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ROUX-EN-Y GASTRIC BYPASS IS MORE EFFECTIVE THAN SLEEVE GASTRECTOMY AGAINST HEPATIC STEATOSIS, IN WESTERN-DIET-OBESE RATS

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ABSTRACT

Purpose: Herein, we compared the effects of Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) on fat liver deposition and expression of hepatic enzymes involved in hepatic *de novo* (DN) lipogenesis and β-oxidation, in western diet (WD)-obese rats.
Methods: At two months after WD consumption, the rats were divided into three groups: WD sham operation (WD-Sham), WD-RYGB and WD-SG. Three months after procedures, hepatic steatosis and lipid metabolism were verified.
Results: Both bariatric operations enhanced glucose tolerance and decreased triglycerides (TG) serum levels. However, total serum cholesterol (CHOL) as well as, hepatic TG and CHOL contents were reduced only in liver of WD-RYGB rats. Hepatic steatosis was corrected in 83% of the WD-RYGB rats, whereas microvesicular steatosis occurred in 100% of the WD-SG livers. Reduction in fatty acid synthase protein content was observed in both WD-RYGB and WD-SG rats. Nevertheless, reduced hepatic acetyl-CoA carboxylase (ACC) and enhanced phospho-ACC/ACC and carnitine palmitoyltransferase protein levels were observed only in WD-RYGB rats.
Conclusions: NAFLD is more marked reduced in obese rats that underwent RYGB than SG procedures. This RYGB effect may be associated with decreased hepatic DN lipogenesis, associated with enhancement in β-oxidation, which reduced TG content in the liver of WD rats.

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INTRODUCTION

The non-alcoholic fatty liver (NAFLD) is characterized by lipids accumulation in the liver and may progress to non-alcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma (Cohen*et al*., 2011). A prospective study reported that 84% of the obese patients present NAFLD before bariatric operations (Morita *et al*., 2015). Bariatric procedures improve the histopathological characteristics and enzymes levels associated with NAFLD and decrease the risk of liver failure (Mummadi *et al*., 2008). Currently, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most frequent bariatric operation performed worldwide (Neylan *et al*., 2016). Whereas RYGB is a mixed (restrictive and malabsorptive) procedure with a stomach reduction and a deviation of part of the small intestine (Rubino *et al*., 2010), SG is a restrictive operation that removes the fundus and greater curvature portion of stomach (Deitel *et al*., 2007). RYGB and SG, performed in obese patients, consist in an efficient strategy to improve glycemic control or even remission of type 2 diabetes (T2D) (Rubino *et al*., 2010; Schauer *et al*., 2012; Courcoulas *et al*., 2014). Also, both operations improve lipids metabolism

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and NAFLD (Mummadi *et al*., 2008; Afifi & Abbas, 2011; Dixon, 2014; He *et al*., 2015; Mosinski *et al*., 2016; Alli *et al*., 2017). However, few studies directly compare the efficacy of RYGB and SG operations upon liver morphological characteristics and lipid metabolism in NAFLD (Froylich *et al*., 2016; Maffazioli *et al*., 2016). This difficulty is due, in part, to the limitations of tests with tissues from obese humans that underwent bariatric procedures. Thus, experimental models of obese rodents could be a good strategy to compare the effects of these two bariatric operations in NAFLD. Herein, we have used here rats maintained on a diet more closely related to the variety of palatable and caloric foods, prevalent in western society, and associated with the current obesity epidemic, named western diet (WD). Rodents treated with WD presented higher adiposity, dyslipidemia, glucose intolerance, insulin resistance and liver steatosis (Sampey *et al*., 2011). Herein, using obese rats by WD, we compared the effects of RYGB and SG operations on hepatic steatosis and measured the expression of enzymes involved in hepatic *de novo* (DN) lipogenesis and β-oxidation.

METHODS

Experimental groups: All experiments protocols were approved by the UNIOESTE's Committee on Ethics in Animal Experimentation (06/09/2015). Two-month-old male *Wistar* rats (n=36) were housed in standard cages (2 rats per cage) and maintained on a 12h light/dark cycle and controlled temperature. For obesity induction, the rats received the western diet (WD), whose composition was previously reported (Balbo *et al.*, 2016). At two months after WD consumption, the rats were randomly distributed into three groups: WD sham operation (WD-Sham, n = 17), WD Roux-en-Y gastric bypass (WD-RYGB, n = 10) and WD sleeve gastrectomy (WD-SG, n = 11). The sham and bariatric procedures are described below. After operation, the rats continue to receive the WD during a period of 3 months when all rat groups were euthanized.

RYGB, SG and Sham operations: Five days before the operations all groups received a high-energy liquid diet *ad libitum*. At the day of the operation, the rats were fasted for 12-16 h and were anesthetized with 1% isoflurane (Isoforine®, SP, BRA) and air/oxygen. After induction of anesthesia, the rats received intramuscularly a single dose of 50 mg/kg ceftriaxone (Eurofarma, SP, BRA) and a subcutaneous injection of 50 mg/kg dipyrone (Teuto, GO, BRA) and 20 mL of 0.9% saline solution.

RYGB operation: in this procedure, the abdomen was opened through an incision in the epigastric middle line. The first step was to prepare the cardia region of the stomach and make the section with minimal bleeding. The left gastric vessels and their first branches were connected or cauterized and after separated from the esophagus. The stomach was cut and a gastric pouch, approximately 5% of the original stomach size, was created. The excluded stomach was sutured with 7-0 polypropylene yarn with continuous stitch. Then, jejunum was transected 10 cm distal to the ligament of Treitz. The distal limb of jejunum was anastomosed to the small gastric pouch with a side-to-side gastrojejunostomy. The proximal limb of jejunum was reconnected downward at a distance of 15 cm from the gastrojejunostomy with a side-to-side jejunojejunostomy. At the end of RYGB procedure, three handles were formed: the biliopancreatic, the feed and the joint handle.

SG operation: after the incision in the epigastric middle line of the rats, a gastric section was made with scissors from the angle of His to 3 mm proximal duodenum with an approximated 80% resection of the stomach, including complete resection of the fundus. It was performed 3 to 4 stitches separated in the transected stomach using polypropylene 7-0. A continuous suture was performed in two plans with polypropylene yarn 7-0 in the remaining stomach to anchor the separate stitch made previously. The residual stomach corresponded to a volume of 20% of the total stomach volume.

Sham operation: after an incision in the epigastric middle line of the rats, the liver was careful displaced, and the stomach and the abdominal cavity were exposed, and the intestinal loops were massaged with the aid of a sterile scalpel handle. In all operations, the laparotomy was closed with a continuous suture by plans, including peritoneum and aponeurotic plans with polypropylene yarn 4-0. The skin was sutured with continuous suture using polypropylene yarn 4-0. At the post operation period, the rats receive during 3 consecutive days a daily subcutaneous injection of 20 mL of 0.9% saline solution to prevent dehydration. Dipyrone 50 mg/kg was administered again at the end of the operation. During the seven days after operation, all rat groups received a high-energy liquid diet *ad libitum*. After this period, all rats received solid WD per 3 months.

Intraperitoneal Glucose Tolerance Test (ipGTT): For the glucose tolerance test, at 2 months after surgeries, all rats were 8h-fasted, and blood glucose was measured with a handheld glucometer (Abbott®, Optium Xceed, Alameda, CA). Then, the rats received an intraperitoneal administration of 2g/kg glucose and additional blood samples were recorded at 15, 30, 60, 120 and 180 min.

Obesity parameters and serum biochemical analysis: At 3 months after the operations, glycemia was recorded after 8 h of fasting in all rats. Subsequently, the body weight (BW) and the nasoanal length were measured to obtain the Lee index [BW $(g)^{1/3}$/ nasoanal length (cm) x 1000]. The rats were euthanized by decapitation and total blood was collected ant the serum was used to measure total cholesterol (CHOL) and triglycerides (TG) using colorimetric commercial kits (LaborClin®, Bioliquid, BRA). In addition, the retroperitoneal and perigonadal fat pads were removed and weighed.

TG and CHOL Content in the Liver: Fragments of the liver were collected, and lipids were extracted by the Folch's method. The extract was evaporated and diluted in isopropanol for determination of the TG and CHOL, as described above.

Liver Histology: Liver samples were fixed in 10% formalin for 24 h, dehydrated in alcohol, permeabilized with xylene and then embedded in Paraplast. Sections of 5 µm in thickness were stained with hematoxylin and eosin. Liver histology was examined and graded according to the magnitude of steatosis, based on Brunt's (Brunt *et al.*, 1999) classification with modifications for rodents. In addition, Mallory's trichrome staining was performed to identify collagen fibers.

Western blotting: A fragment of the liver from all rat groups was solubilized in extraction buffer (containing: 100 mM tris pH 7.5, 10 mM sodium pyrophosphate, 100 mM sodium

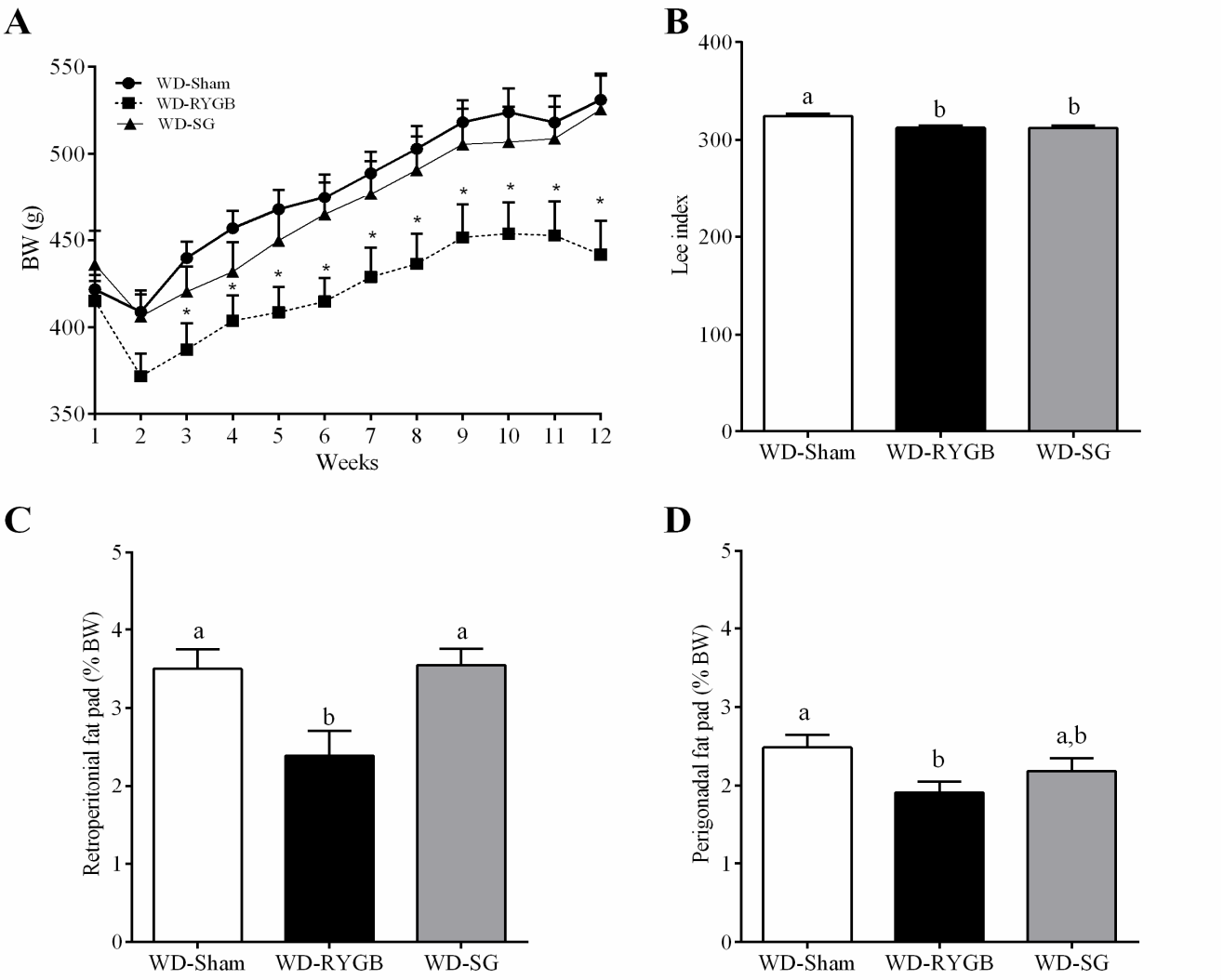

Figure 1. Body weight (BW) evolution (A) during 3 months after the Sham, RGYB and SG operations in WD rats. *Indicate a significant difference between WD-RGYB and WD-Sham rats (P < 0.05). Media ± SEM of the Lee index (B), and the weight of the retroperitoneal (C) and perigonadal (D) fat pads in WD-Sham (n=15), WD-RGYB (n= 10) and WD-SG (n=13) rats after 3 months of the operations.Different lettersoverthebarsrepresentsignificant differences(one-wayANOVAfollowedbytheTukey post-test, P < 0.05)

fluoride, 10 mM EDTA, 10 mM sodium vanadate, 2 mM phenylmethylsulfonyl fluoride and 1% Triton-X 100) at 4ºC using a mechanical homogenizer. Then, the samples were centrifuged at 12,600 g at 4ºC for 30 min to remove insoluble material. The protein concentration in the supernatants was assayed using the Bradford dye method, using BSA as a standard curve. For SDS gel electrophoresis the samples were homogenized with loading buffer containing beta-mercaptoethanol. After heating at 100 ºC for 5 min, the proteins were separated by electrophoresis (100 µg protein/lane in 6.5 or 10% gels) and transferred to nitrocellulose membranes. The membranes were incubated with specific primary antibodies against: phospho (p) ^{Ser79}-acetyl-CoA carboxylase and acetyl-CoA carboxylase (pACC and ACC, Cell Signaling Technology, MA, USA); fatty acid synthase and carnitine palmitoyltransferase 1a (FASN and CPT-1a, Santa Cruz Biotechnology, CA, USA) and microsomal triglyceride transfer protein and α-tubulin (MTTP and α-tubulin, Sigma-Aldrich, MO, USA). Visualization of specific protein bands was carried out by incubating the membranes with secondary antibodies (Zymed Laboratories, CA, USA) and chemiluminescent reagents followed by registration with L-Pix Chemi Express System (Loccus Biotechnology, SP, BRA). The band intensities were quantified with the software LabImage 1D (Loccus Biotechnology, SP, BRA).

Statistical Analysis: The data were expressed as means ± SEM and were analyzed by one-way analysis of variance (ANOVA) followed by the Tukey post-test ($P < 0.05$) and were performed using GraphPad Prism version 5.00 software (GraphPad Inc, CA, USA).

RESULTS

General rat parameters

Figure 1A shows that after operation, body weight (BW) increase in all groups. However, WD-RYGB rats displayed a reduction in body weight at 3 weeks until the end of the experimental period, compared with WD-Sham and WD-SG rats ($P < 0.05$). Reinforcing this result, the total BW gain, measured during 3 months after the operations, was approximately 66% lower in WD-RYGB rats (38 ± 13g) than that was observed for WD-Sham (118 ± 15 g; $P < 0.01$). However, the total BW gain in WD-SG rats did not differ (79 ± 12 g) from WD-Sham. At 3 months after operations, WD-RYGB and WD-SG rats displayed a reduction of approximately 4% in the Lee index, compared with WD-Sham rats (Fig. 1B). Whereas, the retroperitoneal and perigonadal fat stores were significantly reduced only in RYGB rats (Fig. 1C and 1D).

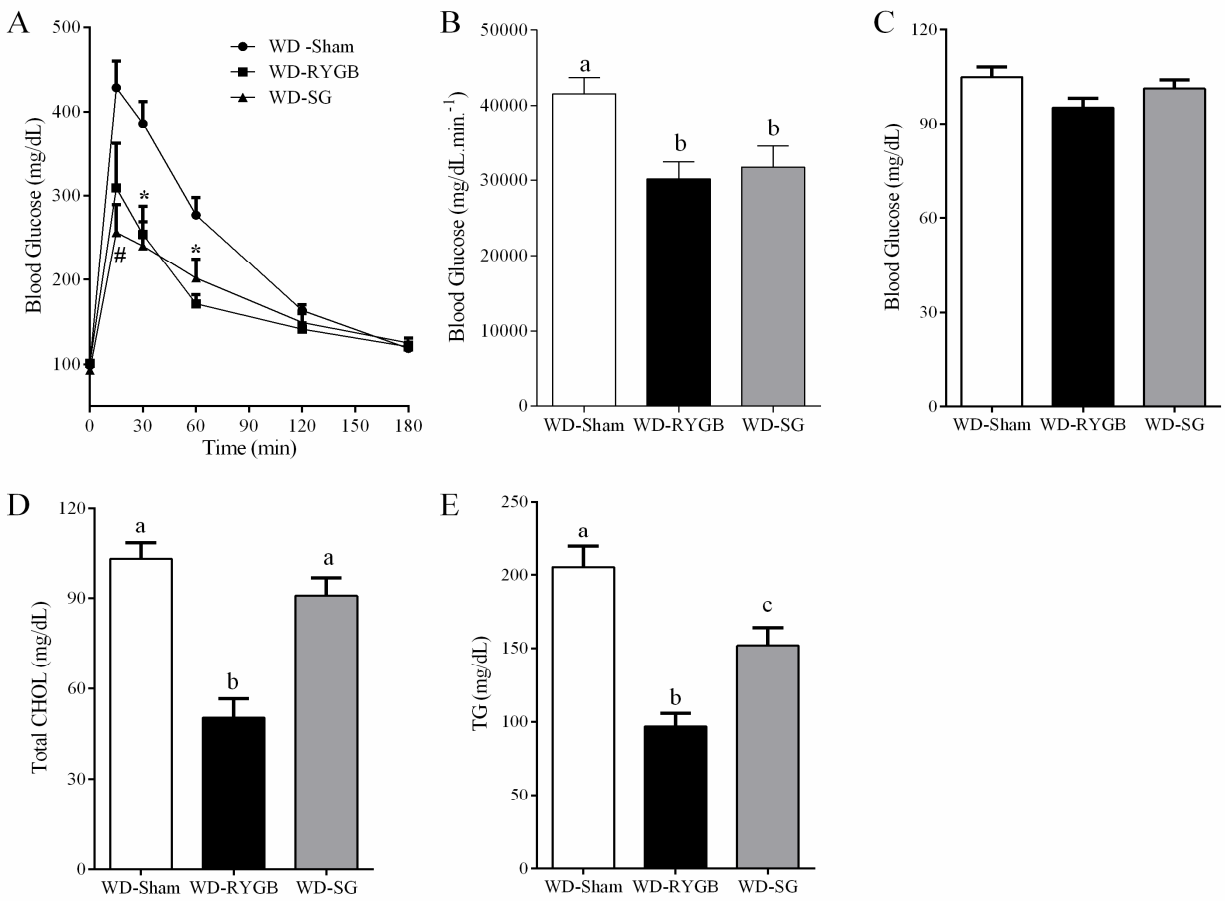

Figure 2: (A) Plasma glucose concentrations during the ipGTT at 2 months after the bariatric or sham operations. The figure shows the blood glucose concentrations before and after an ip injection of glucose (2 g/kg BW). #WD-RYGB is different from WD-Sham. *WD-SG is different from WD-Sham. (B) Total glycemia expressed as area under glycemia curve (AUC), during the ipGTT (WD-Sham = 14, WD-RYGB = 11 and WD-SG =10). Serum glucose (C), total CHOL (D) and TG concentrations after 3 months of the operations in WD-Sham, WD-RYGB and WD-SG rats (n = 7-16). Data are means ± SEM. Different letters over the bars represent significant differences (one-way ANOVA followed by Tukey post-test, P < 0.05)

Glucose tolerance and serum biochemical parameters: At 2 months after bariatric and sham operations, rats of all groups were submitted to ipGTT. After glucose load, glycemia reached maximal values at 15 min in all groups (Fig. 2A). WD-RYGB rats displayed lower glycemia at 30 and 60 min of the test, compared with WD-Sham (Fig. 2A). Whereas, WD-SG showed lower glycemia at 15, 30 and 60 min, compared with WD-Sham group (Fig. 2A). The total blood glucose during the ipGTT was 27% and 24% lower in WD-RYGB and WD-SG rats, respectively, compared with WD-Sham group (Fig. 2B). After 3 months of operations, fasting glucose levels were similar in all groups (Fig. 2C). However, WD-RYGB rats presented 62% and 39% lower serum CHOL and TG levels, respectively, when compared to WD-Sham (Fig. 2D and 2E). While in WD-SG rats a decrease of only 5% in serum TG levels, in comparison with WD-Sham, was observed (Fig. 2E).

Liver morphology and lipid contents: Histological analysis, according to the Brunt's NAFLD score, revealed that all WD-Sham obese rats displayed hepatic fatty deposition graded at 2 and 3 (Tab. 1), mainly characterized by micro and macrovacuolar steatosis that displaced the nuclei towards the hepatocyte periphery (Fig. 3A). After 3 months, only 17% of the liver samples of WD-RYGB group showed hepatic isolated lipid droplets, dispersed in the cytoplasm, that were graded at 1, but 83% of WD-RYGB rats were without steatosis (Fig. 3A). Contrariwise, microvacuolar steatosis (degree 1) was present in 100% of livers from WD-SG rats (Fig. 3A). In addition, liver fibrosis, which occurs in most types of chronic liver diseases, was not observed in any experimental group (Fig. 3B). Supporting histological analyses, at 3 months after bariatric procedures and with the continuity of the consumption of WD, WD-RYGB rats had their hepatic TG and CHOL content reduced by 24% and 34%, compared with WD-Sham rats (Fig. 3D and 3E). In livers from WD-SG rats the TG and CHOL contents were similar to WD-Sham, however a tendency of reduction was observed (Fig. 3D and 3E). Importantly, structural and functional alterations, observed in the liver from the different groups, were not associated with modifications in liver weight (Fig. 3C).

Table 1. Degree of steatosis in the livers of WD-Sham (n = 09), WD-RYGB (n = 06) and WD-SG (n = 05) rats at 3 months after the operations

Groups	Degree 0	Degree 1	Degree 2	Degree 3
WD-Sham	0	78%	22%	0
WD-RYGB	83%	17%	0	0
WD-SG	0	100%	0	0

Western diet sham operation (WD-Sham); Western diet Roux-en-Y gastric bypass (WD-RYGB); Western diet sleeve gastrectomy (WD-SG).

Hepatic expression of proteins involved in the lipid metabolism: In WD-RYGB rats the hepatic expression of ACC and FASN enzymes were 3.2 and 5.2 times lower than WD-Sham rats (Fig. 4). However, the ratio of $pACC^{Ser79}$/ACC protein and CPT-1a protein levels were 47% and 144% higher, in the liver from WD-RYGB than WD-Sham rats (Fig. 4).

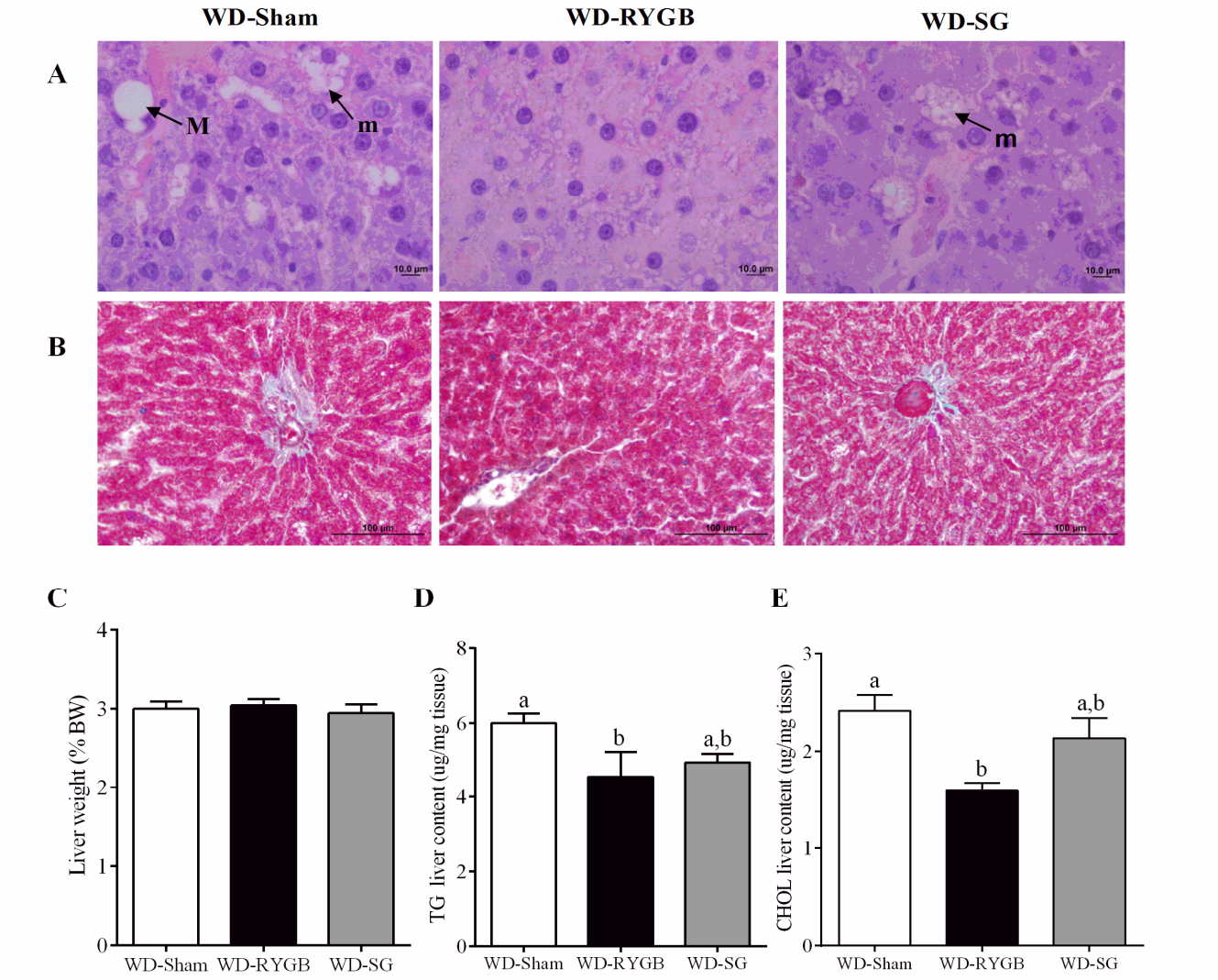

Figure 3. Representative images of 5 µm-sections of the liver of WD-Sham, WD-RYGB and WD-SG rats, after 3 months of the operations, stained with hematoxylin and eosin (A; scale bar = 10 µm) or Mallory's trichrome (B; scale bar = 100 µm). m = microvesicular steatosis; M = macrovesicular steatosis. Means ± SEM of the liver weight (C), and TG (D) and CHOL (E) content in the liver of WD-Sham (n = 13), WD-RYGB (n = 5) and WD-SG (n = 7) rats. Different letters over the bars represent significant differences (one-way ANOVA followed by Tukey post-test, P < 0.05)

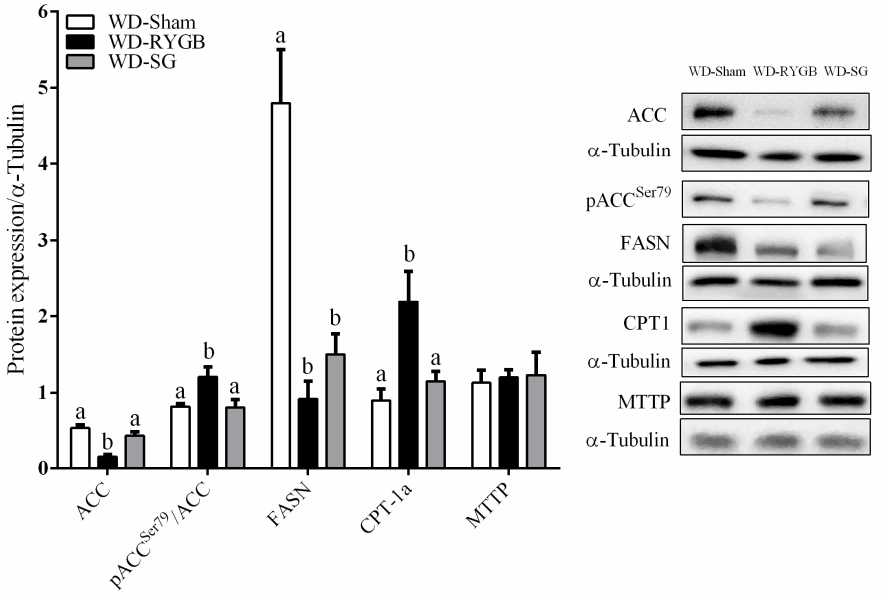

Figure 4. Hepatic ACC, pACC^{Ser79}/ACC, FASN, CPT-1a and MTTP protein expression in WD-Sham, WD-RYGB and WD-SG rats after 3 months of operations (n = 4-10). Fragments of the liver were processed by Western blotting. α-tubulin was used as internal control of the protein expression. Data are means ± SEM. Different letters over the bars represent significant differences (one-way ANOVA followed by Tukey post-test, P < 0.05)

The WD-SG group displayed a reduction of 68% only in hepatic FASN protein expression, compared to WD-Sham rats (Fig. 4). No differences in the expression of hepatic MTTP was observed between groups (Fig. 4).

DISCUSSION

The bariatric operations are considered more effective for the treatment of obesity than diet, exercises or pharmacological management interventions (Gloy *et al.*, 2013). The two most bariatric procedures performed, RYGB and SG, help obese people to lose weight and control BW, as well as, to resolve health issues associated with obesity, such as NAFLD.4 Since the literature lacks comparative studies demonstrating the effectiveness of these two operations upon NAFLD, we compare the efficacy of both surgeries, evidencing that RYGB is more effective than SG to reduce hepatic steatosis and the expression of protein involved in hepatic DN lipogenesis and β-oxidation. Both mixed and restrictive procedures, as RYGB and SG were effective to induce weight loss in high-fat diet obese mice even with the continuity of the hypercaloric regimen. However, RYGB and biliopancreatic diversion (BPD) lead to more pronounced weight loss, compared with SG, in high-fat diet mice (Yin *et al.*, 2011). Importantly, the reduction in body adiposity in these mice occurs, predominantly, with RYGB and BPD procedures, than SG or gastric banding (Yin *et al.*, 2011). In addition, after 3 months of RYGB or SG, only RYGB operation sustained BW loss and reductions in fat mass in high-fat diet mice (Siqueira *et al.*, 2006).

In agreement, our results also demonstrated that WD-obese rats, submitted to RYGB, showed a progressive and more pronounced reduction in BW and adiposity than SG- WD rats. RYGB and SG are known to improve glucose homeostasis (Rubino *et al.*, 2010; Yin *et al.*, 2011). However, in high-fat diet obese mice, SG operation improved glucose tolerance only for 4 weeks, and much more prolonged in RYGB mice (Yin *et al.*, 2011). We have observed here that, after 2 months, improvement in glucose tolerance occurred in both WD-RYGB and WD-SG rats (Fig. 2A and 2B). Probably, with more prolonged period of observation differences between groups concerned with glucose tolerance will be registered. In addition to the disruption in control of body glucose, obesity is also associated with dyslipidemia, characterized by an increase in serum TG-rich lipoproteins, decrease high-density lipoprotein (HDL)-CHOL, but increase low-density lipoprotein (LDL) levels (Siqueira *et al.*, 2006). Despite demonstrations that bariatric procedures may improve serum lipids levels (Aguilar-Olivos *et al.*, 2016), no consistent data, comparing the RYGB and SG effects upon lipids profile, are found in the literature. In obese adolescents that underwent RYGB or SG operations, a significant reduction in plasma total CHOL and LDL levels was verified only in RYGB (Maffazioli *et al.*, 2016). Conversely, in T2D obese patients, submitted to RYGB or SG, a decreased postprandial triglyceridemia and CHOL levels was observed, as early as 2 weeks after the procedure. Unfortunately, these patients were considered as only a group, impeding to discriminate the effects of each procedure (Griffo *et al.*, 2014). Here, we observed that in WD-RYGB the reduction in TG plasma levels was more marked than that in WD-SG rats. In addition, only RYGB procedure efficiently decreased serum total CHOL levels in WD rats. The pathogenesis of dyslipidemia is closely associated with NAFLD. In fact, the plasma lipid levels are associated with the magnitude of steatosis and fibrosis in patients with non-alcoholic steatohepatitis (Männistö *et al.*, 2014). Although the bariatric procedures ameliorated NAFLD in humans and obese rodents (Stefater *et al.*, 2011; Dixon, 2014), it remains unclear whether RYGB and SG procedures produce similar effects against NAFLD at the same time. In T2D obese humans, after 12 months RYGB or SG operations, the serum aspartate aminotransferase and alanine aminotransferase levels were lower in SG, suggesting that this procedure may affect liver function in a lesser extent than RYGB (Billeter *et al.*, 2016). However, liver biopsies from obese humans, submitted to RYGB or SG, showed that RYGB decreased hepatic steatosis, inflammation, fibrosis and hepatocyte ballooning, while SG operation only decreased hepatic steatosis (Froylich *et al.*, 2016). Our study also evidenced that RYGB operation is more effective against NAFLD, since WD-RYGB rats displayed a reduction in TG and CHOL liver content, normalizing liver steatosis in 83% of WD-RYGB rats. While, 100% of the WD-SG rats still showed liver steatosis, and no significant reduction in hepatic TG and CHOL content. For NAFLD development, the increase in TG accumulation in hepatocytes may be a consequence of modifications in hepatic lipid metabolism, with increase in DN lipogenesis; and/or the decrease in fatty acid (FA) β-oxidation; with or without the decrease in VLDL secretion (Berlanga *et al.*, 2014). Our results showed that RYGB operation reduced the hepatic DN lipogenesis, since ACC and FASN protein contents were reduced, but pACC/ACC ratio was enhanced in the liver of WD-RYGB rats. Also, these rodents presented higher CPT-1a protein expression, indicating increased hepatic FA oxidation. However, SG displayed only a minor effect against DN lipogenesis, since it was observed in WD-SG rats only a reduction in hepatic FASN protein. Besides the effect of RYGB upon hepatic lipid metabolism, observed here, previous reports also suggest that the mechanism by which this bariatric procedure improves NAFLD may be linked to the amelioration of the insulin action, originated from weight loss. In high-fat diet rats, submitted to RYGB operation, the improvement in NAFLD was linked to an attenuation of hepatic apoptosis by reducing the activation of the endoplasmic reticulum stress pathway (Mosinski *et al.*, 2016). Also, the bariatric operations may increase the enterohepatic circulation, enhancing the plasma levels of bile acids (Albaugh *et al.*, 2017). The tacked G-protein 5 and the farnesoid X are receptors activated by bile acids and these receptors can reduce CHOL and TG content and decrease the expression of genes involved in DN lipogenesis, in hepatocytes (Pathak *et al.*, 2017). In summary, we observed that after 3 months and with the continuity of WD, NAFLD is less frequent in obese rats that underwent RYGB, compared with SG procedures. This RYGB effect was due to a decrease in hepatic DN lipogenesis associated with an increase in CPT-1a protein content, which may enhance FA oxidation, ultimately resulting in reduction of TG content in the liver and serum of WD rats.

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