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Original article

Effect of Roux-en-Y gastric bypass and diet-induced weight loss on diabetic kidney disease in the Zucker diabetic fatty rat

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Abstract

Background: Reductions in urinary protein excretion after Roux-en-Y gastric bypass (RYGB) surgery in patients with diabetic kidney disease have been reported in multiple studies.
Objectives: To determine the weight loss dependence of the effect of RYGB on urinary protein excretion by comparing renal outcomes in Zucker diabetic fatty rats undergoing either gastric bypass surgery or a sham operation with or without weight matching.
Setting: University laboratories.
Methods: Zucker diabetic fatty rats underwent surgery at 18 weeks of age. A subgroup of sham operated rats were weight matched to RYGB operated rats by restricting food intake. Urinary protein excretion was assessed at baseline and at postoperative weeks 4 and 12. Renal histology and macrophage-associated inflammation were assessed at postoperative week 12.
Results: Progressive urinary protein excretion was attenuated by both RYGB and diet-induced weight loss, albeit to a lesser extent by the latter. Both weight loss interventions produced equivalent reductions in glomerulomegaly, glomerulosclerosis, and evidence of renal macrophage infiltration.
Conclusion: Weight loss per se improves renal structure and attenuates renal inflammatory responses in an experimental animal model of diabetic kidney disease. Better glycemic control post-RYGB may in part explain the greater reductions in urinary protein excretion after gastric bypass surgery. (Surg Obes Relat Dis 2016;▮:00–00.)

Keywords: RYGB; Gastric bypass; Bariatric; Diabetic kidney disease; Weight loss; Renal inflammation; Urinary protein excretion; Zucker diabetic fatty rat

In the classical model of diabetic kidney disease (DKD) progression, incipient nephropathy characterized by progressive microalbuminuria and initial hyperfiltration gives way over a 10–20 year period to overt urinary protein excretion and accelerated decline of renal function as assessed by glomerular filtration rate [1]. The progression of disease is associated with renal inflammation and is driven by hypertension and hyperglycemia. Despite increased use of multimodal therapeutic regimens targeted

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at pharmacologic remediation of these vascular risk factors, DKD still often follows an inexorable course toward end-stage renal disease requiring dialysis or transplantation [2].

Roux-en-Y gastric bypass (RYGB) is now increasingly considered as an option for treatment of type 2 diabetes, in combination with medical therapy, in those patients qnot meeting treatment targets or with diabetic complications [3,4]. Surgery is more effective than medical therapy alone at inducing weight loss and improving glycemic control [4]. RYGB also rapidly reduces urinary protein excretion in patients with type 2 diabetes [5,6]. This is coincident with evidence of remediation of renal inflammation as measured by markers of proinflammatory activity such as urinary monocyte-chemoattractant protein-1 (MCP-1) [5,6].

Improvements in urinary protein excretion and renal inflammation correlate with the degree of postoperative weight [5,6]. Weight loss per se may therefore drive remediation of DKD. Although a direct causal role for reductions in adiposity seems plausible, it remains speculative in the absence of comparative studies examining the relative effect of matched surgical and nonsurgical weight loss. The relative importance of the weight loss component of RYGB is challenging to test in clinical studies, as it is difficult to produce weight loss equivalent to RYGB using a nonsurgical treatment in humans [7].

Using the Zucker diabetic fatty (ZDF) rat model of DKD [8], we recently reported that a 12-week dietary restriction regimen tailored to deliver RYGB-equivalent weight loss reduced total weight in ZDF rats by approximately 20% relative to ad libitum fed rats [9]. We used this model in the present study to compare the relative effect of both RYGB and equivalent weight loss achieved through caloric restriction on DKD in the ZDF rat (Fig. 1).

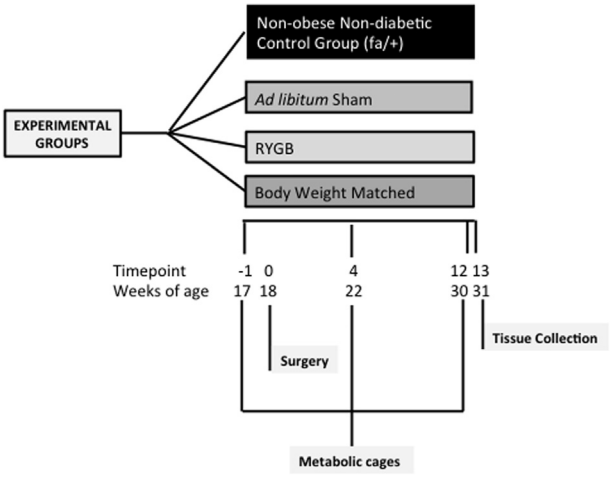

Fig. 1. Experimental design. Homozygous Zucker diabetic fatty rats (ZDF-fa/fa) were allocated to Roux-en-Y gastric bypass (RYGB) (n = 15) or sham surgery comprising intestinal transection and reanastomosis (n = 14). In the sham surgery group, rats were either allocated to dietary restriction to induce weight loss equivalent to the RYGB group (weight matched, n = 8) or allowed ad libitum access to food (ad libitum sham, n = 6). Heterozygous Fa/+ animals served as nonobese and nondiabetic controls (n = 5). Serial urine samples were collected 4 and 12 weeks after surgery before humane euthanasia at the start of the 13th postoperative week.

Methods

Animals

ZDF rats are homozygous null mutant for the long isoform of the leptin receptor and develop hyperphagia, progressive obesity, diabetes, and renal microvascular complications [8]. Ten-week-old male ZDF rats (fa/fa) (n = 29) (Charles River Laboratories, France) and heterozygote nonobese, nondiabetic healthy control 10-week-old ZDF rats (fa/+) (n = 5) were group housed in a temperature- and humidity-controlled room with a 12-hour light/dark cycle (lights on from 0200 to 1400). Rats had free access to tap water and Purina Lab diet 5008 (Purina Mills, St. Louis, MO) throughout the protocol, except where otherwise noted. All experimental procedures were approved by the Veterinary Office of the Canton Zurich, Switzerland, and complied with national laws and current ethical guidelines.

The surgical procedures have been previously described [9]. Briefly, in RYGB the jejunum was dissected 60 mm distal from the ligament that attaches the jejunum to the colon transversum. A 7-mm side-to-side small bowel anastomosis was performed between the biliopancreatic limb and the lower jejunum 250–300 mm proximal to the cecum to create the common channel. After exposure and careful mobilization of the gastroesophageal junction, the stomach was transected just below the gastroesophageal junction to create a small gastric pouch about 2% of the original stomach size. The stomach remnant was subsequently closed, and the small gastric pouch was anastomosed end-to-side to the alimentary limb, which was ~500 mm in length.

For the sham surgery, the entire gastrointestinal tract was mobilized, and a 10-mm gastrostomy was performed on the anterior wall of the stomach with subsequent closure in 2 layers. A 7-mm jejunotomy was then performed and subsequently closed.

Glycaemic control monitoring

Blood glucose was measured in all rats 4 times weekly with a point-of-care glucometer (Breeze2; Bayer, Zurich, Switzerland). Using these values, a glucose area under the curve was calculated to evaluate glycemic exposure over the course of the study. Urine was collected over 24 hours in a metabolic cage during the week before surgery (−1 week) and at 4 and 12 weeks postoperatively, respectively. Urine was stored at −20°C.