



# Beta cell function and mass in individuals with and without remission of type 2 diabetes after Roux-en-Y gastric bypass

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## Abstract

**Aims/hypothesis** In people with type 2 diabetes and obesity, Roux-en-Y gastric bypass (RYGB) can induce remission of diabetes. While RYGB has been reported to improve beta cell function in individuals with type 2 diabetes, it is unclear whether this is accompanied by changes in beta cell mass. In this explorative proof-of-concept study, we compared beta cell mass, measured by [<sup>68</sup>Ga]Ga-NODAGA-exendin-4 positron emission tomography/computed tomography (PET/CT) imaging, between individuals achieving remission of type 2 diabetes following RYGB and those not achieving remission.

**Methods** Individuals with ( $n=8$ ) and without ( $n=9$ ) remission of type 2 diabetes up to 4 years after RYGB were injected with  $100 \pm 5.6$  MBq of [<sup>68</sup>Ga]Ga-NODAGA-exendin-4 to quantify beta cell mass using PET/CT imaging. Beta cell function was determined by the AUC for C-peptide and the ratio between the AUC for C-peptide and AUC for glucose obtained from a combined arginine stimulation test (ARGT) and OGTT. Acquired variables are expressed as mean  $\pm$  SD or median (IQR) based on normality.

**Results** Individuals with remission of type 2 diabetes had a shorter diabetes duration than those without remission. After RYGB, beta cell function was higher in individuals with remission of type 2 diabetes than individuals without remission, based on both ARGTS ( $AUC_{C-peptide}/fasting\ glucose\ 1.1 \pm 0.41$  vs  $0.32 \pm 0.16$  nmol  $\times$  min/mmol,  $p=0.001$ ) and OGTTs ( $AUC_{C-peptide}:AUC_{glucose}\ 0.15$  [0.11–0.24] vs  $0.032$  [0.023–0.054],  $p=0.005$ ). In contrast, beta cell mass did not differ between individuals with or without remission of type 2 diabetes ( $3.6$  [3.4–5.4] vs  $3.8$  [1.9–4.5] kBq/MBq,  $p=0.87$ ) and did not correlate with beta cell function or body weight parameters. HOMA2-%B, also representing beta cell function, was better in the remission group and significantly improved in these individuals after RYGB, whereas it remained unchanged in non-remitters.

**Conclusions/interpretation** Individuals with remission of type 2 diabetes after RYGB have better beta cell function than those not achieving remission, but the groups did not differ with respect to beta cell mass. Our preliminary data argue against a stimulating effect of RYGB on beta cell mass, although revival of non-functional (so-called dormant) beta cells is a possible explanation for remission.

**Trial registration** ClinicalTrials.gov NCT02542059

**Keywords** Bariatric surgery · Beta cell function · Beta cell mass · Exendin · Molecular imaging · PET imaging · RYGB · Type 2 diabetes

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## Research in context

### What is already known about this subject?

- Roux-en-Y gastric bypass (RYGB) results in significant weight loss and may induce remission of type 2 diabetes
- Beta cell function improves in people with type 2 diabetes after RYGB
- The effect of RYGB on beta cell mass in people with diabetes has not been studied

### What is the key question?

- Does beta cell mass differ between individuals with and without remission of type 2 diabetes after RYGB?

### What are the new findings?

- Beta cell mass does not appear to differ between individuals with and without remission of type 2 diabetes after RYGB, despite clear improvement in beta cell function in individuals with compared with those without diabetes remission
- Beta cell mass does not correlate with either beta cell function or body weight parameters

### How might this impact on clinical practice in the foreseeable future?

- More research is needed to explore the possibility that non-functional (dormant) beta cells are revived by RYGB, which may explain the observation of improved beta cell function without a concomitant increase in beta cell mass after RYGB surgery

## Abbreviations

[ <sup>68</sup> Ga]Ga-NODAGA-exendin-4	Radiolabelled exendin
ARGT	Arginine stimulation test
CT	Computed tomography
FG	Fasting glucose
GLP-1R	Glucagon-like peptide-1 receptor
PET	Positron emission tomography
RYGB	Roux-en-Y gastric bypass

## Introduction

The global prevalence of obesity is increasing, which is a risk factor for type 2 diabetes, and the vast majority of people with type 2 diabetes are living with overweight or obesity [1]. Sufficient weight loss, irrespective of whether this is achieved by dietary, pharmacological or surgical interventions, can lead to remission of type 2 diabetes [2]. Although all three methods are promising in reversing type 2 diabetes, the effects of bariatric surgery are more sustainable over time and relapse of type 2 diabetes is less likely even after weight regain [2]. Remission of type 2 diabetes after bariatric surgery has been attributed to a combination of improvements in beta cell function and insulin sensitivity [3, 4]. This appears to be particularly true for Roux-en-Y gastric bypass (RYGB), which may result in type 2 diabetes remission rates

as high as 75%, much higher than after sleeve gastrectomy [5]. The fact that improvements in insulin sensitivity in individuals with obesity with type 2 diabetes are similar after RYGB and sleeve gastrectomy [6], and that diabetes remission is retained with weight gain after RYGB [5], suggests a particular beneficial effect of RYGB on beta cells.

Although weight loss is thought to particularly improve insulin sensitivity, it may also enhance insulin secretion through recovery of beta cell function [7]. Whether and to what extent remission of type 2 diabetes after RYGB is related to enhanced beta cell mass remains poorly understood. In animals, increased beta cell mass has been observed after gastric bypass surgery [8], but this has not been determined in humans. Using positron emission tomography/computed tomography (PET/CT) with [<sup>68</sup>Ga]Ga-NODAGA-exendin-4 (radiolabelled exendin), beta cell mass can be determined non-invasively by targeting glucagon-like peptide-1 receptors (GLP-1Rs) [9–11]. In this explorative study, we applied [<sup>68</sup>Ga]Ga-NODAGA-exendin-4 PET/CT imaging to compare beta cell mass between individuals with and those without remission of type 2 diabetes after RYGB.

## Methods

**Participants** We recruited individuals with type 2 diabetes from the bariatric surgery outpatient clinic of Rijnstate Hospital (Arnhem, the Netherlands) who had undergone RYGB surgery at least 1 year before. Sex derived from patient

records and self-reported ethnicity were recorded, but no selection was performed based on these characteristics. Religion and socioeconomic status were not considered as eligibility factors, as we aimed to achieve representation of a larger and more diverse population of interest.

We only included individuals with a first bariatric intervention. Complete remission of type 2 diabetes was defined as having HbA<sub>1c</sub> levels within the normal range (<48 mmol/mol [ $<6.5\%$ ]) [12] and normal fasting blood glucose levels (<5.6 mmol/l) for at least 1 year directly after RYGB in the absence of glucose-lowering therapy. Type 2 diabetes was not considered to have remitted when HbA<sub>1c</sub> was above the normal range ( $\geq 48$  mmol/mol [ $\geq 6.5\%$ ]) and/or when glucose-lowering drugs were used (see electronic supplementary material (ESM) Table 1) [12]. In addition, HbA<sub>1c</sub> levels and use of glucose-lowering drugs in the non-remission group were evaluated from RYGB until inclusion. Exclusion criteria are described in ESM Methods.

All study procedures were performed at Rijnstate Hospital and Radboud University Medical Center (Nijmegen, the Netherlands). All procedures were approved by the local Institutional Ethics Review Committee and all participants provided written informed consent in accordance with the provisions of the Declaration of Helsinki (ClinicalTrials.gov: NCT02542059).

**Combined arginine stimulation test and OGTT** Participants underwent a medical interview and the combined arginine stimulation test (ARGT) and OGTT, performed in the morning after a 12 h fast, to determine beta cell function. Details of the beta cell function tests are provided in ESM Methods.

**PET/CT acquisition** To quantify pancreatic beta cell mass, exendin-PET/CT scans were performed. Participants fasted for 4 h and, if applicable, halted short-acting insulin 6 h prior to the scan to prevent hypoglycaemia. Subsequently, they received  $100 \pm 6$  MBq of [<sup>68</sup>Ga]Ga-NODAGA-exendin-4 as an i.v. bolus over 1 min. Blood pressure and blood glucose levels were monitored immediately before and 15 and 60 min after [<sup>68</sup>Ga]Ga-NODAGA-exendin-4 administration. The radiopharmaceutical was prepared as previously described [9]. Further details on the PET/CT scans, reconstruction and quantitative image analysis are described in ESM Methods.

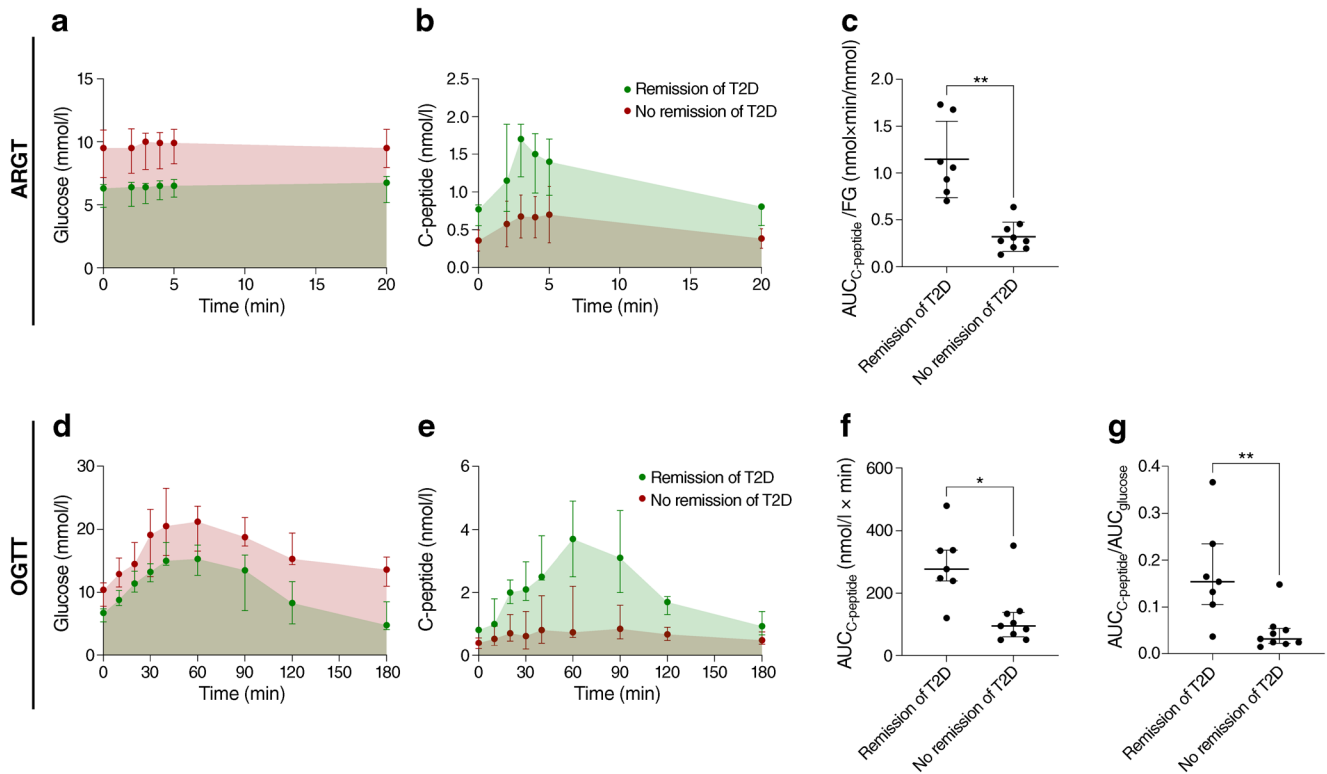
**Statistical analysis** This was an explorative proof-of-concept study; hence, no power calculation was performed. Data were analysed using GraphPad Prism, version 10.0.0 (San Diego, CA, USA). A  $\chi^2$  test was used to determine group differences in categorical values (sex and insulin use before RYGB). Group differences in beta cell function ( $AUC_{C-peptide}$ ,  $AUC_{glucose}$ , their ratio and HOMA2 indices [13]) and beta cell mass were assessed by either an independent *t* test

(two-tailed) including Welch's correction or a Mann–Whitney *U* test, depending on normality assessed by the Shapiro–Wilk test. Timepoint differences in beta cell function data (stimulated C-peptide and glucose) within and between the groups were assessed by two-way repeated measures ANOVA. Beta cell mass is a parameter with considerable variance as observed in previous data [10, 11]. Therefore, we assumed a non-normal distribution and confirmed this assumption using the Shapiro–Wilk test. Linearity between variables was checked using Pearson's correlation (two-tailed). Linear regression was used to assess the relation between beta cell mass (dependent variable) and remission group (yes/no; independent variable) while adjusting for diabetes duration. Linear regression was performed in IBM SPSS Statistics for Windows, version 29 (IBM, USA). Acquired variables were expressed as mean  $\pm$  SD, median (IQR) or number (%). A *p* value  $<0.05$  was considered statistically significant.

## Results

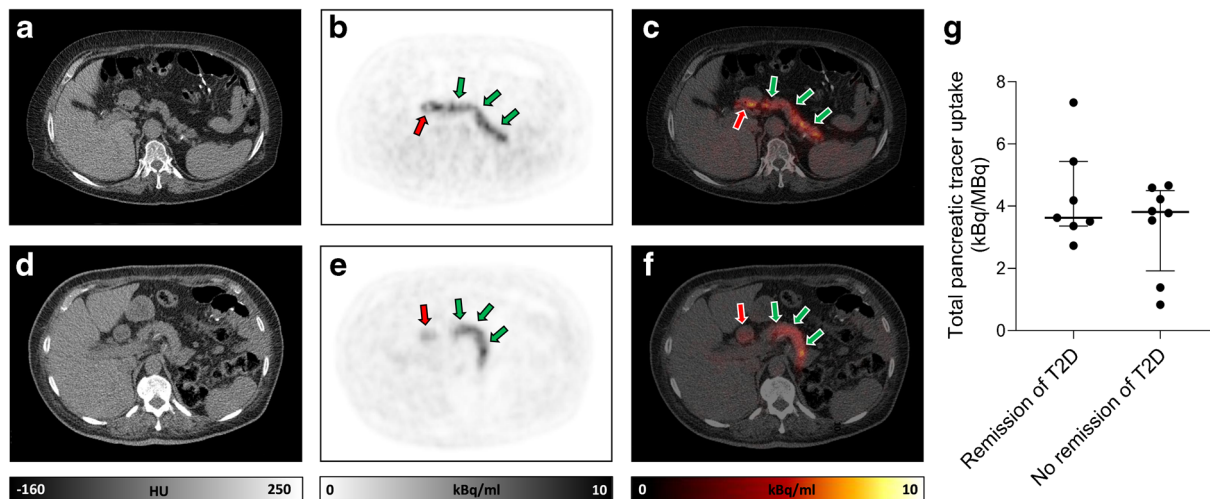
We included 17 individuals with type 2 diabetes who had undergone RYGB, eight of whom had complete remission of type 2 diabetes and nine who had no remission of type 2 diabetes. The ARGT results of one remitter were excluded from analysis because of blood sampling errors, which resulted in limited data. Additionally, the PET scans of one remitter and one non-remitter were excluded from the PET analysis due to halo artefacts around the kidney, which did not allow reliable quantification of radiolabelled exendin uptake in the pancreas. The two groups did not differ with respect to age, BMI, time between surgery and inclusion, and total body weight loss (ESM Table 2). Individuals with remission had a significantly shorter diabetes duration before RYGB, and lower HbA<sub>1c</sub> before and after RYGB than individuals without remission. Remitters were found to be more insulin-resistant and non-remitters more insulin-deficient, based on HOMA2 indices (ESM Fig. 1). When comparing differences in HOMA indices within a group, insulin sensitivity (HOMA2-%S) and beta cell function (HOMA2-%B) both improved after RYGB in the remission group, but not in those without remission (ESM Table 3).

Beta cell function derived from both ARGTS and OGTTs was significantly better in individuals with remission than individuals without remission (Fig. 1). Indeed, the acute C-peptide response to arginine, corrected for fasting glucose (FG), was higher in individuals with remission of type 2 diabetes after RYGB than in those not achieving remission ( $AUC_{C-peptide}/FG$   $1.1 \pm 0.41$  vs  $0.32 \pm 0.16$  nmol  $\times$  min/mmol,  $p=0.001$ ). Similarly,  $AUC_{C-peptide}:AUC_{glucose}$  derived from OGTT was also higher in remitters than non-remitters ( $0.15$  [ $0.11$ – $0.24$ ] vs  $0.032$  [ $0.023$ – $0.054$ ],  $p=0.005$ ).



**Fig. 1** Beta cell function tests. ARGTT showing (a) glucose profile, (b) C-peptide profile and (c)  $AUC_{C-peptide}$  corrected for fasting glucose (FG); OGTT showing (d) glucose profile, (e) C-peptide profile, (f)

$AUC_{C-peptide}$  and (g)  $AUC_{C-peptide}/AUC_{glucose}$  in individuals with and without remission of type 2 diabetes after RYGB. Data are presented as median (IQR). \* $p < 0.05$ , \*\* $p < 0.01$ . T2D, type 2 diabetes



**Fig. 2** Uptake of radiolabelled exendin in the pancreas. Transversal images of (a, d) CT, (b, e) PET and (c, f) PET/CT fusion from a participant with remission of type 2 diabetes (a–c) and a participant without remission of type 2 diabetes (d–f). The red and green arrows in (b), (c), (e) and (f) depict the uptake of radiolabelled exendin in the

duodenum and the pancreas, respectively. (g) Radiolabelled exendin-PET/CT analysis in individuals with and without remission of type 2 diabetes after RYGB. Data are presented as median (IQR). HU, Hounsfield unit; T2D, type 2 diabetes

Clear uptake of radiolabelled exendin in the pancreas was visible in all individuals in both groups (Fig. 2a–f). Total pancreatic uptake of radiolabelled exendin, representing beta cell mass, did not differ between individuals with and without remission (3.6 [3.4–5.4] vs 3.8 [1.9–4.5] kBq/MBq, respectively,  $p=0.87$ ; Fig. 2g), which did not change after correcting for diabetes duration ( $F [1, 12]=1.72$ ,  $p=0.21$ ; ESM Table 4). Mean differences in beta cell mass between the two groups are provided in ESM Table 5. Beta cell mass did not correlate with beta cell function, diabetes duration or body weight parameters (ESM Fig. 2).

## Discussion

Our proof-of-concept study shows improvement in beta cell function after RYGB in those with but not in those without remission of type 2 diabetes. However, these differences in beta cell function were not mirrored by differences in beta cell mass, as this did not differ between the two groups.

This is the first proof-of-concept study to investigate the effect of RYGB on beta cell mass in humans using [ $^{68}\text{Ga}$ ]Ga-NODAGA-exendin-4, the best characterised beta cell tracer [9–11]. Our preliminary data on the null effect of RYGB on beta cell mass contrast with data obtained in animals. Lindqvist et al reported higher beta cell mass in pigs after RYGB than in sham-operated control pigs, but did not investigate the effect on type 2 diabetes [8].

In line with previous studies [3, 4], we observed improvement in beta cell function in individuals who achieved remission of type 2 diabetes after RYGB. Our observation that beta cell function improved in remitters without an apparent concomitant increase in beta cell mass has a number of potential explanations. First, reversal of glucose toxicity in individuals with diabetes remission could benefit both beta cell function and insulin sensitivity [14]. Second, improved hepatic fat metabolism could enhance beta cell function in diabetes remission, described in the twin-cycle hypothesis [7]. Significant body weight loss may reverse fat accumulation in the pancreas and thereby protect beta cells, which may explain subsequent diabetes remission. A third explanation may be less de-differentiation of beta cells in people with remission of type 2 diabetes. An in vitro study showed that beta cells can be converted into alpha- or delta-like cells [15]. Whether such de-differentiated cells still express GLP-1Rs necessary for their detection by our imaging technique is unclear.

Revival of dormant beta cells could also explain the discrepancy between beta cell mass and beta cell function in remitters, which aligns with a previously suggested hypothesis [16]. A subpopulation of dormant hypoxic pancreatic islet cells was found in rodents, which changed in number on large modifications of islet mass, suggesting a compensatory mechanism for beta cell function [17]. For

example, the proportion of dormant islet cells doubled in the native endogenous pancreas following whole-pancreas transplantation. Remission of type 2 diabetes after RYGB may be explained by (re-)activation of such dormant beta cells, so that overall beta cell function improves, while beta cell mass, encompassing both functional and non-functional cells, does not change. Even after weight gain, diabetes remission after RYGB was maintained [5]. This observation further supports activation of dormant beta cells as a concept to explain remission of type 2 diabetes after RYGB.

A major strength of our study is that the study groups were similar with respect to age, BMI, weight loss and the period between surgery and performance of study procedures, so that many confounders potentially affecting beta cell function and mass could be excluded. In addition, we were able to concomitantly measure beta cell mass, using the extensively validated [ $^{68}\text{Ga}$ ]Ga-NODAGA-exendin-4 PET/CT technique, and beta cell function, using both ARGTs and OGTTs. However, there are also limitations. First, the study had a small sample size, limiting statistical power. Second, the sex distribution in our population was skewed, with only two of the 17 participants being men.

In summary, despite better beta cell function in participants with remission of type 2 diabetes after RYGB than in those not achieving remission, beta cell mass after RYGB did not appear to differ between the two groups. Our preliminary data argue against an influence of RYGB on beta cell mass.

**Supplementary Information** The online version of this article (<https://doi.org/10.1007/s00125-025-06659-1>) contains peer-reviewed but unedited supplementary material.

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**Data availability** Data are available on request from the authors.

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**Authors' relationships and activities** BEG is a member of the editorial board of *Diabetologia* but was not involved in handling the manuscript during the editorial process. All other authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

**Contribution statement** LND, BEG, CJT, MB and MG contributed to the design of this study. ST, LND and AH were involved in the acquisition of data. All authors contributed to the interpretation of the acquired data. Data analysis, generation of all figures/tables and writing the original draft was performed by ST. All authors were involved in the review and editing process and approved the final version. The guarantor of this work is MG, who accepts full responsibility for the work. ST and MG had access to all data and take responsibility for its integrity.

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