NEW METHODS

Gastric mucosal devitalization is safe and effective in reducing body weight and visceral adiposity in a porcine model

Vivek Kumbhari, MD,[1] Stefanie Lehmann, PhD, MPH,[2] Nadine Schlichting, PhD,[2] Marco Heinrich, PhD,[2] Yvonne Kullnick, MSc,[2] Ulf Retschlag, MSc,[2] Markus Enderle, MD,[3] Arne Dietrich, MD,[4] Mouen A. Khashab, MD,[1] Anthony N. Kalloo, MD,[1] Andreas Oberbach, MD, PhD, DrPH, MPH[1,2]

Baltimore, Maryland, USA; Leipzig, Tübingen, Germany

Background and Aims: The early improvement in metabolic profile after sleeve gastrectomy (SG) indicates that the significant benefits of metabolic surgery are gastric in origin. We have previously demonstrated that devitalization of the gastric mucosa (without a reduction in gastric volume) in metabolically disturbed obese rats results in an improvement of obesity and its associated comorbidities. The aims of this study were to assess the technical feasibility, efficacy, and safety of gastric mucosal devitalization (GMD) in a large animal (porcine) model.

Methods: A 3-arm (GMD versus SG versus sham [SH]) prospective randomized controlled trial with an 8-week follow-up period was performed. The primary endpoint was relative weight loss. Secondary endpoints were absolute body weight, abdominal visceral adiposity, abdominal subcutaneous adiposity, organ lipid content, and serum ghrelin level.

Results: GMD resulted in a significant relative weight loss of 36% over SH at 8 weeks ($P < .05$). There was no significant difference in relative weight loss between GMD and SG at 4 weeks; however, SG resulted in a 29% superior relative weight loss at 8 weeks ($P < .05$). With regard to visceral adiposity, there was a significant benefit of GMD over SH at 8 weeks. Despite differences in relative weight loss, there was no significant difference in visceral adiposity between SG and GMD at 8 weeks. Significant improvements in GMD over SH were noted with regard to skeletal and heart muscle lipid content. GMD pigs at 8 weeks demonstrated regeneration of the gastric mucosa without ulceration or significant scarring. Despite mucosal regeneration, the abundance of serum ghrelin was significantly lower in the GMD cohort compared with the SG and SH cohorts.

Conclusions: GMD was technically feasible and resulted in relative weight loss and an improvement in visceral adiposity. The benefits noted were out of proportion to what would be expected with weight loss alone.

INTRODUCTION

The worldwide prevalence of overweight and obesity in children, adolescents, and adults has reached pandemic proportions.[1] Metabolic surgery, such as Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG), is the most effective and durable weight loss and metabolic therapy.[2,3] Metabolic surgery alters the

Abbreviations: APC, argon plasma coagulation; CI, confidence interval; GMD, gastric mucosal devitalization; RYGB, roux-en-Y gastric bypass; SAT, subcutaneous adipose tissue; SG, sleeve gastrectomy; SH, sham; VAT, visceral adipose tissue.

DISCLOSURE: *Dr Kumbhari is a consultant for Boston Scientific, Apollo Endosurgery, ReShape Life Sciences, and Medtronic. Dr Enderle is the vice president of research and an employee of Erbe GmbH Germany. Dr Khashab is a consultant for Boston Scientific and Olympus America. Dr Kalloo is a founding Member, equity Holder, and consultant for Apollo Endosurgery. All other authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
https://doi.org/10.1016/j.gie.2018.02.022

Received November 28, 2017. Accepted February 11, 2018.

Current affiliations: Department of Medicine and Division of Gastroenterology and Hepatology, The Johns Hopkins Medical Institutions, Baltimore, Maryland, USA (1); Department of Diagnostics and New Technologies, Fraunhofer Institute for Cell Therapy and Immunology, Leipzig, Germany (2); Research Department, Erbe GmbH, Tübingen, Germany (3); Integrated Research and Treatment Centre Obesity Diseases, Leipzig University, Leipzig, Germany (4).

Reprint requests: Andreas Oberbach, MD, PhD, DrPH, MPH, CardiOMICs Experimental Surgery Group, Department of Diagnostics and New Technologies, Fraunhofer Institute for Cell Therapy and Immunology, Perlickstraße 1, 04103 Leipzig, Germany.

If you would like to chat with an author of this article, you may contact Dr Oberbach at andreas.oberbach@medizin.uni-leipzig.de.

physiologic regulation of body fat mass, demonstrating the critical role of the GI tract in the regulation of metabolic function.[4] The mechanisms of action are neither mechanical restriction nor macronutrient malabsorption and remain poorly understood.[5,6] Furthermore, there appears to be weight-dependent and weight-independent mechanisms of action.[7,8] Unfortunately, because of its invasiveness and irreversibility, metabolic surgery is severely underused.[9] The development of minimally invasive flexible endoscopic methods to mimic the effect of metabolic surgery provides an opportunity to fulfill the large unmet need.[10]

The primary site of regulation of glucose and lipid metabolism remains ambiguous. Human and rodent studies of RYGB allude to the importance of bypassing the duodenum.[11] Conversely, SG does not alter nutrient flow across the duodenum yet induces similar metabolic effects to RYGB, signifying that the stomach may be a critical regulator of glucose and lipid homeostasis.[2,5] Some have proposed that the accelerated nutrient transit through the GI tract seen with SG causes more undigested nutrients to reach the distal ileum resulting in postprandial increase in glucagon-like Peptide 1; however, mechanistic evidence for this is lacking.[12] A common element to both surgeries is the exclusion or resection of the gastric mucosa, an often-underappreciated neuroendocrine organ.[13-15]

Our group has been investigating the hypothesis that excision of the gastric mucosa is a key contributor to the improvement in obesity-related comorbidities perceived after SG.[16,17] We previously demonstrated, in an obese rat model, that the gastric mucosa is an independent regulator of glucose and lipid metabolism.[18] In that study, gastric mucosal devitalization (GMD) reduced body weight and visceral adiposity, improved serum lipid and glucose profiles, and reduced liver lipid content.[18] Considering those promising results, our goal was to translate our technique of GMD into a large animal model to assess its technical feasibility, efficacy, and safety. The porcine model was chosen because it has similar GI anatomy to humans and allows utilization of commercially available endoscopic equipment. Furthermore, porcine models are a familiar platform to investigate endoscopic bariatric therapies before pilot clinical studies.[19,20]

METHODS

Study design

We performed a 3-arm prospective randomized controlled trial with an 8-week follow-up period. A total of 23 healthy litter-matched male German saddleback pigs aged 11 weeks and weighing 30 to 35 kg were obtained from a commercial, closed-herd pig vendor (Lehr- und Versuchsgut Oberholz, Großpösna, Saxony, Germany). This breed of domestic pig was chosen because of their relatively high body fat mass. Two pigs underwent GMD; one was killed immediately after the procedure and the other at 4 weeks to assess gastric histology and perform immunofluorescence for ghrelin (Fig. 1). For the purposes of the trial, 21 pigs were randomized equally into 3 groups: GMD (n = 7), SG (n = 7), and sham (SH) (n = 7) (Fig. 1).

The primary outcome was a reduction in the proportional change in body weight. Prespecified secondary outcomes included absolute body weight, abdominal visceral adiposity, abdominal subcutaneous adiposity, organ lipid content, and serum ghrelin level.

The study conditions of the animals are described in detail in the Supplementary Methods (available online at www.giejournal.org). All animal procedures followed the international guidelines for the prevention of animal cruelty and were approved by the Landesdirektion Leipzig, the local authority for animal care.[21,22]

Interventions

Gastric mucosal devitalization. Similar to our previously published study in an obese rat model, we elected to use argon plasma coagulation (APC) to devitalize the gastric mucosa.[18] To allow for selective ablation of the gastric mucosa and to minimize a tissue effect in deeper gastric wall layers, a submucosal fluid cushion (0.9% isotonic saline solution/1% methylene blue) was created before APC.[23] Based on a literature search[23,24] together with the results of a detailed pilot porcine dose-finding study,[25] we calculated that pulsed APC effect 2 at 120 W with an argon flow rate of 1 L/minute by non-contact technique (VIO 300D/APC2-HF-generator; Erbe Elektromedizin, Tübingen, Germany) of the entire gastric body and fundus appeared technically feasible, effective, and safe. The dose-finding study allowed the GMD operator to gain proficiency in the technique such that a homogeneous ablation could be performed.

Pigs were placed in the supine position and a 2-channel therapeutic gastroscope was inserted (GIF2T160; Olympus Europe, Hamburg, Germany). The 2-channel scope allowed for adequate suctioning of intraluminal gasses while simultaneously applying APC. Before application of APC, a 510K cleared (K143306) needleless injection system (flexible Erbe waterjet probe, outer diameter 1.3 mm, length 1.2 m connected with ERBEJET 2; Erbe Elektromedizin, Tübingen, Germany) was used to create the submucosal fluid cushion by placing the needleless catheter at an angle of 45° to the mucosa and injecting the fluid at 60 bar for 5 seconds (Fig. 2A). Subsequently, a 510K cleared (K060163) catheter with an outer diameter of 3.6 mm, length 220 mm and a ceramic heat-resistant tip was connected to the Erbe VIO 300 D and was used to deliver APC (Erbe Elektromedizin, Tübingen, Germany) (Fig. 2B and C). APC was delivered homogeneously until the tissue was