GASTRIC BYPASS SURGERY IMPROVES ALBUMINURIA AND PODOCYTE INJURY IN EXPERIMENTAL DIABETIC KIDNEY DISEASE

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Background

- Upwards of 30% of patients with Type 2 Diabetes develop Diabetic Kidney Disease (DKD), with patients showing both declining renal function and albuminuria having 10-year mortality rates of up to 47%[1]
- Roux-en-Y gastric bypass (RYGB) is the most efficacious intervention for T2DM and improvements in weight and metabolic control are typically accompanied by reductions in albuminuria[2,3]
- We previously demonstrated in The Zucker Diabetic Fatty rat (ZDF) that reductions in proteinuria post-RYGB were paralleled by reductions in renal inflammation and improvements in histopathological indices of glomerular injury[4].

Aims

1. To assess the impact of RYGB on glomerular injury in ZDF rats focusing on glomerular volume, podocyte number and health

2. To establish whether RYGB equivalent improvements in body weight and fasting glycaemia achieved through a diet and pharmacology based “medical bypass (MB)” have an equivalent effect on albuminuria and glomerular ultrastructure

3. To compare the global renal transcriptomic responses to both RYGB and MB

Methods

Study 1-Twelve-week old obese and diabetic male ZDF rats (fa/fa-homozygous mutant leptin receptor null) underwent RYGB or sham surgery involving laparotomy and body weight, fasting plasma glucose, albuminuria over the subsequent 7 weeks and glomerular histology and ultrastructure assessed in necropsy specimens.

Study 2-Twelve-week old male ZDF rats underwent RYGB or sham surgery. A sub group of sham-operated rats were calorie restricted and received insulin, liraglutide, metformin, ramipril, rosuvastatin and fenofibrate for 2 months (MB). Body weight, fasting glycaemia, glucose tolerance, glomerular ultrastructure and global renal transcriptomic responses were assessed at follow up.

Age and sex matched non-diabetic, non-obese Fa/+ rats acted as healthy controls in both studies.

Results

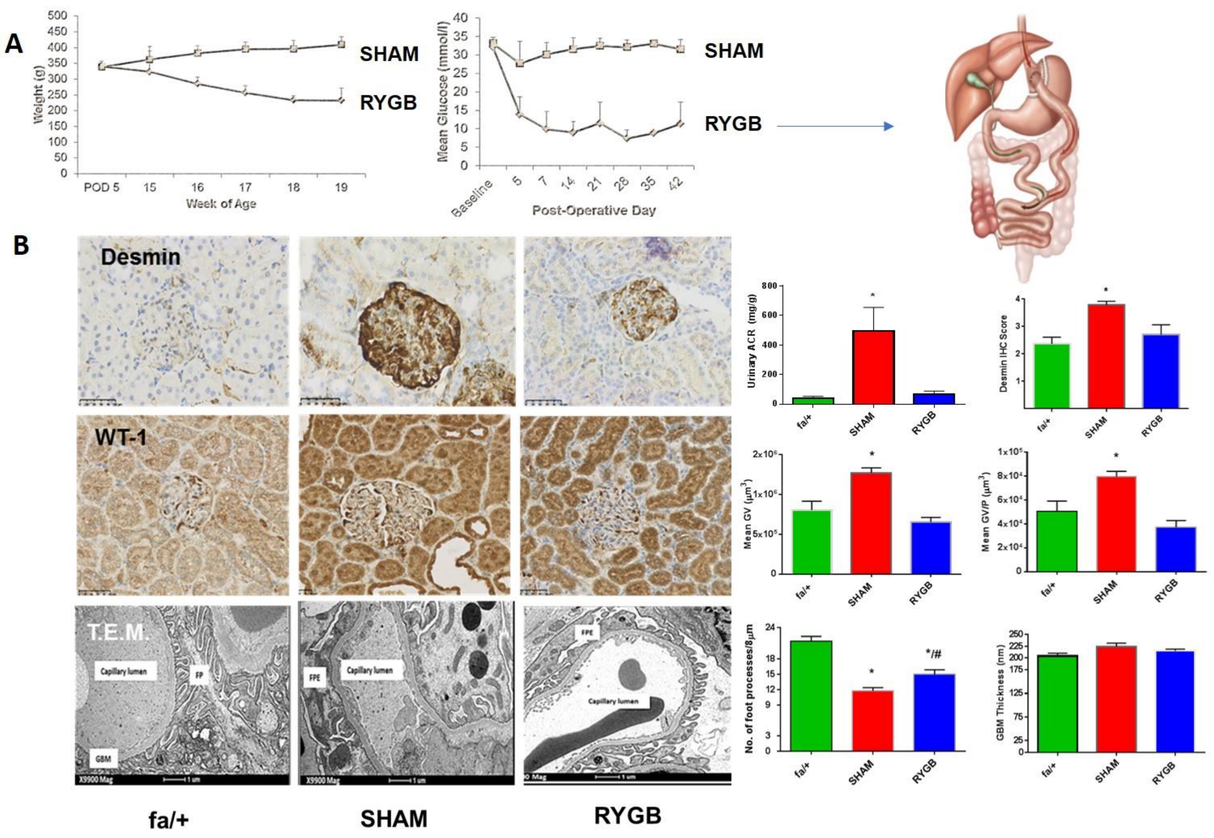

Figure 1 RYGB Attenuates Albuminuria and Glomerular Pathology in ZDF Rats
A)Body weight and fasting glucose after RYGB **B)** Urinary albumin excretion ,immunohistochemical and ultrastructural indices of glomerular injury after RYGB.
ACR-albumin creatinine ratio, IHC-immunohistochemistry, GV-glomerular volume, GV/P-Glomerular volume served per podocyte, FP-foot processes, FPE-foot process effacement, GBM-glomerular basement membrane. $^{*}p<0.05$ *versus fa/+* $^{\#}p<0.05$ *versus SHAM*

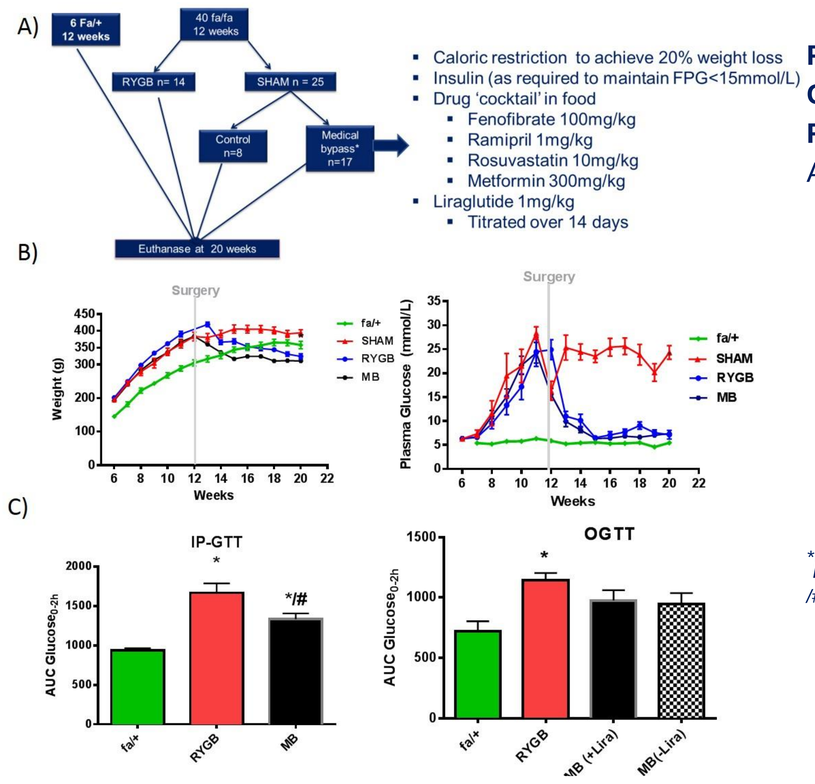

Figure 2 Body weight and Glycaemic Control Following RYGB and MB
A)Study design and MB regimen B) Body weight and fasting glucose C) Intra-peritoneal glucose tolerance test (IP-GTT) and oral glucose tolerance test (OGTT) at 7 weeks post-intervention with sub-grouping of MB group to receive (+lira) or not receive liraglutide (-lira) on day of test.
$^{*}p<0.05$ versus all other groups + $^{\#}p<0.05$ versus SHAM

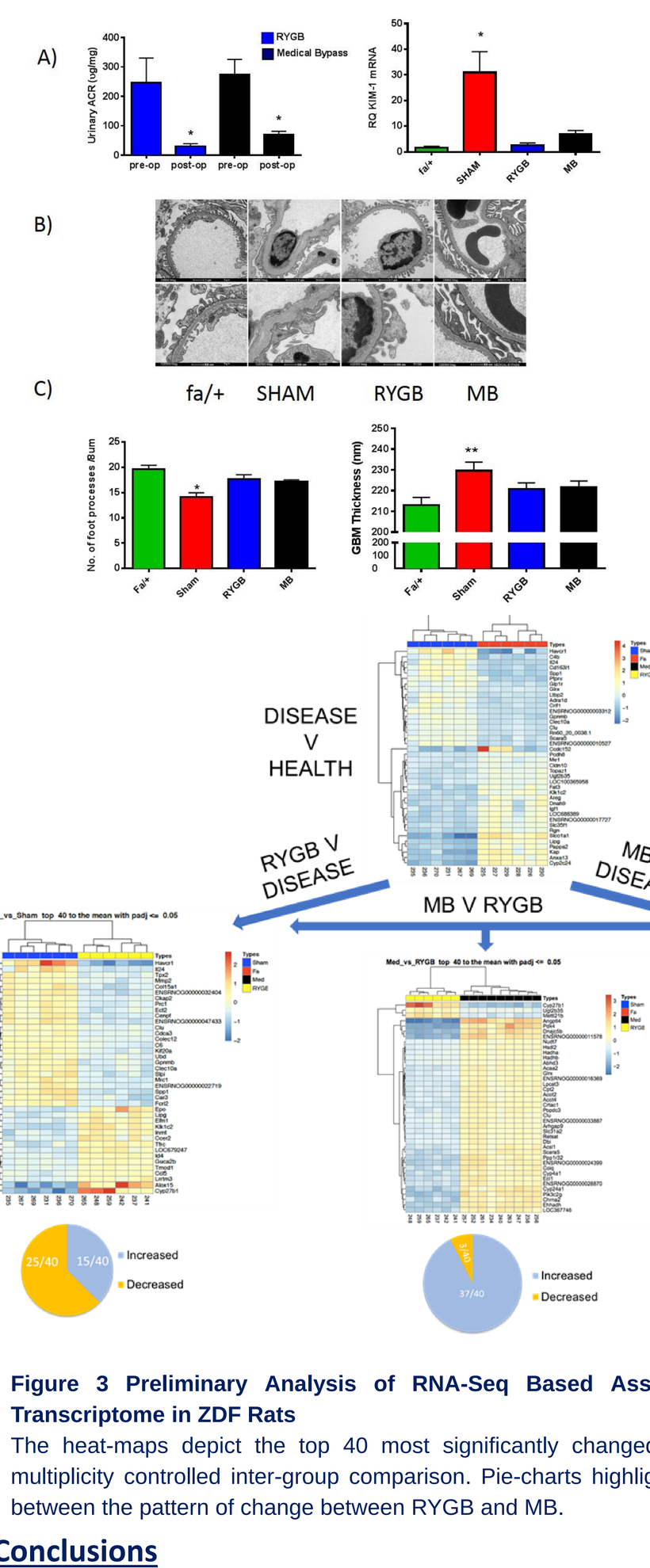

Figure 3 RYGB and MB Attenuate Albuminuria and Improve Podocyte Health in ZDF Rats
A) Albuminuria and renal KIM-1 mRNA
B) Representative Transmission electron microscopy images
C)Quantitative ultrastructural assessment of podocyte foot process frequency and GBM thickness.
ACR-albumin creatinine ratio, KIM-1-kidney injury molecule 1, GBM-glomerular basement membrane. $^{*}p<0.05$ *versus all other groups* $^{**}p<0.05$ *SHAM versus fa/+*

Figure 3 Preliminary Analysis of RNA-Seq Based Assessment of Global Renal Transcriptome in ZDF Rats
The heat-maps depict the top 40 most significantly changed mRNA quantities for each multiplicity controlled inter-group comparison. Pie-charts highlight the qualitative differences between the pattern of change between RYGB and MB.

Conclusions

- RYGB arrests progression of diabetic kidney disease in ZDF rats.
- Equivalent outcomes in relation to albuminuria and glomerular ultrastructure are obtained by RYGB and MB, albeit significant differences exist between the renal transcriptome induced by RYGB and MB.
- Bioinformatic analysis will be conducted to identify useful components of the RYGB response to be targeted in non-surgical bariatric mimetic approaches.
- Transcriptomic markers of maladapative renal responses to RYGB will also be identified as their mitigation could improve the efficacy of the procedure in relation to renal microvascular complications of T2DM

References

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