Renoprotective Effects of the Combination of Empagliflozin and Liraglutide Compared With Roux-en-Y Gastric Bypass in Early-Stage Diabetic Kidney Disease: A Post Hoc Analysis of the Microvascular Outcomes after Metabolic Surgery (MOMS) Randomized Controlled Clinical Trial

Ricardo V. Cohen,[1]
Tarissa Beatrice Zanata Petry,[1]
Alexander Dimitri Miras,[2]
Cristina Mamédio Aboud,[1]
Brett Johnson,[2]
Tiago Mendonça dos Santos,[3] *and*
Carel W. le Roux[4]

Diabetes Care 2021;44:e177–e179 | https://doi.org/10.2337/dc21-1192

Baseline albuminuria in patients with diabetic kidney disease (DKD) is strongly associated with progressive deterioration in kidney function (1). The remission of microalbuminuria in patients with type 2 diabetes and obesity attenuates the decline in estimated glomerular filtration rate (2). In the Microvascular Outcomes after Metabolic Surgery (MOMS) randomized controlled trial (RCT) (3), we demonstrated that the combination of best medical care and Roux-en-Y gastric bypass (RYGB) surgery is more effective in inducing remission of microalbuminuria than best medical care alone.

During the MOMS RCT, type 2 diabetes care guidelines were updated to reflect the potent renoprotective effects of sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists in people with DKD (4). Thus, the rate of use of the combination of these two agents (Combo) in the study was increased. In this post hoc analysis of the MOMS RCT, our objective was to determine whether the combination of two potent renoprotective medications can match the reductions of albuminuria observed after RYGB.

The MOMS RCT protocol has previously been described in detail (3). In brief, 100 patients with CKDG1–3a, A2–3, urine albumin–to–creatinine-ratio (uACR) >30 mg/g, type 2 diabetes, and a BMI of 30–35 kg/m^2 were randomized 1:1 to either best medical care or RYGB. Of the 49 patients, 27 (55%) randomized to best medical treatment received the Combo (empagliflozin 25 mg once daily and liraglutide 1.8 mg once daily) within the first 2 years of the study and formed the subgroup of interest for this post hoc analysis. A total of 44 patients who underwent RYGB and completed 2 years of follow-up were included in this analysis. uACR, estimated glomerular filtration rate, glycated hemoglobin (HbA_{1c}), fasting plasma glucose, blood pressure, lipid profiles, and body weight were assessed at baseline and 2 years.

Both interventions resulted in significant reductions in uACR, but RYGB was significantly superior (mean difference 14.99 [95% CI 1.10; 28.87], $P = 0.035$) (Table 1). The percentage of patients who achieved remission of albuminuria/DKD was 59.3% in the Combo and 81.8% in the RYGB group ($P = 0.043$).

RYGB was superior to the Combo for reductions in HbA_{1c} (mean difference 0.49 [95% CI 0.05; 0.93], $P = 0.029$) and LDL cholesterol (20.55 [6.30; 34.81], $P = 0.005$) but not systolic blood pressure (−0.75 [−8.51; 7.02], $P = 0.82$). The American Diabetes Association (ADA) triple end point was achieved in 25.9% in the Combo group and 44.2% in the RYGB group ($P = 0.11$).

In this post hoc analysis of the MOMS trial, the effect of inclusion of two potent renoprotective agents in best medical care for people with DKD did not quite match the renoprotective effects of RYGB. The surgical intervention remained superior in reducing albuminuria, remission of DKD, and improvements in cardiometabolic risk factors, including HbA_{1c} and LDL cholesterol. Despite the statistical superiority of surgery, the differences

[1]*The Center for Obesity and Diabetes, Oswaldo Cruz German Hospital, São Paulo, Brazil*
[2]*Department of Metabolism, Digestion and Reproduction, Imperial College London, London, U.K.*
[3]*Insper Institute of Education and Research, São Paulo, Brazil*
[4]*University College Dublin School of Medicine, Dublin, Ireland*

Corresponding author: Alex Miras, a.miras@nhs.net

Received 6 June 2021 and accepted 7 July 2021

Clinical trial reg. no. NCT01821508, clinicaltrials.gov

Table 1—Within- and between-group comparisons of renal and cardiometabolic outcomes at 2 years of follow-up

	Combo (n = 27)				RYGB (n = 44)				Combo × RYGB	
	Baseline	24 months	Effect size (95% CI)†	P	Baseline	24 months	Effect size (95% CI)†	P	Effect size (95% CI)†	P
HbA_{1c} (%)	9.0 (8.3; 9.7)	6.7 (6.4; 7.1)	−2.3 (−3.0; −1.5)	<0.001	9.0 (8.4; 9.5)	6.3 (6.0; 6.5)	−2.7 (−3.3; −2.2)	<0.01	0.49 (0.05; 0.93)	0.029
uACR	89.7 (62.7; 116.7)	33.0 (22.1; 44.0)	−56.7 (−81.5; −31.9)	<0.001	104.8 (83.6; 126.0)	18.0 (9.5; 26.6)	−86.8 (−106.2; −67.3)	<0.001	14.99 (1.10; 28.87)	0.035
Systolic blood pressure (mmHg)	140.4 (131.2; 149.6)	130.3 (124.2; 136.4)	−10.1 (−20.0; −0.3)	0.045	140.0 (133.3; 146.6)	131.1 (126.2; 135.9)	−8.9 (−16.2; −1.7)	0.018	−0.75 (−8.51; 7.02)	0.848
LDL cholesterol (mg/dL)	114.0 (98.7; 129.4)	106.3 (95.4; 117.5)	−7.8 (−2,189; 6.4)	0.275	102.8 (90.8; 114.8)	85.7 (76.9; 94.5)	−17.1 (−28.1; −6.0)	0.003	20.55 (6.30; 34.81)	0.005
ADA triple end point, n/N (%)	0/13 (0)	7/27 (25.9)	25.9 (9.4; 42.5)	0.002	0/25 (0)	19/43 (44.2)	44.2 (29.3; 59.0)	<0.001	18.26 (−3.96; 40.48)	0.11
DKD, n/N (%)	27/27 (100)	10/26 (38.5)	−61.5 (−80.2; −42.8)	<0.001	44/44	7/43 (16.3)	−83.7 (−94.8; −72.7)	<0.001	−22.18 (−43.90; −0.47)	0.045
Body weight (kg)	92.5 (87.2; 97.7)	86.31 (81.0; 91.6)	−6.1 (−8.4; −3.9)	<0.001	92.9 (88.7; 97.0)	69.2 (65.1; 73.4)	−23.6 (−25.4; −21.9)	<0.001	17.06 (10.28; 23.85)	<0.001

Continuous data are presented as mean (95% CI). †Mean difference: HbA_{1c}, uACR, systolic blood pressure, LDL cholesterol, and body weight. Relative risk: ADA triple end point and diagnosis of DKD.

in primary and secondary outcomes of the trial were of modest biological significance.

While modern pharmacotherapy for type 2 diabetes cannot fully recapitulate the pleiotropic impact of RYGB on DKD at the current time, with the rapid evolution of medicines, this might be possible in the future.

Funding. This study was partly supported by research grants from Oswaldo Cruz German Hospital, Science Foundation Ireland (grant 12/YI/B2480), and the Swedish Medical Research Council (2015-02733). The Section of Endocrinology and Investigative Medicine at Imperial College London is funded by grants from the Medical Research Council, Biotechnology and Biological Sciences Research Council, and National Institute for Health Research (NIHR); an Integrative Mammalian Biology Capacity Building Award; and an FP7-HEALTH-2009-241592 EuroCHIP grant and is supported by the NIHR Biomedical Research Centre funding scheme.

The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health and Social Care.

Duality of Interest. This study was also supported by funding from Johnson & Johnson Brasil. R.V.C. reports receiving grants from Johnson & Johnson Brasil during the conduct of the study. T.B.Z.P. reports receiving grants from Johnson & Johnson Brasil during the conduct of the study. A.D.M. reports receiving honoraria for lectures and serving on the scientific advisory board from Novo Nordisk, GI Dynamics, and Boehringer Ingelheim outside the submitted work. C.W.l.R. reports receiving honoraria for lectures and serving on the scientific advisory board from Novo Nordisk, GI Dynamics, Sanofi, Johnson & Johnson Brasil, Keyron, Herbalife Nutrition, and Boehringer Ingelheim outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. R.V.C., T.B.Z.P., and C.W.l.R. contributed to the study concept and design. R.V.C., T.B.Z.P., C.M.A., and C.W.l.R. contributed to acquisition, analysis, or interpretation of data. R.V.C., A.D.M., C.M.A., B.J., and C.W.l.R. contributed to drafting of the manuscript. R.V.C., A.D.M., C.M.A., T.B.Z.P., and C.W.l.R. contributed to critical revision of the manuscript for important intellectual content. T.M.d.S. contributed to statistical analysis. R.V.C. obtained funding. R.V.C., T.B.Z.P., C.M.A., and B.J. contributed to administrative, technical, or material support. R.V.C. and C.W.l.R. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR. Combining GFR and

albuminuria to classify CKD improves prediction of ESRD. J Am Soc Nephrol 2009;20:1069–1077
2. Gaede P, Tarnow L, Vedel P, Parving HH, Pedersen O. Remission to normoalbuminuria during multifactorial treatment preserves kidney function in patients with type 2 diabetes and microalbuminuria. Nephrol Dial Transplant 2004;19:2784–2788
3. Cohen RV, Pereira TV, Aboud CM, et al. Effect of gastric bypass vs best medical treatment on early-stage chronic kidney disease in patients with type 2 diabetes and obesity: a randomized clinical trial. JAMA Surg 2020;155:e200420
4. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701