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A probability score for preoperative prediction of type 2 diabetes remission following RYGB surgery

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Abstract

BACKGROUND—Type 2 diabetes (T2D) is a metabolic disease with significant medical complications. Roux-en-Y gastric bypass (RYGB) surgery is one of the few interventions that remit T2D in ~60% of patients. However, there is no accurate method for predicting preoperatively the probability for T2D remission.

METHODS—A retrospective cohort of 2,300 RYGB patients at Geisinger Clinic was used to identify 690 patients with T2D and complete electronic data. Two additional T2D cohorts (N=276, and N=113) were used for replication at 14 months following RYGB. Kaplan-Meier analysis was used in the primary cohort to create survival curves until remission. A Cox proportional hazards model was used to estimate the hazard ratios on T2D remission.

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Conflicts of interests
The authors have no conflicts of interest to declare.

Author contributions
CDS admitted all the patients to the weight loss bariatric program at Geisinger Clinic. CGW performed all the analytical aspects of the study including the design of the *DiaRem* score algorithm. WES, ATP, JG, and AI performed all RYGB surgeries. GSG, PB, JS, and BI helped with the patient participation, the design of the study, and the manuscript preparation. MPC and RB provided one of the replication cohorts (Scottsdale, Arizona) and analytical support. GA conceived and designed the study, participated in patient selection, and wrote the manuscript with help from all the coauthors.

FINDINGS—Using 259 preoperative clinical variables, four (use of insulin, age, HbA1c, and type of antidiabetic medication) were sufficient to develop an algorithm that produces a type 2 diabetes remission (*DiaRem*) score over five years. The *DiaRem* score spans from 0 to 22 and was divided into five groups corresponding to five probability-ranges for T2D remission: 0–2 (88%–99%), 3–7 (64%–88%), 8–12 (23%–49%), 13–17 (11%–33%), 18–22 (2%–16%). The *DiaRem* scores in the replication cohorts, as well as under various definitions of diabetes remission, conformed to the *DiaRem* score of the primary cohort.

INTERPRETATION—The *DiaRem* score is a novel preoperative method for predicting the probability (from 2% to 99%) for T2D remission following RYGB surgery.

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INTRODUCTION

Type 2 diabetes (T2D) is a chronic metabolic disease with potentially severe medical and socioeconomic effects.[1] Roux-en-Y gastric bypass (RYGB) surgery is a particularly effective intervention in humans that remits T2D[2–4], with ~60% of patients achieving T2D remission.[5, 6] RYGB has also been proposed as a therapy for T2D resolution in cases where weight loss may not be the primary objective[7, 8] including cases with low body mass index (BMI) ranging from 25 to 35 Kg/m^2.[9, 10] It would therefore benefit patients and clinicians to have a means for predicting the probability of T2D remission by RYGB, using preoperative criteria.

Various mechanisms have been proposed for predicting T2D remission after RYGB surgery. Durable T2D remission has been associated with early diabetes stage[11] and significant percent excess body weight loss (% EWL)[12], while, failure to achieve long-term remission has been associated with inadequate weight loss.[13] Young age and low BMI (25–35 Kg/m^2) are also predictors of long-term T2D remission[9, 10], while, use of insulin, high percent glycated hemoglobin A1c (HbA1c), and low %EWL are predictors of decreased rates of remission after RYGB surgery.[14] Glycemic response to gastric bypass has also been correlated with BMI, duration of diabetes, fasting C-peptide, and weight loss.[15] A few reports using algorithmic prediction models have shown that preoperative BMI, HbA1c, plasma glucose, hypertension, and better control of diabetes can predict diabetes remission after RYGB.[16, 17]

Our goal was to develop a simple and effective method based on preoperative clinical criteria for predicting diabetes remission by RYGB. After screening 259 variables, four of them formed an algorithmic model and a scoring system that predicts probabilities ranging from 2% to 99% for diabetes remission after RYGB.

RESEARCH DESIGN AND METHODS

Study design and participants

A retrospective cohort of 2,300 patients that underwent Roux-en-Y gastric bypass at Geisinger Clinic between 1/1/2004 and 2/15/2011[18] was used to identify 690 T2D patients with available electronic medical records (EMR). The cohort consisted predominantly of severely obese (mean BMI 49.2 kg/m^2) White Caucasians (97%) from central Pennsylvania who had voluntarily enrolled into our RYGB surgery program.[18, 19] The mean age of the primary cohort was 51.2 years and the female/male ratio of 73/27% (Tables 1, S1). These 690 T2D cases were divided into T2D patients not using insulin preoperatively (the “T2D” group) and T2D patients using insulin preoperative (the “T2D+I” group) (Table S1). Each category was further divided into patients with early or late T2D remission (details in

sections below). A flow chart of patient groups and samples sizes is provided in Figure 1. These studies were approved by the Geisinger Clinic Institutional Review Board (IRB). All participants provided informed written consent.

Definition of type 2 diabetes and remission of type 2 diabetes

The definition of type 2 diabetes was according to the American Diabetes Association (ADA) guidelines.[20] T2D was defined by fasting glucose > 126 mg/dL or HbA1c > 6·5%. Additional confirmation was obtained by examining the EMR for the ICD9 code for T2D diabetes. Preoperative medication use included biguanides (metformin), insulin sensitizer, sulfonylureas, insulin, or combinations of these before surgery.

Remission of T2D was defined according to ADA criteria.[21] Specifically, "partial" remission of T2D was defined by HbA1c < 6·5%, fasting blood glucose levels < 125 mg/dL and no use of anti-diabetic medications, for a minimum of 12 months. "Complete" remission was defined by HbA1c < 6.0%, fasting glucose < 100 mg/dL, and no use of antidiabetic medication for least 12 months. The *DiaRem* score was developed by using patients in "partial" and "complete" remission combined.

Early and late remission of diabetes

Early T2D remission was defined as the period of remission commencing within the first two months after surgery and lasting for at least an additional 12 months. The period of two months after surgery was required to ensure that patients in this classification had their glucose and HbA1c normalized before they were taken off any anti-diabetic medications. Late T2D remission was defined as the remission commencing more than two months after surgery and lasting at least for another 12 months.

Development of the algorithm, weighting of scores, and statistical analyses

A total of 259 clinical variables (including 51 co-morbidities, 93 medications, 78 laboratories, 19 survey scores, and 18 other miscellaneous factors (age, gender, smoking, alcohol, use, etc.) were considered as we have previously described.[18] Multiple logistic regression models were used to identify independent predictors of early diabetes remission. To evaluate predictors of late diabetes remission, the patients with early remission were excluded, and multivariate Cox regression models were used to identify time until late remission. When building the multivariate models, each of the clinical variables listed above were evaluated in univariate models, and those with p-values < 0.10 were considered for inclusion in the multivariate model. Continuous covariates were checked for non-linearity by categorizing the data into groups (for example, using quartiles of the distribution or scientifically valid cutoff values). For each model, the subset was entered into the relevant multiple regression model with the goal of identifying a set of clinical variables that independently predict remission. Model results were evaluated to identify a consistent subset of variables that predict T2D remission for each regression model. A final Cox regression model for time until T2D remission using this consistent subset of variables was evaluated. The resulting hazard ratios were used to guide the creation of a weighting system (Table S5). We evaluated interactions between all items in the *DiaRem* score and with baseline BMI but none were significant. All tests were two-sided and $p < 0{\cdot}05$ was considered significant. SAS version 9·2 was used for statistical analyses.

Means (standard deviation) and percentages were used to describe the demographics, BMI, and diabetes/lipid laboratory measurements. Kaplan-Meier (K-M) analysis was used to create K-M survival curves of time until remission. Patients that never reached remission were censored. The K-M curves were stratified by pre-operative insulin use and were

compared using a Log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio for insulin use on T2D remission.

Other cohorts used in replication analysis of the DiaRem score

To evaluate the validity of the *DiaRem* score, two independent cohorts were used:

- Scottsdale, Arizona: (Scottsdale Healthcare Bariatric Center, AZ made kindly available by Dr. Robin Blackstone). The remission algorithm was based on the initial 14 months post-surgery as defined in a recent manuscript.[5] The diabetes remission criteria were for partial remission under ADA-recommendations, as follows: diabetes-free > 14 months after RYGB, no antidiabetic medications, HbA1c < 6·0%, and glucose < 125 mg/dL.
- Danville, Pennsylvania, 2nd Geisinger Clinic's cohort: The *DiaRem* score was analyzed using a second sample from Geisinger Clinic's RYGB program who had surgery between 2/16/2011 and 12/31/2011. None of these patients had been used in the original analysis. The diabetes remission criteria were for partial remission under ADA-recommendations, as follows: diabetes-free >14 months after RYGB, no antidiabetic medications, HbA1c < 6·5, and glucose < 125 mg/dL. Basic characteristics of this cohort (termed "PA") (N = 113), and the Arizona cohort (termed "AZ") (N = 276) are presented in Table 1.

For patients within each cohort, the *DiaRem* score was calculated, the patients were categorized into the *DiaRem* groups defined in the primary analysis (0–2, 3–7, 8–12, 13–17, 18–22), and the percent remission within each group was calculated. Cochran-Armitage trend tests were used to confirm that lower *DiaRem* scores were associated with higher chance of remission.

Role of the funding source

The sponsors had no role in the study design, data interpretation, or the writing of the manuscript. The corresponding author had full access to all the data and had final responsibility for the decision to submit the manuscript.

RESULTS

Overall, 436 patients (63%) out of a total of 690 had partial or complete diabetes remission. Based on Kaplan-Meier analysis, the overall remission at 14-months, 2-years, 3-years, 4-years, and 5-years was 49%, 58%, 65%, 66%, and 68%, respectively.

Preoperative use of insulin predisposes to low rates of T2D remission (partial + complete)

Kaplan-Meier survival estimates using the definition of "partial + complete" remission of diabetes according to ADA recommendations, showed that 70·6% T2D patients (i.e., T2D patients not using insulin) had early T2D remission up to 14 months after RYGB, whereas 10·3% of T2D+I patients (i.e., insulin users) had early T2D remission (Tables S1 & S2, Figure 2A). In Cox regression, the hazard ratio comparing T2D+I to T2D was 7·25 (95% CI=[5·52, 9·52], P-value < 0·0001), meaning that T2D+I patients were 7·25 times less likely to have diabetes remission. By the fifth year after surgery, 90·1% T2D patients had T2D remission while 31·1% T2D+I had T2D remission (Figure 2A). Further Kaplan-Meier analysis using the definition of "complete" diabetes remission according to ADA recommendations (Table S3) predicted lower probabilities of remission for patients not taking insulin (42·4%–77·7%, Figure 2B) as well for patients taking insulin (4·4%–15·4%, Figure 2B), compared to the "partial + complete" definition of diabetes remission.

Preoperative prediction of early and late remission in T2D and T2D+I patients

The two subsets of T2D and T2D+I patients were further divided into two groups of early and late remission in order to dissociate in the first group the effects of weight loss. In the T2D group of patients, early remission was correlated with younger age (for each 10 year decrease), low HbA1c (< 6.5%), high insulin levels (> 30 μU/mL), and to a lesser degree with LDL (≥ 125 mg/dL) (Tables 2 and S4). Factors associated with a decreased chance of early remission included combined use of other insulin sensitizing agents (non-metformin) with sulfonylureas and the use of Leukotriene modifiers. Late T2D remission in the T2D group was also correlated with younger age, lower HbA1c, higher insulin levels, and higher % EWL after surgery (for every 10% increase) (Tables 2 and S4). Decreased chance of late remission was associated with combined use of other insulin sensitizing agents (non-metformin) with sulfonylureas. In the T2D+I group of patients, early remission was correlated with younger age, lower HbA1c, the use of an incretin mimetic (defined as use or no use of the incretin), and to a lesser degree to hypertension (Tables 3 and S5). Late remission, in the T2D+I group, was correlated with higher % EWL, younger age, and lower HbA1c (Tables 3 and S5).

Weighting of variables used in predicting T2D remission prior to RYGB surgery

Two preoperative variables, age (every 10 years) and HbA1c (< 6.5%), were associated with both early and late remission of diabetes in all T2D patients irrespective of insulin use. In addition, combined use of an insulin sensitizing agent other than metformin with sulfonylurea (i.e., ISA+Sulf) correlated with both early and late remission in the non-insulin T2D group of patients. These 3 variables (i.e., age, HbA1c, and type of antidiabetic medication), along with preoperative treatment with insulin (defined as use or no use of insulin) were used in a Cox regression model (Table 4). The hazard ratios from this model were used for developing the scoring algorithm that penalized for older age (i.e., 40–90 years: 1 point, 50–59: 2 points, etc.), high HbA1c (i.e., 6.5–6.9: 2 points, 7.0–8.9: 4 points, etc.), use of sulfonylureas and another ISA (3 points), and use of insulin (10 points) which was the heaviest penalty applied (Table 5).

Using the DiaRem score for predicting the probability for T2D remission

We performed Kaplan-Meier estimates over five years to determine the percent (%) probability for T2D remission after RYGB surgery, stratified by the *DiaRem* score into five groups: 0–2 (88%–99%), 3–7 (64%–88%), 8–12 (23%–49%), 13–17 (11%–33%), 18–22 (2%–16%) (Table S6). Low *DiaRem* scores (i.e., the 0–2 grouping) predicted 88%–99% probability for T2D remission, while, high *DiaRem* scores (18–22) predicted low probability for T2D remission (Figure 3A).

In our primary cohort of patients that had remission, 22% had partial and 78% had complete remission. We thus performed further Kaplan-Meier estimates and re-derived the *DiaRem* score over 5-years using our primary cohort and strictly the ADA-recommended criteria only for "complete" remission (Table S7). The *DiaRem* score trended similarly to our standard model of "partial + complete" remissions combined but yielded lower probabilities of remission: *DiaRem* 0–2 (61%–94%), 3–7 (32%–72%), 8–12 (10%–34%), 13–17 (5%–16%), 18–22 (0%) (Figure 3B).

Replication of the DiaRem score

The performance of the *DiaRem* score was evaluated using two geographically independent RYGB cohorts from Scottsdale, Arizona (partial T2D remission: HbA1c <6.0%, no antidiabetic medication) and a new, previously unused, subset from Danville, Pennsylvania (partial T2D remission: HbA1c < 6·5, fasting glucose < 125 mg/dL, no antidiabetic

medications) with data available for the first 14 months after surgery (Table 1). As expected, there were significant differences between *DiaRem* scores within each cohort (Cochran-Armitage trend test, P < 0·0001), while, the *DiaRem* scores of the three (i.e., the primary and the two replication) cohorts trended similarly (Figure 4). When pooling the data from all three cohorts, the predicted probabilities for 14-month remission by the *DiaRem* score, were as follows: *DiaRem* 0–2 (87%), 3–7 (66%), 8–12 (32%), 13–17 (16%), 18–22 (5%), which are close to or within the 5-year *DiaRem* score probability ranges described earlier: *DiaRem* 0–2 (88%–99%), 3–7 (64%–88%), 8–12 (23%–49%), 13–17 (11%–33%), 18–22 (2%–16%).

We also re-derived in the Arizona cohort *DiaRem* scores according to five different definitions of diabetes remission (classified as "partial" according to ADA recommendations) by using fasting glucose levels (FG), and/or HbA1c percent levels, and/or the use of antidiabetic medication, and corresponding to five different remission rates (percent), as follows: [AZ-1 (59·4%): FG <100 mg/dL, no medication, AZ-2 (55·6%): HbA1c <6.0%, no medication, AZ-3 (46·9%): HbA1c <5.7%, no medication, AZ-4 (46·7%): FG <100 mg/dL, HbA1c <6.0%, AZ-5: FG <100 mg/dL, HbA1c <5.7%] at 14 months after RYGB surgery.[5] We found that the *DiaRem* scores trended similarly among the five different remission models (Figure S1).

DISCUSSION

The goal of this study was to develop a simple and accurate method for predicting T2D remission resulting from RYGB surgery using preoperative clinical measures. First, a Cox regression analysis showed that T2D+I patients were 7·25 less likely to have diabetes remission (modeled as "partial + complete" remission combined) and therefore we classified T2D patients into two categories: non-insulin users (T2D) and insulin users (T2D+I). This confirmed a previous report[5], while, the Kaplan-Meier survival estimates showed that only 10·3% of T2D+I patients had early T2D remission compared to the non-insulin using T2D patients of whom 70·6% had early T2D remission. When using the definition of "complete" diabetes remission, the predicted probabilities of remission were even lower for both categories of patients. As a result, our weighting system penalized insulin use with the most severe (highest) score ("10") in the *DiaRem* scoring system. Secondly, we accounted for short- and long-term effects of RYGB on improving T2D remission. In the T2D patients, factors that were associated with increased early remission (partial + complete) were younger age, lower pre-operative HbA1c, also shown by others[22], pre-operative use of less complex therapy, and high pre-operative serum insulin. Increased late remission was associated with the same measures and also with greater postoperative % EWL, which has been associated with T2D remission after RYGB[23]. % EWL, however, was not a strong enough variable in our weighting models and was not included in developing the *DiaRem* score. And neither was preoperative body weight. Preoperative BMI was recently proposed as an inappropriate selection criterion for offering RYGB surgery[24] as a means for resolving diabetes even for patients with low BMI (25–35 Kg/m^2).[25] In agreement with this notion, our weighting system did not find preoperative BMI as a sufficiently strong predictor and therefore it was not included in the *DiaRem* Score.

Long duration of diabetes has been associated with decreased remission rates.[22] Duration of diabetes was not available in our EMR. Age, however, was available and we found that older individuals had lower chances for diabetes remission. We hypothesize that older, severely obese, patients with diabetes may have had the disease for a longer period of time. This is likely to have negative effects on beta cell function and require complex pharmacotherapy including insulin, which as we show here, can significantly diminish remission rates. In the T2D+I group, increased early remission was also associated with younger age, lower pre-operative HbA1c and, for the first time in any group, with pre-

operative use of incretin mimetic agents. We also replicated in the T2D+I group the association of a pre-operative diagnosis of hypertension with decreased early remission, as previously reported.[14, 17]

The *DiaRem* score was thus developed using four preoperative clinical variables and was divided into five groups corresponding to five probability-ranges for T2D remission. It should be noted that the *DiaRem* score predicts T2D remission irrespective of early or late occurrence and includes patients in "partial" remission who may be progressing to "complete" remission. In our cohort with T2D remission, 22% of patients had partial and 78% had complete remission, according to ADA-recommended criteria.[21] The performance of the *DiaRem* score at 14 months was further evaluated in two replication cohorts using the definition of "partial" remission of diabetes. Overall, *DiaRem* scores from the three (i.e., primary and the two replication) cohorts followed similar trends suggesting that the model was faithfully replicated despite of differences in ethnicity, diet, pre- and post-operative management of diabetes, geography/climate, etc. In general, perfect replication probability within an explicit model is usually unattainable because of statistical uncertainty regarding the size of the initial observed effect.[26]

There is some discordance between centers in the use of the definition of diabetes remission depending on the chosen levels of HbA1c, fasting glucose, and the duration of remission.[5, 27] We therefore re-derived Kaplan-Meier estimates using the "complete" definition of diabetes remission which trended similarly to our "partial + complete" model of diabetes remission but predicted lower probabilities. This was to be expected because the former model is more stringent in evaluating improved glycemic control. In addition, we recalculated the *DiaRem* score probabilities in the Arizona cohort at 14 months after surgery using five different definitions of "partial" diabetes remission, which this did not adversely affect the performance of the *DiaRem* algorithm. We favor our primary cohort model of "partial + complete" diabetes remission because it captures the transitory state from partial to complete remission of diabetes and reflects the overall improvement in glycemic control as a result of RYGB surgery.

Our study has some limitations such as the high mean BMI of the primary cohort and that the majority of patients (97%) were White Caucasian. Moreover, the *DiaRem* score was developed only for RYGB surgery. Separate *DiaRem* scores may need to be developed for other types of surgeries such as sleeve gastrectomy. The *DiaRem* score, however, offers for the first time a preoperative tool for predicting diabetes remission after RYGB surgery by using four readily obtainable clinical variables. For example, an individual with a BMI of 39 kg/m^2 and a *DiaRem* score of 22 may benefit in terms of body weight loss but would have low probability of diabetes remission from RYGB surgery, and may thus opt to using intensive lifestyle changes or incretins prior to surgery, which as we show here may improve the odds of remission for individuals taking insulin. Further research is warranted to confirm the preoperative use of incretin mimetics in the improvement of glycemic control after RYGB surgery, as reported here. In conclusion, the *DiaRem* score is a tool for accurately predicting preoperatively the utility of RYGB surgery in remitting diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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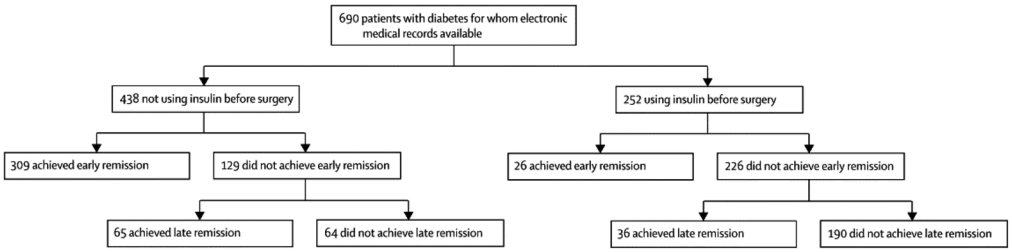

Figure 1. Flow chart describing the patient selection strategy for the Primary cohort

The indicated sample sizes (N) were used for the corresponding type of analysis, before and after stratification by insulin use [i.e., overall remission (partial + complete), predictors of early or late (partial + complete) remission].

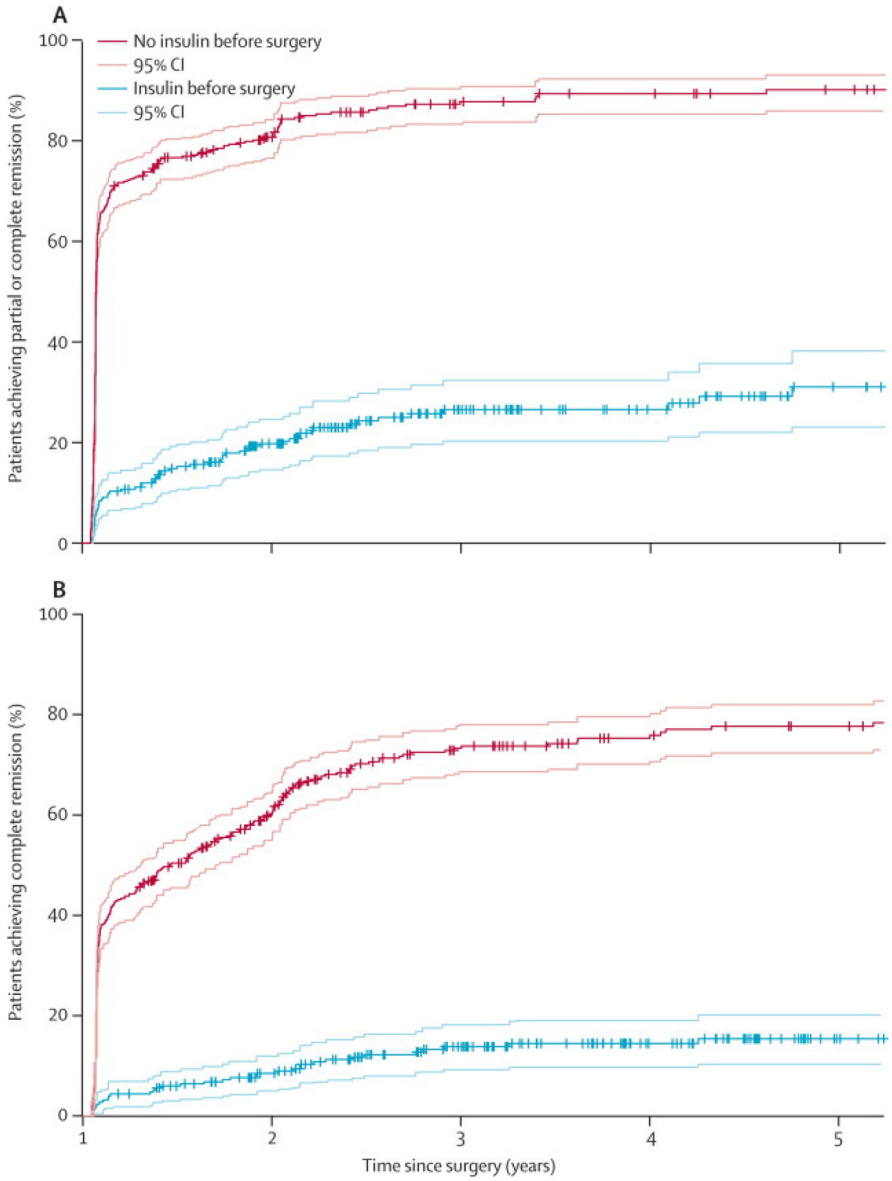

Figure 2. Kaplan-Meier survival estimates with 95% confidence intervals over five years showing the percent (%) number of patients with diabetes remission after RYGB surgery, stratified by pre-operative use of insulin

(**A**) Percent remission according to the definition of "partial + complete" remission of T2D. Patients that were not using insulin preoperatively had a probability range of 70·6%-90·1% for achieving remission of T2D (early or late). T2D patients using insulin preoperatively (T2D+I), on the other hand, had a probability range of 10·3%–31·1% for achieving remission of T2D (early or rate). (**B**) Percent remission according to the definition of "complete" remission of T2D. Patients that were not using insulin preoperatively had a probability range of 42·4%–77·7% for achieving remission of T2D (early or late). T2D patients using insulin preoperatively (T2D+I), on the other hand, had a probability range of 4·4%–15·4% for achieving remission of T2D (early or rate). More cohort information is provided in the Supplemental information section (Tables S1–S3).

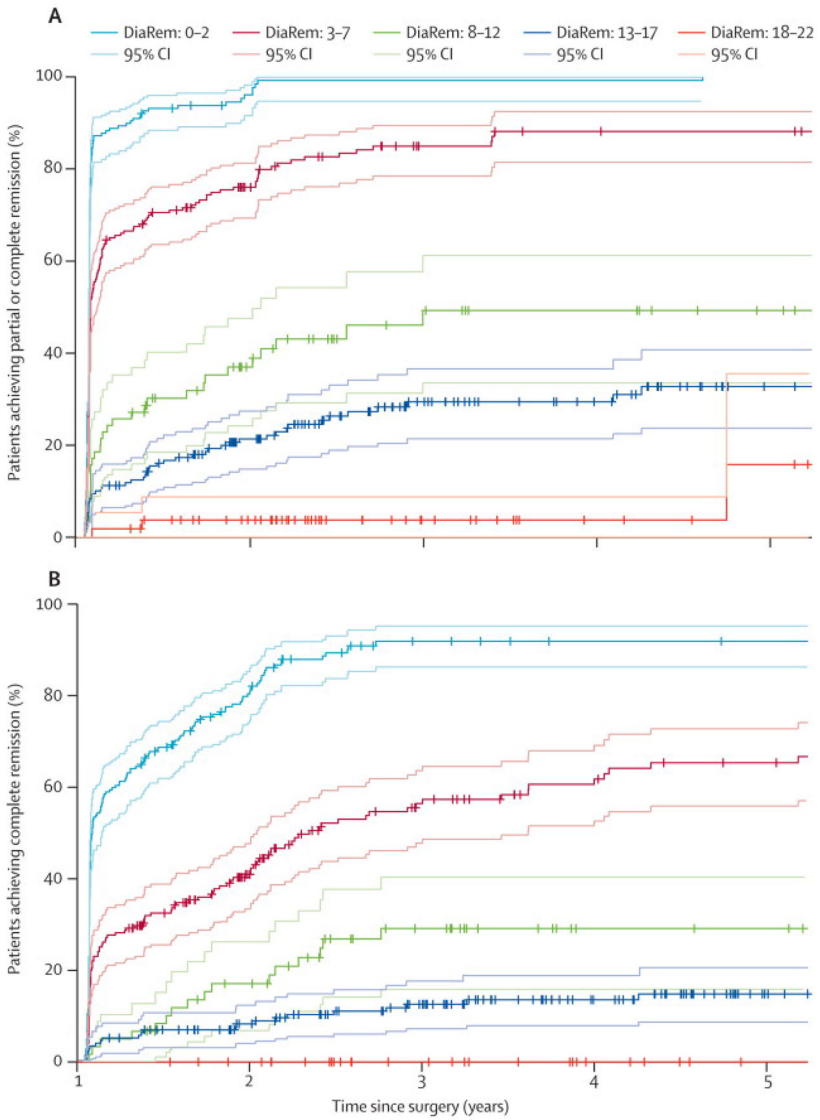

Figure 3. Kaplan-Meier survival estimates with 95% confidence intervals (CIs) over five years showing the percent (%) probability for T2D remission after RYGB surgery, stratified by the *DiaRem* score

(**A**) According to the definitions of "partial + complete" diabetes remission, the lowest *DiaRem* score (i.e., the 0–2 grouping) predicted high probability for T2D remission (88%–99%), while, the highest *DiaRem* score (18–22) predicted low probability for going into T2D remission (2%). Intermediate *DiaRem* scores predicted intermediate probabilities for T2D remission. (**B**) According to the definition of "complete" diabetes remission, the lowest *DiaRem* score again predicted high probability for T2D remission (61%–94%), while, the highest *DiaRem* score predicted no remission (0%). Intermediate *DiaRem* scores predicted intermediate probabilities for remission. Each *DiaRem* score line is shown in black color and the corresponding CIs are shown in alternating dotted or dashed gray lines. More cohort information is provided in the Supplemental information section (Tables S6 & S7).

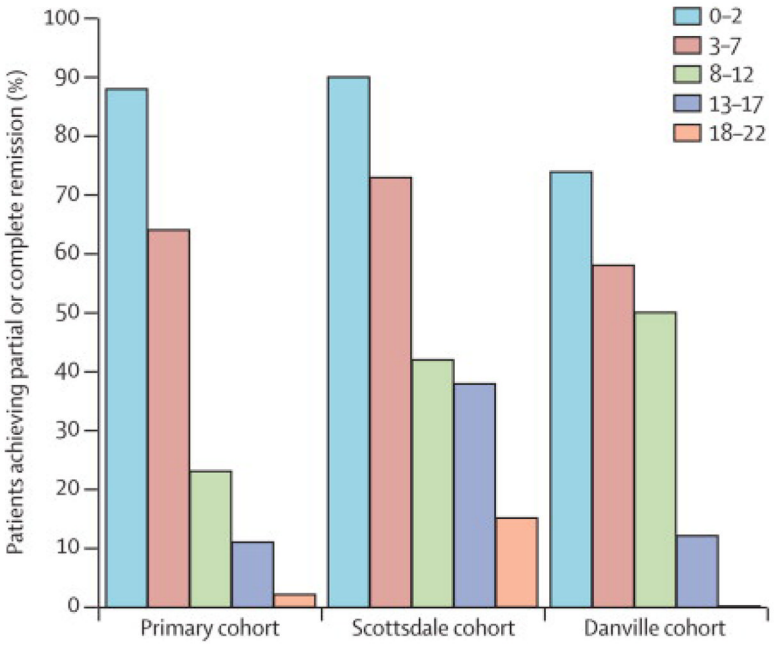

Figure 4. *DiaRem* scores predicting percent (partial + complete) T2D remission in three independent cohorts, 14 months after RYGB surgery

Primary: the main cohort from central Pennsylvania that was used to develop the *DiaRem* score. **AZ**: the first replication cohort from Scottsdale, Arizona. **PA**: the second replication cohort also from Central Pennsylvania. Cochran-Armitage trend tests were used to confirm that lower *DiaRem* scores were associated with higher chance of remission in each cohort ($P < 0{\cdot}0001$). When pooling together the *DiaRem* scores from the three cohorts, the following mean probability ranges were obtained: *DiaRem* 0–2: 87%, 3–7: 66%, 8–12: 32%, 13–17: 16%, 18–22: 5%. Basic characteristics of the three cohorts are provided in Table 1.

Table 1
Demographics and basic characteristics of the primary and replication cohorts

Primary: the primary cohort from central Pennsylvania that was used to develop the *DiaRem* score prediction tool. AZ: the first replication cohort from the Scottsdale area in Arizona. PA: the second replication cohort from central Pennsylvania. The data shown are at 14 months following RYGB surgery, in all three cases. ISA: insulin sensitizing agent. (Age: years; HbA1c: percent; Serum insulin: μU/mL).

	Primary cohort	AZ cohort	PA cohort	P-value
Sample size	690	276	113	-
Geographic location	Central PA	Scottsdale, AZ	Central PA	-
% Female	73%	68%	74%	0·272
% Caucasian	97%	89%	96%	<0·0001
Age (years): <40 (%)	14%	13%	15%	
40–49	30%	34%	32%	0·119
50–59	37%	41%	36%	
60+	19%	11%	17%	
Pre-surgery BMI (kg/m^2), mean (SD)	49·4 (8·3)	48·4 (8·3)	49·5 (9·3)	0·200
HbA1c (%): <6·5	38%	28%	43%	
6·5–6·9	16%	18%	14%	0·056
7·0–8·9	30%	39%	34%	
9·0+	15%	15%	9%	
Metformin use	78%	74%	83%	0·103
Sulfonylureas use	31%	33%	32%	0·851
Other ISA	32%	41%	20%	0·0004
Insulin use	36%	28%	38%	0·032
Serum Insulin (μU/mL): >=30	72%	71%	71%	0·868
DiaRem score: 0–2	27%	18%	27%	
3–7	30%	43%	32%	
8–12	10%	14%	11%	0·0031
13–17	24%	17%	22%	
18–22	8%	7%	8%	

Table 2

Predictors for early and late T2D remission after RYGB surgery for patients not using insulin (T2D) preoperatively

Early remission (partial + complete) was defined by reaching diabetes-free status during the first two months after surgery. Late remission (partial + complete) was defined by reaching diabetes-free status more than two months after surgery. In univariate analysis for early T2D remission, there were 59 variables with p-value < 0·10 (35 with p-values < 0·05). In univariate analysis for late T2D remission, there were 54 variables with p-value < 0·10 (37 with p-values < 0·05). In both events, individual variables were added until the models below were developed. (% EWL: percent excess body weight loss).

Early T2D remission				
		Odds ratio	**95% Confidence interval**	**p-value**
Age (years)	Each 10 year decrease	1·41	[1·10, 1·80]	0·0071
Pre-operative HbA1c (%)	<6·5	11·53	[4·32, 30·79]	<0·0001
	6·5–6·9	6·27	[2·21, 17·77]	0·0006
	7·0–8·9	1·83	[0·70, 4·83]	0·220
	9·0+	Reference	-	-
Pre-operative diabetes medications	Other*	3·13	[1·70, 5·75]	0·0003
	ISA+Sulf‡	Reference	-	-
Serum Insulin (μU/mL)	<17	Reference	-	-
	17–30	1·13	[0·64, 2·02]	0·668
	30+	2·75	[1·43, 5·28]	0·0024
Pre-operative use of leukotriene modifiers	Yes	0·28	[0·11, 0·70]	0·0062
	No	Reference	-	-
Pre-operative LDL (mg/dL)	<125	Reference	-	-
	≥125	2·26	[1·17, 4·38]	0·016
Late T2D remission				
		Hazard ratio	**95% Confidence interval**	**p-value**
Post-op % EWL	Each 10% increase	1·31	[1·18, 1·45]	<0·0001
Age (years)	Each 10 year decrease	1·45	[1·10, 1·92]	0·0085
Pre-operative HbA1c (%)	<6·5	4·73	[1·78, 12·59]	0·0019
	6·5–6·9	1·65	[0·57, 4·79]	0·359
	7·0–8·9	1·98	[0·76, 5·18]	0·165
	9·0+	Reference	-	-
Pre-operative diabetes medications	Other*	2·71	[1·32, 5·56]	0·0064
	ISA+Sulf‡	Reference	-	-
Serum Insulin (μU/mL)	<17	Reference	-	-
	17–30	1·77	[0·96, 3·27]	0·070

Early T2D remission				
		Odds ratio	95% Confidence interval	p-value
	30+	2·13	[1·06, 4·29]	0·035

* Other: none, Metformin (Met) only, Sulfonylurea (Sulf) only, insulin sensitizing agent other than metformin (ISA), Met+Sulf, Met+ISA.

‡ ISA+Sulf: insulin sensitizing agent other than metformin + sulfonylurea therapy combined.

Table 3

Predictors of early and late T2D remission after RYGB surgery for patients using insulin (T2D+I) preoperatively

Early remission (partial + complete) was defined by reaching diabetes-free status during the first two months after surgery and late remission (partial + complete) was defined by reaching diabetes-free status more than two months after surgery. In univariate analysis for early remission, there were 26 variables with p-value < 0·10 (14 with p-values < 0·05). In univariate analysis for late remission, there were 33 variables with p-value < 0·10 (17 with p-values < 0·05). Individual variables were added until the models below were developed. (% EWL: percent excess body weight loss).

Early T2D remission				
		Odds ratio	**95% Confidence interval**	**p-value**
Age (years)	Each 10 year decrease	2·21	[1·32, 3·70]	0·0024
Pre-operative HbA1c (%)	<6·5	6·81	[1·95, 23·86]	0·027
	6·5–6·9	3·20	[0·73, 13·98]	0·122
	7·0–8·9	1·27	[0·37, 4·44]	0·706
	9·0+	Reference	-	-
Hypertension diagnosis	Yes	0·40	[0·16, 0·99]	0·046
	No	Reference	-	-
Use of incretin mimetic agent	Yes	3·61	[1·08, 12·14]	0·038
	No	Reference	-	-
Late T2D remission				
		Hazard ratio	**95% Confidence interval**	**p-value**
Post-op % EWL	Each 10% increase	1·16	[1·05, 1·29]	0·0029
Age (years)	Each 10 year decrease	1·79	[1·20, 2·63]	0·0036
Pre-operative HbA1c (%)	<6·5	3·31	[1·19, 9·18]	0·022
	6·5–6·9	1·67	[0·42, 6·75]	0·469
	7·0–8·9	1·97	[0·81, 4·83]	0·137
	9·0+	Reference	-	-

Table 4

DiaRem score weights with corresponding elements and their hazard ratios (HR) used for weighting each variable contributing to the _DiaRem_ score

The hazard ratios represent failure to remit T2D (partial + complete). The hazard ratio for each *DiaRem* score (or penalty) was as follows: Score=1: Age 40–50 (HR=1·08); Score=2: Age 50–59 (HR=1·31), HbA1c 6·5%–6·9% (HR=1·46); Score=3: Age 60+ (HR=1·78), ISA+Sulf (HR=2·07); Score=4: HbA1c 7·0–8·9 (HR=2·51); Score=6: HbA1c 9+ (HR=3·35); Score=10: Insulin meds (HR=5·90). The Full Cox regression model was used to estimate the hazard ratios using all T2D patients (N=690).

Failure of T2D remission				
		Hazard ratio	**95% Confidence interval**	**P-value**
Pre-operative Insulin medication	Yes	5·90	[4·41, 7·90]	<0·0001
	No	Reference	-	-
Age (years)	<40	Reference	-	
	40–50	1·08	[0·82, 1·41]	0·602
	50–60	1·31	[1·00, 1·73]	0·053
	60+	1·78	[1·27, 2·49]	0·0009
Pre-operative HbA1c (%)	<6·5	Reference	-	-
	6·5–6·9	1·46	[1·12, 1·89]	0·0045
	7·0–8·9	2·51	[1·96, 3·23]	<0·0001
	9·0+	3·35	[2·24, 5·03]	<0·0001
Pre-operative diabetes medications	Other*	Reference	-	-
	ISA+Sulf‡	2·07	[1·50, 2·84]	<0·0001

*Other: none, Metformin (Met) only, Sulfonylurea (Sulf) only, insulin sensitizing agent other than metformin (ISA), Met+Sulf, Met+ISA.

‡ISA+Sulf: insulin sensitizing agent other than metformin + sulfonylurea therapy combined.

Table 5

A pre-operative diabetes remission (*DiaRem*) score predicting the probability of diabetes remission after RYGB surgery

Our analysis identified two variables that were associated with remission (partial or complete) of diabetes in all T2D patients irrespective of insulin use (i.e., age and pre-operative HbA1c). In addition, antidiabetic medication was significantly associated with early as well as late remission in the non-insulin T2D group of patients (i.e., use of ISA+Sulf). These 3 variables and treatment with Insulin were used to develop the *DiaRem* score based on a weighting system for each variable (Table 4). The *DiaRem* prediction score has a range of 0–22 and was stratified into 5 groups: 0–2 (highest probability), 3–7, 8–12, 13–17, 18–22 (lowest probability). ISA: insulin sensitizing agent other than metformin.

Prediction factor		**Score**
Age (years)	If age < 40, enter 0 → If age 40–49, enter 1 → If age 50–59, enter 2 → If age 60+, enter 3 →	
HbA1c (%)	If HbA1c < 6.5, enter 0 → If HbA1c 6.5–6.9, enter 2 → If HbA1c 7.0–8.9, enter 4 → If HbA1c 9.0+, enter 6 →	
Other diabetes medications	If not using sulfonylureas or not using ISA, enter 0 → If on sulfonylureas and ISA, enter 3 →	
Treatment with Insulin	If not using insulin, enter 0 →	
	If using insulin, enter 10 →	
***DiaRem* Score** (sum of individual components) →		