, Elk Grove Village, IL).

Gene expression

Total RNA was isolated using RNAqueous Micro Total RNA kit (Invitrogen, Carlsbad, CA). RNA was converted to complementary DNA with iScript Reverse Transcription kit (BioRad Laboratories, Hercules, CA). Next, gene expression was carried out by digital droplet polymerase chain reaction (PCR). The PCR reaction was set up using ddPCR probes Supermix, 1 μ L of TaqMan primer/probes, and complementary DNA from 50 ng of total RNA. The reaction mix was separated into nanodroplets using the automated droplet generator (BioRad). PCR was carried out for 40 cycles per the manufacturer's instructions using TaqMan primers to probe for MCP-1 (Assay ID Hs00234140_m1) mRNA. Droplets

were counted using the QX200 Droplet Reader, and data were analyzed and copy count calculated using QuantaSoft software.

Statistics

All presurgery and follow-up data were analyzed by 1-way repeated measures analysis of variance followed by Tukey's post hoc test. Linear regression was performed on ET-1 versus percent body weight loss and adipose tissue mRNA, and an F test was performed to determine whether the line is significantly different from 0. Run's test was performed to determine if the data differed from a straight line. Sample size of 10 was calculated to observe a 35% reduction in plasma ET-1 with 80% power. Statistical significance was set at $\alpha = .05$.

Results

Table 1 indicates baseline (presurgery), 6 weeks postsurgery, and 6 months post surgery values for body weight and plasma parameters. This cohort consisted of 1 man and 11 women. Average body weight before surgery was 128 ± 22 kg; 6 weeks after surgery it was 113 ± 22 kg ($11.3\% \pm 2.4\%$ body weight loss), and 6 months after surgery it was 101 ± 50 kg ($21.4\% \pm 5.7\%$ body weight loss) (Fig. 1A). Likewise, patients in this cohort saw an average cumulative reduction in body mass index (BMI) by 4.8 ± 1.6 kg/m² and 9.3 ± 3.1 kg/m² (6 weeks and 6 months after SG, respectively) (Fig. 1B). Excess body weight loss was $22\% \pm 7.2\%$ after 6 weeks and $41\% \pm 14.6\%$ after 6 months (Table 1). There was a high degree of variability in percent body weight loss 6 months after surgery (minimum = 10.1, maximum = 27.5, median = 23.0), suggesting that there may be multiple factors involved that regulate body weight loss after SG. In addition, there were significant decreases in waist circumference and hip circumference at both 6 weeks ($P < .05$ versus presurgery) and 6 months ($P < .05$ versus presurgery) after SG. Corresponding with the improvements observed in body weight was a significant 12 mm Hg decrease in systolic ($P < .05$ versus presurgery), but not diastolic, blood pressure. There were no significant differences at any time point in any of the measured plasma variables compared with before surgery levels (Table 1).

Plasma ET-1 and insulin were measured before SG, 6 weeks after, and 6 months after bariatric surgery. There was a significant 24% increase in plasma ET-1 at 6 weeks postsurgery ($P < .05$ versus presurgery) followed by a 27% decrease at 6 months postsurgery compared with baseline levels (Fig. 2A). Insulin levels declined by 78% from baseline at the 6-week postsurgery time point with no detectable difference between the 6-week and 6-month time points (Fig. 2B).

To determine if there is a relationship between plasma ET-1 and weight loss after SG, a linear regression was performed on presurgery ET-1 levels versus percent body weight loss and BMI reduction at 6 months after surgery. Presurgery plasma ET-1 levels correlated ($r^2 = .48$, $P < .05$) with percent body weight loss at 6 months (Fig. 3A) and the degree of BMI reduction at 6 months (Fig. 3B) post-SG surgery. Finally, it has been shown that adipose inflammation is associated with reduced weight loss after gastric bypass surgery with ET-1 acting as a potent inflammatory stimulator [16]. Therefore, we measured monocyte MCP-1

RNA message from visceral adipose to determine whether increased levels of ET-1 are associated with adipose inflammation (Fig. 4). Indeed, there was a correlation between presurgery plasma ET-1 and MCP-1 mRNA levels in adipose ($r^2 = .59$, $P < .05$), suggesting that ET-1 may affect weight loss after SG by promoting inflammation.

Discussion

The major conclusions from the current study are as follows: (1) after SG, there is an initial increase in plasma levels of ET-1 followed by a decline by 6 months after SG, (2) plasma ET-1 levels are associated with less body weight loss after SG, and (3) higher ET-1 levels are associated with increased inflammatory marker MCP-1 in adipose tissue. These results suggest that ET-1 may be inhibiting weight loss after SG through proinflammatory mechanisms or that plasma ET-1 may be a potential biomarker to predict weight loss after bariatric surgery.

Our results indicate a sharp rise in plasma ET-1 levels from baseline to 6 weeks post SG. One explanation for this increase in ET-1 is that it occurs in response to stress from SG surgery. Stress, whether acute or chronic, increases ET-1 production. For instance, air-jet stress and psychosocial stress in response to cage switching in rodents cause an acute increase in plasma ET-1 [17,18]. ET-1 is also thought to play a role in early life stress-induced changes in cardiovascular function in rodents [19]. In humans, acute stressors also increase ET-1 production [20]. Chronic stress-related adverse early childhood experiences also have been shown to increase ET-1 [21]. The increase in ET-1 does not appear to be related to a reduction in food intake, which occurs after bariatric surgery, because it has been demonstrated that food restriction in rodents reduces plasma ET-1 [22]. Therefore, short-term increases in ET-1 production may be an indicator of stress related to SG surgery or forced lifestyle modifications that occur after SG. More work to determine the mechanisms that cause an increase in plasma ET-1 at 6 weeks after SG are warranted.

Long term, we observed a reduction in plasma ET-1 at 6 months after patients underwent SG surgery. This is consistent with reported data from patients undergoing RYGB gastric bypass in which Ghanim et al. reported a 17% reduction in plasma ET-1 levels 6 months after gastric bypass [23]. These data suggest that ET-1 is elevated because of increased adiposity. More work will have to be done to determine the major signals for increased ET-1 in obese individuals, but one possibility is through hypoxia that occurs in the adipose of extremely obese individuals [24]. Hypoxia is a known stimulator of ET-1 production [25], and we would expect tissue oxygen levels to increase after dramatic weight loss. The major source of plasma ET-1 is endothelial cells [13]. Thus, we postulate that in obesity, adipose tissue hypoxia stimulates ET-1 production by vascular endothelial cells or adipocytes. After dramatic reductions in adiposity, as occurs after gastric bypass, ET-1 levels would fall, as seen in our patient cohort. This reduction in ET-1 may be a major factor involved in chronic reductions in blood pressure and adiposity and improved insulin sensitivity after gastric bypass surgery [26,27].

The finding that presurgery ET-1 levels are associated with less body weight loss after SG raises 2 major questions. First, is ET-1 inhibiting weight loss? Second, is plasma ET-1 a

byproduct of other processes that occur in response to SG? Several lines of evidence suggest that ET-1 may play a role in promoting adiposity. Endothelin has been shown to affect lipid metabolism in cultured adipocytes. Activation of the ET_A receptor stimulates lipolysis in both human- and rat-cultured adipocytes [8]. On the other hand, activation of the ET_B receptor blocks the antilipolytic effect of insulin [9]. Moreover, a single nucleotide polymorphism in the ET_B receptor is associated with reduced risk of obesity in 2 separate populations in Spain [28]. Taken together, these data suggest that higher plasma ET-1 may inhibit weight loss after bariatric surgery. More studies aimed at determining the physiological role of ET-1 and its contribution to obesity are required for definitive answers.

Adipose tissue inflammation has been shown to be associated with obesity. After bariatric surgery, inflammatory markers such as IL-6 and tumor necrosis factor α were acutely increased (6 weeks to 3 months postsurgery) followed by long-term reduction [29]. This is similar to the current observation in plasma ET-1, which was higher at the 6-week time point but reduced at 6 months postsurgery compared with baseline. Our data suggest that high levels of ET-1 may contribute to the proinflammatory state associated with obesity. ET-1 stimulation of the ET_A receptor is known to activate proinflammatory pathways in several cell tissues including blood vessels and renal epithelial cells [13,16]. In addition, it has been speculated that increased inflammation after surgery may contribute to complications associated with bariatric surgery. We will need to conduct a larger study to determine whether measuring inflammatory markers from adipose or if a simple plasma ET-1 measurement, or both, will aid in predicting weight loss after bariatric surgery.

Since the discovery of ET-1, several pharmacologic inhibitors of both ET_A and ET_B receptors have been developed. Currently, 3 ET-1 antagonists, bosentan, ambrisentan, and macitentan, are prescribed for the treatment of pulmonary hypertension with proven overall safety and efficacy. In addition, no study to our knowledge has examined the use of these medications to treat obesity-related diseases, apart from diabetic nephropathy. In animal models, ET-1 antagonism has been shown to improve insulin sensitivity in a model of sleep apnea and the obese Zucker fatty rat [30,31], although changes in adiposity have not been reported.

This study has some important limitations that could be addressed in future studies to further solidify the link between ET-1 and weight loss outcomes after bariatric surgery. One of these limitations is that our sample size was limited and consisted of mostly women. Sex differences in both response to SG and baseline ET-1 levels could either over-emphasize or underemphasize the results of this study. Furthermore, the small sample size may have confounded this issue. Another limitation is that data surrounding MCP-1 mRNA levels could only be analyzed before surgery. Unfortunately, the study design did not allow the sampling of visceral fat after surgery, limiting our ability to analyze changes in inflammatory markers during the course of weight loss. This would be an interesting point to analyze in future studies. Finally, plasma from follow-up (6-week and 6-month) was only available from 8 of the 12 patients. Therefore, we were not able to include these patients in the repeated measures analysis of plasma ET-1 and insulin. The effect sizes for these parameters were large enough to still perform statistical analyses.

In conclusion, our results suggest that ET-1 may play a role in weight loss after SG or may serve as a biomarker for weight loss. If the former is true, ET-1 antagonists may be a potential therapeutic to improve outcomes after SG. We believe that these drugs may be useful in promoting safe weight loss after bariatric surgery.

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References

- [1]. Kehagias I, Karamanakos SN, Argentou M, Kalfarentzos F. Randomized clinical trial of laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy for the management of patients with BMI < 50 kg/m². *Obes Surg* 2011;21(11):1650–6. [PubMed: 21818647]
- [2]. Woelnerhanssen B, Peterli R, Steinert RE, Peters T, Borbely Y, Beglinger C. Effects of postbariatric surgery weight loss on adipokines and metabolic parameters: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy—a prospective randomized trial. *Surg Obes Relat Dis* 2011;7(5):561–8. [PubMed: 21429816]
- [3]. Chambers AP, Smith EP, Begg DP, et al. Regulation of gastric emptying rate and its role in nutrient-induced GLP-1 secretion in rats after vertical sleeve gastrectomy. *Am J Physiol Endocrinol Metab* 2014;306(4):E424–32. [PubMed: 24368666]
- [4]. de Hollanda A, Jimenez A, Corcelles R, Lacy AM, Patrascioiu I, Vidal J. Gastrointestinal hormones and weight loss response after Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2014;10(5):814–9. [PubMed: 24969090]
- [5]. Weil BR, Westby CM, Van Guilder GP, Greiner JJ, Stauffer BL, DeSouza CA. Enhanced endothelin-1 system activity with overweight and obesity. *Am J Physiol Heart Circ Physiol* 2011;301(3):H689–95. [PubMed: 21666117]
- [6]. Sokolovsky M. Endothelin receptor subtypes and their role in trans-membrane signaling mechanisms. *Pharmacol Ther* 1995;68(3):435–71. [PubMed: 8788566]
- [7]. Bouallegue A, Daou GB, Srivastava AK. Endothelin-1-induced signaling pathways in vascular smooth muscle cells. *Curr Vasc Pharmacol* 2007;5(1):45–52. [PubMed: 17266612]
- [8]. Eriksson AK, van Harmelen V, Stenson BM, et al. Endothelin-1 stimulates human adipocyte lipolysis through the ET A receptor. *Int J Obes (Lond)* 2009;33(1):67–74. [PubMed: 18982011]
- [9]. van Harmelen V, Eriksson A, Astrom G, et al. Vascular peptide endothelin-1 links fat accumulation with alterations of visceral adipocyte lipolysis. *Diabetes* 2008;57(2):378–86. [PubMed: 18025413]
- [10]. Juan CC, Chang CL, Lai YH, Ho LT. Endothelin-1 induces lipolysis in 3T3-L1 adipocytes. *Am J Physiol Endocrinol Metab* 2005;288(6): E1146–52.
- [11]. Ruetten H, Thiemermann C. Endothelin-1 stimulates the biosynthesis of tumour necrosis factor in macrophages: ET-receptors, signal transduction and inhibition by dexamethasone. *J Physiol Pharmacol* 1997;48(4):675–88. [PubMed: 9444616]
- [12]. Browatzki M, Schmidt J, Kubler W, Kranzhofer R. Endothelin-1 induces interleukin-6 release via activation of the transcription factor NF-kappaB in human vascular smooth muscle cells. *Basic Res Cardiol* 2000;95(2):98–105. [PubMed: 10826501]
- [13]. Speed JS, Heimlich JB, Hyndman KA, et al. Endothelin-1 as a master regulator of whole-body Na⁺ homeostasis. *FASEB J* 2015;29(12):4937–44. [PubMed: 26268928]
- [14]. Nicoletti A, Michel JB. Cardiac fibrosis and inflammation: interaction with hemodynamic and hormonal factors. *Cardiovasc Res* 1999;41(3):532–43. [PubMed: 10435025]

- [15]. Schiffrin EL. Role of endothelin-1 in hypertension and vascular disease. *Am J Hypertens* 2001;14(6 Pt 2):83S–9S. [PubMed: 11411770]
- [16]. Speed JS, Pollock DM. Endothelin, kidney disease, and hypertension. *Hypertension* 2013;61(6):1142–5. [PubMed: 23608655]
- [17]. Fox BM, Becker BK, Loria AS, et al. Acute pressor response to psychosocial stress is dependent on endothelium-derived endothelin-1. *J Am Heart Assoc* 2018;7(4):e007863.
- [18]. Speed JS, D'Angelo G, Wach PA, Sullivan JC, Pollock JS, Pollock DM. High salt diet increases the pressor response to stress in female, but not male ETB-receptor-deficient rats. *Physiol Rep* 2015;3(3):e12326.
- [19]. Loria AS, D'Angelo G, Pollock DM, Pollock JS. Early life stress downregulates endothelin receptor expression and enhances acute stress-mediated blood pressure responses in adult rats. *Am J Physiol Regul Integr Comp Physiol* 2010;299(1):R185–91. [PubMed: 20410476]
- [20]. Treiber FA, Kapuku GK, Davis H, Pollock JS, Pollock DM. Plasma endothelin-1 release during acute stress: role of ethnicity and sex. *Psychosom Med* 2002;64(5):707–13. [PubMed: 12271101]
- [21]. Su S, Wang X, Kapuku GK, et al. Adverse childhood experiences are associated with detrimental hemodynamics and elevated circulating endothelin-1 in adolescents and young adults. *Hypertension* 2014;64(1):201–7. [PubMed: 24777980]
- [22]. Mehta RS, Hartle DK. Effects of total fasting or chronic food restriction on plasma endothelin levels in rats. *Physiol Behav* 1994;56(2):407–10. [PubMed: 7938257]
- [23]. Ghanim H, Monte S, Caruana J, Green K, Abuaysheh S, Dandona P. Decreases in neprilysin and vasoconstrictors and increases in vasodilators following bariatric surgery. *Diabetes Obes Metab* 2018;20(8):2029–33. [PubMed: 29652095]
- [24]. Lawler HM, Underkofler CM, Kern PA, Erickson C, Bredbeck B, Rasouli N. Adipose tissue hypoxia, inflammation, and fibrosis in obese insulin-sensitive and obese insulin-resistant subjects. *J Clin Endocrinol Metab* 2016;101(4):1422–8. [PubMed: 26871994]
- [25]. Heimlich JB, Speed JS, Bloom CJ, O'Connor PM, Pollock JS, Pollock DM. ET-1 increases reactive oxygen species following hypoxia and high-salt diet in the mouse glomerulus. *Acta Physiol (Oxf)* 2015;213(3):722–30. [PubMed: 25219340]
- [26]. McGavigan AK, Henseler ZM, Garibay D, et al. Vertical sleeve gastrectomy reduces blood pressure and hypothalamic endoplasmic reticulum stress in mice. *Dis Model Mech* 2017;10(3):235–43. [PubMed: 28093508]
- [27]. Lawson WJ, Shirey K, Spann RA, Zamarripa CA, Hosler JP, Grayson BE. Vertical sleeve gastrectomy improves indices of metabolic disease in rodent model of surgical menopause. *Menopause* 2017;24(4):426–36. [PubMed: 27801704]
- [28]. Martinez-Barquero V, de Marco G, Martinez-Hervas S, et al. Polymorphisms in endothelin system genes, arsenic levels and obesity risk. *PloS One* 2015;10(3):e0118471.
- [29]. Illan-Gomez F, Gonzalez-Ortega M, Orea-Soler I, et al. Obesity and inflammation: change in adiponectin, C-reactive protein, tumour necrosis factor-alpha and interleukin-6 after bariatric surgery. *Obes Surg* 2012;22(6):950–5. [PubMed: 22527592]
- [30]. Polak J, Punjabi NM, Shimoda LA. Blockade of endothelin-1 receptor type B ameliorates glucose intolerance and insulin resistance in a mouse model of obstructive sleep apnea. *Front Endocrinol (Lausanne)* 2018;9:280. [PubMed: 29896159]
- [31]. Berthiaume N, Carlson CJ, Rondinone CM, Zinker BA. Endothelin antagonism improves hepatic insulin sensitivity associated with insulin signaling in Zucker fatty rats. *Metabolism* 2005;54(11):1515–23. [PubMed: 16253642]

Fig. 1.
(A) Cumulative percent body weight loss and (B) cumulative change in body mass index (BMI) from baseline in patients at 6 weeks and 6 months after vertical sleeve gastrectomy. Data expressed as mean $\pm$ SD; n = 12.

Fig. 2.
 (A) Plasma endothelin-1 (ET-1) and (B) plasma insulin levels in patients before, 6 weeks after, and 6 months after vertical sleeve gastrectomy. * $P < .05$; $n = 8$.

Fig. 3. Prevertical sleeve gastrectomy plasma endothelin-1 versus (A) percent body weight loss, (B) change in body mass index (BMI), and (C) percent excess body weight loss 6 months after vertical sleeve gastrectomy. Solid line represents linear regression and statistics derived from F test; $n = 12$.

Fig. 4. Prevertical sleeve gastrectomy plasma endothelin-1 versus messenger RNA copy number of macrophage chemoattractant protein-1 (MCP-1) in visceral adipose. Solid line represents linear regression and statistics derived from F test; $n = 12$.

Table 1

Clinical characteristics of subjects before gastric sleeve surgery, 6 weeks after, and 6 months after surgery

Mean value of various health parameters			
	Presurgery	6-week follow-up	6-month follow-up
Body weight, kg	128 ± 22	113 ± 22 *	101 ± 23 * [†]
Excess body weight loss, %		22 ± 7.2	41 ± 14.6
BMI, kg/m ²	46.4 ± 7	41.6 ± 8 *	37.1 ± 8 * [†]
Hip circumference, cm	130 ± 20	119 ± 20 *	43 ± 19 * [†]
Waist circumference, cm	142 ± 10	132 ± 13 *	119 ± 13 * [†]
Systolic pressure, mm Hg	138 ± 19	127 ± 11	126 ± 11 *
Diastolic pressure, mm Hg	79 ± 11	80 ± 9	76 ± 7
Pulse rate, beats/min	81 ± 18	80 ± 15	74 ± 11
Alanine aminotransferase, IU/L	28 ± 11		20 ± 11
Aspartate aminotransferase, IU/L	21 ± 7		22 ± 10
Bilirubin, mg/dL	.5 ± .2		.5 ± .3
Creatinine, mg/dL	.8 ± .02		.7 ± .1
Glucose, mg/dL	101 ± 19		97 ± 13
White blood cells, 10 ⁹ /L	8 ± 3		7 ± 2
Hematocrit, %	41 ± 3		41 ± 3
Triglycerides, mg/dL	122 ± 54		124 ± 72

BMI = body mass index.

* $P < .05$ versus presurgery.[†] $P < .05$ versus 6-week follow-up.