Long-term Relapse of Type 2 Diabetes After Roux-en-Y Gastric Bypass: Prediction and Clinical Relevance

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OBJECTIVE

Roux-en-Y gastric bypass (RYGB) induces type 2 diabetes remission (DR) in 60% of patients at 1 year, yet long-term relapse occurs in half of these patients. Scoring methods to predict DR outcomes 1 year after surgery that include only baseline parameters cannot accurately predict 5-year DR (5y-DR). We aimed to develop a new score to better predict 5y-DR.

RESEARCH DESIGN AND METHODS

We retrospectively included 175 RYGB patients with type 2 diabetes with 5-year follow-up. Using machine learning algorithms, we developed a scoring method, 5-year Advanced-Diabetes Remission (DiaRem) (5y-Ad-DiaRem), predicting longer-term DR postsurgery by integrating medical history, bioclinical data, and antidiabetic treatments. The scoring method was based on odds ratios and variables significantly different between groups. This score was further validated in three independent RYGB cohorts from three European countries.

RESULTS

Compared with 5y-DR patients, 5y-Relapse patients exhibited more severe type 2 diabetes at baseline, lost significantly less weight during the 1st year after RYGB, and regained more weight afterward. The 5y-Ad-DiaRem includes baseline (diabetes duration, number of antidiabetic treatments, and HbA_{1c}) and 1-year follow-up parameters (glycemia, number of antidiabetic treatments, remission status, 1st-year weight loss). The 5y-Ad-DiaRem was accurate (area under the receiver operating characteristic curve [AUROC], 90%; accuracy, 85%) at predicting 5y-DR, performed better than the DiaRem and Ad-DiaRem (AUROC, 81% and 84%; accuracy, 79% and 78%, respectively), and correctly reclassified 13 of 39 patients misclassified with the DiaRem. The 5y-Ad-DiaRem robustness was confirmed in the independent cohorts.

CONCLUSIONS

The 5y-Ad-DiaRem accurately predicts 5y-DR and appears relevant to identify patients at risk for relapse. Using this score could help personalize patient care after the 1st year post-RYGB to maximize weight loss, limit weight regains, and prevent relapse.

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Bariatric surgery (BS) is recommended for patients with a BMI $\geq$40 kg/m^2 or $\geq$35 kg/m^2 when associated with comorbidities (1), induces major weight loss (2,3), improves glycemic control, and induces partial or complete diabetes remission (DR) (4). DR is defined by fasting plasma glucose (FPG) and HbA_{1c} normalization ($<$7 mmol/L and $<$6% [42 mmol/mol], respectively) without any glucose-lowering medication at 1 year post-BS (5).

BS is superior to intensive medical therapy (i.e., medication and/or lifestyle interventions alone [6,7]) in inducing DR (8,9), with 60–75% of post-Roux-en-Y gastric bypass (RYGB) patients experiencing remission. Therefore, recent guidelines consider BS/metabolic surgery in the type 2 diabetes (T2D) treatment algorithm for obese patients with lower BMIs (i.e., BMI $\geq$30 kg/m^2 with poor glycemic control) (9,10). Experts thus anticipate a dramatic surge in the already large number of BS interventions worldwide (1).

Currently, there is a major concern in the mid- to long-term maintenance of glycemic control post-BS, because observational long-term follow-up studies and randomized controlled trials (8,11,12) indicate a decreased rate of DR over time. Nearly half of the patients experiencing DR at 1 year relapse 5 years post-RYGB, with a described mean DR rate of 30%. These relapses are frequently concomitant with weight regain and the deterioration of lipid homeostasis after 1 year (13). These observations signal the need to establish useful and clinically applicable tools to predict metabolic/BS outcomes (9), both in the short- and longer-term post-BS. Using these tools, we inform patients about what they can expect and adapt patient follow-up according to predicted trajectories.

Scoring systems to predict 1-year DR (1y-DR) generally combine clinical variables mostly related to diabetes severity (14–17). For example, the ABCD score (combining Age, BMI, C-peptide, and Duration of T2D) (15,18) predicts that patients with a score $>$6 will not enter 1y-DR; however, our team demonstrated that the ABCD score was less accurate than the Diabetes Remission (DiaRem) score (19). The DiaRem, based on preoperative age, HbA_{1c}, and the use of glucose-lowering treatments, has 84% predictive accuracy for DR 1 year post-RYGB, but its predictive accuracy is limited in the middle scoring zone (8–17) (19,20). We recently improved the DiaRem predictive performance by proposing the Advanced DiaRem (Ad-DiaRem) (21), which adds diabetes duration and the number of glucose-lowering agents, including new antidiabetic agents, and optimizes the weight of each item used in the DiaRem (21). The Ad-DiaRem, developed to predict 1y-DR post-RYGB, remains to be tested beyond 1 year of follow-up.

Only a limited number of studies have tested the DiaRem in cohorts with T2D beyond 1 year post-RYGB (22). In 400 patients with T2D, the DiaRem accurately predicted patients with nonremission after 1-year post-RYGB (i.e., all patients with a score $>$18), but its predictive performance was modest for longer-term DR (5–8 years). Only 50% of the patients with the lowest DiaRem score (0–2) exhibited DR after 8 years (23). When tested in another group, 20% of patients with scores $>$18 experienced 5-year DR (5y-DR), showing a poor predictive value even in high DiaRem scores (22). Another study with 31 patients with T2D monitored 10 years post-RYGB showed that 30% of patients with 5y-DR exhibited a DiaRem score falling into the "middle zone," further highlighting the insufficient predictive accuracy for long-term outcomes (24).

These collective findings prompted us to *1*) characterize factors involved in 5y-DR and T2D relapse post-RYGB, *2*) build an improved scoring system capable of identifying 5y-DR and non–5-year DR (5y-NDR), and *3*) examine the clinical relevance of this new established scoring system in independent cohorts.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This study included a subselection of patients from our prospective BS cohort (Bariatric Surgery Cohort of Institute of Cardiometabolism and Nutrition [BARICAN], *N* = 2,229 patients) at the Pitié-Salpêtrière Hospital Nutrition Department (Paris, France), which is approved by CNIL (Commission nationale de l'informatique et des libertés; No. 1222666) and the French Ministry of Research. All patients provided informed consent. They are part of several studies registered on clinicaltrials.gov (P050318 Les Comités de Protection des Personnes [CPP] approval: 24 November 2006, NCT01655017, NCT01454232). These patients met standard BS recommendations (25) and are monitored according to national and international guidelines.

In the current study, we focused solely on severely obese patients with T2D who underwent RYGB and had a mean follow-up of 5 years. We further restricted our analysis to patients with complete clinical data sets pre-BS and 3, 6, 12 months and 5 years (48–84 months) post-RYGB (*n* = 175) (Supplementary Fig. 1). In addition to the BARICAN cohort, we had access to three confirmation cohorts, which were composed of patients with T2D who underwent RYGB with 5 years of follow-up and for whom the data needed for score calculation was available. These cohorts consisted of 54 patients in France (Louis Mourier Hospital), 20 patients from a randomized controlled trial in Italy (Catholic University) (8), and 50 patients from Germany (Leipzig Hospital). Patients from all cohorts provided informed consent.

Bioclinical and Anthropomorphic Variables

The following data were collected for all patients at every time point, as described (21): the number of glucose-lowering agents, obesity-related comorbidities (hypertension, obstructive sleep apnea, and dyslipidemia), a complete list of treatments, diabetes duration (i.e., duration up to RYGB intervention), blood tests, including lipid panels, liver enzymes, and glucose control (at baseline after a 12-h overnight fast), body composition (total, trunk and limb-fat mass, fat-free mass) evaluated by body DEXA scan (Hologic Discovery, West Bedford, MA), as previously described (26), and depression and anxiety questionnaires (Hospital Anxiety and Depression Scale [27] and Beck Depression Inventory [28]). Weight loss was calculated at each time point using the following formula: (postoperative body weight − preoperative body weight)/preoperative body weight. We used the same approach to quantify body composition changes (in kg and percentages), HbA_{1c}, and fasting glycemia. We calculated the DiaRem (20) and Ad-DiaRem (21) for these patients.

Using Machine Learning to Devise the 5y-Ad-DiaRem

Using previously described methods (21), we applied an original machine learning methodology (29) to establish

the 5y-Ad-DiaRem. We aimed to find *1*) the most relevant predictive variables, *2*) optimal thresholds per selected variable (i.e., [4.8_5.3_5.8] for the 1-year fasting glycemia) to construct bins (intervals between two thresholds), and *3*) the subscores associated with each bin of patients. An optimal solution occurs if simultaneously learned interpretable binning is mapped to a class variable (5y-DR or NDR) and the weights associated with these bins contribute to the score. We applied a novel statistical machine learning approach called "Fully Corrective Binning" (29). Herein, the problem to learn a score was formulated as a feature selection task, where splitting a bin equates to adding a feature into a model and merging two bins results in deleting a feature from this model. This approach aims to compromise the trade-off between accuracy and sparsity (i.e., the number of bins). The Youden (30) method was used to calculate the thresholds.

Statistical Analyses

Continuous variables are expressed as mean ± SD and categorical variables as numbers (percentages). Baseline comparisons were performed by ANCOVA with the effect of sex and age as covariates. Multivariate logistic regression was performed to estimate odds ratios for the potential predictors of 5-year relapse and/or nonremission. Continuous data of patients in nonremission throughout the follow-up were compared using the Wilcoxon signed rank test. Categorical data were analyzed using χ^2 tests for trends.

To build the 5y-Ad-DiaRem, the missing data were imputed by the median of each variable (29). Analyses were conducted using R 3.3.3 software (www.r-project.org). *P* values were considered significant when <0.05.

RESULTS

Long-term Follow-up of Patients With T2D Post-RYGB

Our test cohort included 175 patients with T2D whose characteristics are summarized in Table 1. As shown in Fig. 1*A*, 61% of severely obese patients with T2D experienced DR (partial [PDR] or complete remission [CDR]) at 1-year post-RYGB. After a mean 5.1 ± 0.7 years of follow-up, DR prevalence decreased to 54% (5y-DR). Thus, 25% of 1y-DR patients (n = 27) relapsed at 5 years post-RYGB (5y-Relapse). In addition, 54 patients (31%) never displayed DR throughout the follow-up (5y-NDR), and 15 patients (22%) who remained with T2D at 1y-NDR further experienced 5y-DR.

We examined patients' bioclinical differences among the three different trajectories: *1*) 5y-NDR, *2*) 5y-Relapse, and *3*) 5y-DR (PDR and CDR). Compared with 5y-NDR, 5y-Relapse patients (Table 1) and 5y-DR patients had similar baseline characteristics, except they displayed a less severe degree of T2D disease: shorter diabetes duration, fewer glucose-lowering agents, fewer insulin therapy requirements, and better T2D control (i.e., HbA_{1c} near the targeted goal of $<$7% [53 mmol/mol]). At baseline, more patients undergoing 5y-remission or later relapse were solely on metformin. By contrast, the use of glucagon-like peptide 1 analogs increased across the three trajectory groups during the follow-up; however, this reflected more severe T2D because patients received multiple glucose-lowering agents (Table 1). The 5y-DR patients were more likely to be women and heavier at baseline, with increased total fat mass but lower trunk fat mass, thus displaying a better body composition. Noteworthy, 27% of patients were taking psychotropic drugs at baseline; however, between trajectory groups, there were no differences in the number of patients treated with these drugs or in the mean prescribed treatment number. Likewise, no difference was seen in scores on the Hospital Anxiety and Depression Scale or Beck Depression Inventory questionnaires (Supplementary Fig. 2 and Supplementary Table 1). These results suggest that depression scores and treatment were not involved in diabetes outcomes post-RYGB.

Lack of Accuracy of Current Scores to Predict 5y-DR

The DiaRem and Ad-DiaRem (20,21) scores' mean values were higher in patients with 5y-NDR than those of 5y-Relapse or 5y-DR patients. As shown on Fig. 1*B* and Supplementary Fig. 3*A*, both scores were unable to properly separate patients' trajectories, displaying a large overlap between 5y-DR, 5y-Relapse, and 5y-NDR patients, especially for scores in the "middle zone" (8–17). Most 5y-Relapse patients had Ad-DiaRem scores $<$10, as expected, because they experienced 1y-DR. Importantly, whereas we confirmed that the DiaRem and Ad-DiaRem performed well at predicting 1-year post-RYGB DR, they failed to accurately predict 5y-DR. The DiaRem and the Ad-DiaRem displayed nonsignificantly different accuracies (79% and 78%, respectively) and areas under the receiver operating characteristic curve (AUROC) (81% and 84%, respectively) at predicting 5y-DR (Fig. 1*C* and Supplementary Table 2). Interestingly, although the Ad-DiaRem was inefficient at properly separating 5y-DR and 5y-Relapse patients, it was robust at classifying patients in 5y-NDR, because nearly all the patients with a score ≥15 remained with T2D at 5 years (Fig. 1*B*).

Body Composition and Glucose Control at 1 Year Are Discriminant for Long-term DR

Because current scores only combining baseline variables were insufficient to accurately predict 5y-DR, we examined the variations of bioclinical variables during the 1st year postsurgery to identify the most discriminant factors between the three trajectory groups (5y-NDR, 5y-Relapse, and 5y-DR). Although 5y-DR patients were heavier at baseline, they lost significantly more weight, total fat, and trunk fat mass at 6 and 12 months post-RYGB compared with 5y-NDR patients (Fig. 1*D*, Table 1, and Supplementary Fig. 3*B*). 5y-DR patients lost more limb fat mass and gained more limb fat-free mass (relatively to body weight), suggesting improved body composition. Contrarily, 5y-Relapse patients lost less weight and less total, limb fat, and trunk fat compared with 5y-DR patients (adjusted for age and sex). Losing less weight during the 1st year was more associated with being in 5y-Relapse compared with 5y-DR (odds ratio [OR] 2.66, $P < 0.05$), but not to 5y-NDR (OR 0.63, $P = 0.13$). Whereas 5y-DR and 5y-NDR had limited but significant body weight regains between 1 and 5 years post-RYGB (+2.5% each, $P < 0.05$), 5y-Relapse patients displayed a significant and more pronounced weight regain over the same period (+8%, $P < 0.001$), including regaining fat mass, which resulted in patients reaching their baseline percentage fat-mass level ($P < 0.05$).

We also observed that glucose control during the 1st year was associated with 5y-DR post-RYGB. Although the three

Table 1—Baseline characteristics of our BARICAN cohort (test cohort)

	Patient T2D status at 5 years after RYGB				
	5y-DR *n* = 94	5y-Relapse *n* = 27	5y-NDR *n* = 54	*P*	Adjusted *P*
Before surgery					
Male, *n* (%)	19 (20.2)	7 (25.9)	13 (24.1)	0.76*	—
Age (years)	46.5 ± 11.0	46.3 ± 8.6	52.4 ± 8.8	0.006	<0.001
Body weight (kg)	132.4 ± 23.8	127.5 ± 15.2	123.5 ± 21.0	0.13	0.09
BMI (kg/m^2)	48.7 ± 7.6	46.0 ± 6.4	45.7 ± 7.3	0.09	0.08
Body composition					
Fat mass (%)	49.2 ± 5.0	46.8 ± 5.5	46.9 ± 5	0.05	0.004
Fat-free mass (%)	48.7 ± 4.8	51.0 ± 5.4	50.8 ± 4.9	0.07	0.005
Android/gynoid fat mass ratio	2.1 ± 0.5	2.2 ± 0.5	2.4 ± 0.6	0.08	0.046
Diabetes condition					
T2D duration (years)	3.5 ± 4.1	5.1 ± 4.0	12.4 ± 6.8	<0.001	<0.001
Number of antidiabetic drugs, *n*	1.1 ± 1.1	1.8 ± 0.8	2.6 ± 1.0	<0.001	<0.001
Number of patients under					
Metformin only, *n* (%)	29 (30.9)	6 (22.2)	3 (5.6)	0.01*	—
Glucagon-like peptide 1 analogs, *n* (%)	3 (3.2)	4 (14.8)	13 (24.1)	0.002*	—
Sulfamides, *n* (%)	0 (0)	1 (3.7)	10 (18.5)	<0.001*	—
Glitazones, *n* (%)	7 (7.4)	0 (0)	3 (5.6)	0.37*	—
Patients requiring insulin, *n* (%)	6 (6.4)	4 (14.8)	35 (64.8)	<0.001*	—
Fasting glycemia (mmol/L)	7.4 ± 2.1	7.8 ± 2.8	8.8 ± 3.2	0.03†	0.03†
HbA_{1c}, %	7.0 ± 1.1	7.2 ± 1.3	8.6 ± 1.9	<0.001†	<0.001†
HbA_{1c}, (mmol/mol)	53 ± 12	55 ± 14	70 ± 21	<0.001†	<0.001†
Patients with HbA_{1c} <7%, *n* (%)	55 (58.5)	16 (59.3)	6 (11.1)	<0.001*	—
Diabetes remission scores					
DiaRem (20)	4.9 ± 3.5	7.1 ± 6.2	14.1 ± 5	<0.001	<0.001
Ad-DiaRem (21)	6.5 ± 3.6	8.0 ± 4.7	15.1 ± 3.5	<0.001	<0.001
DiaBetter (42)	2.8 ± 2.1	3.3 ± 2.6	6.6 ± 2.4	<0.001	<0.001
Comorbidities					
Patients with hypertension, *n* (%)	63 (67.7)	16 (59.3)	45 (84.9)	0.03*	—
Number of antihypertension drugs, *n* (%)	1.1 ± 1.1	0.9 ± 1.1	1.5 ± 1.0	0.09	0.04
Patients with dyslipidemia, *n* (%)	78 (83.0)	23 (88.5)	48 (88.9)	0.56*	—
Antidyslipidemia drugs, *n*	0.4 ± 0.5	0.5 ± 0.5	0.7 ± 0.4	0.0001	<0.001
Patients with sleep apnea, *n* (%)	64 (68.1)	18 (66.7)	42 (77.8)	0.43*	—
Body composition changes 1 year post-RYGB					
Body weight (%)	−29.3 ± 7.0	−22.7 ± 8.0	−24.9 ± 7.0	<0.001	<0.001
% loss of kg fat mass	−42.0 ± 11.5	−33.3 ± 11.6	−36.8 ± 11.5	0.01	0.01
% loss of kg fat-free mass	−15.0 ± 5.4	−12.1 ± 7.2	−13.0 ± 5.8	0.1	0.09
% gain of initial fat-free mass	18.8 ± 9.1	12.9 ± 7.1	14.8 ± 7.7	0.01	0.01
% loss of % limbs fat mass	−12.5 ± 13.3	−5.1 ± 11.8	−11.5 ± 10.8	0.1	0.1
% gain of % limbs fat-free mass	23.4 ± 13.1	17.5 ± 9.4	16.1 ± 11.0	0.01	0.01
% loss of % trunk fat mass	−47.6 ± 13.1	−40.4 ± 13.8	−41.3 ± 13.2	0.04	0.04

The three trajectories (5y-NDR, 5y-Relapse, and 5y-DR) after RYGB were compared at baseline according to participants' 5y-DR outcomes. Variables are presented as mean ± SD or as *n* (%), and *P* values are shown before and after adjustment for age and sex. The predictive scores were computed as specified in the original publications (20,21,38). Body composition changes during the 1st year were calculated as follows: [(1-year value) − (baseline value)]/(baseline value) × 100. *χ^2 test *P* value results for categorical variables. †The number of antidiabetic medication was included in the regression model.

groups improved their T2D, 1-year HbA_{1c} and 1-year FPG values were associated with 5y-NDR (OR 3.63 [$P < 0.001$] and 5.64 [$P < 0.001$]) compared with 5y-DR, respectively) (Table 2 and Supplementary Table 3). However, these clinical variables were not associated with T2D relapse. As expected, 1y-DR status also influenced the 5-year status: being in PDR at 1-year was a risk factor for T2D relapse (OR 5.26, 95% CI 2.1–14.2, $P < 0.001$); likewise, most of the 1y-NDR patients at 1-year remained NDR at 5 years (OR 9.80, 95% CI 4.8–21.1, $P < 0.001$).

Predicting 5y-DR With the 5y-Ad-DiaRem

To develop our new clinical score, for subsequent use in routine care, we selected the most easily accessible clinical variables among those that significantly differed between the three groups at baseline or 1-year post-RYGB, based on their OR values for being placed in the 5y-Relapse or 5y-NDR groups with 5y-DR as reference (Table 2 and Supplementary Table 3). Hence, the following variables were included: baseline diabetes duration (OR 1.48 [5y-Relapse vs. 5y-DR] and OR 6.73 [5y-NDR vs. 5y-DR]), baseline number of glucose-lowering agents (OR 1.85 and 4.98), baseline HbA_{1c} (OR 1.19 and 6.69), 1-year remission status, 1-year FPG (OR 1.16 and 1.95), 1-year number of glucose-lowering agents, and weight loss percentage from baseline to 1 year. Furthermore, random forest analysis evaluated the effect of each of those variables

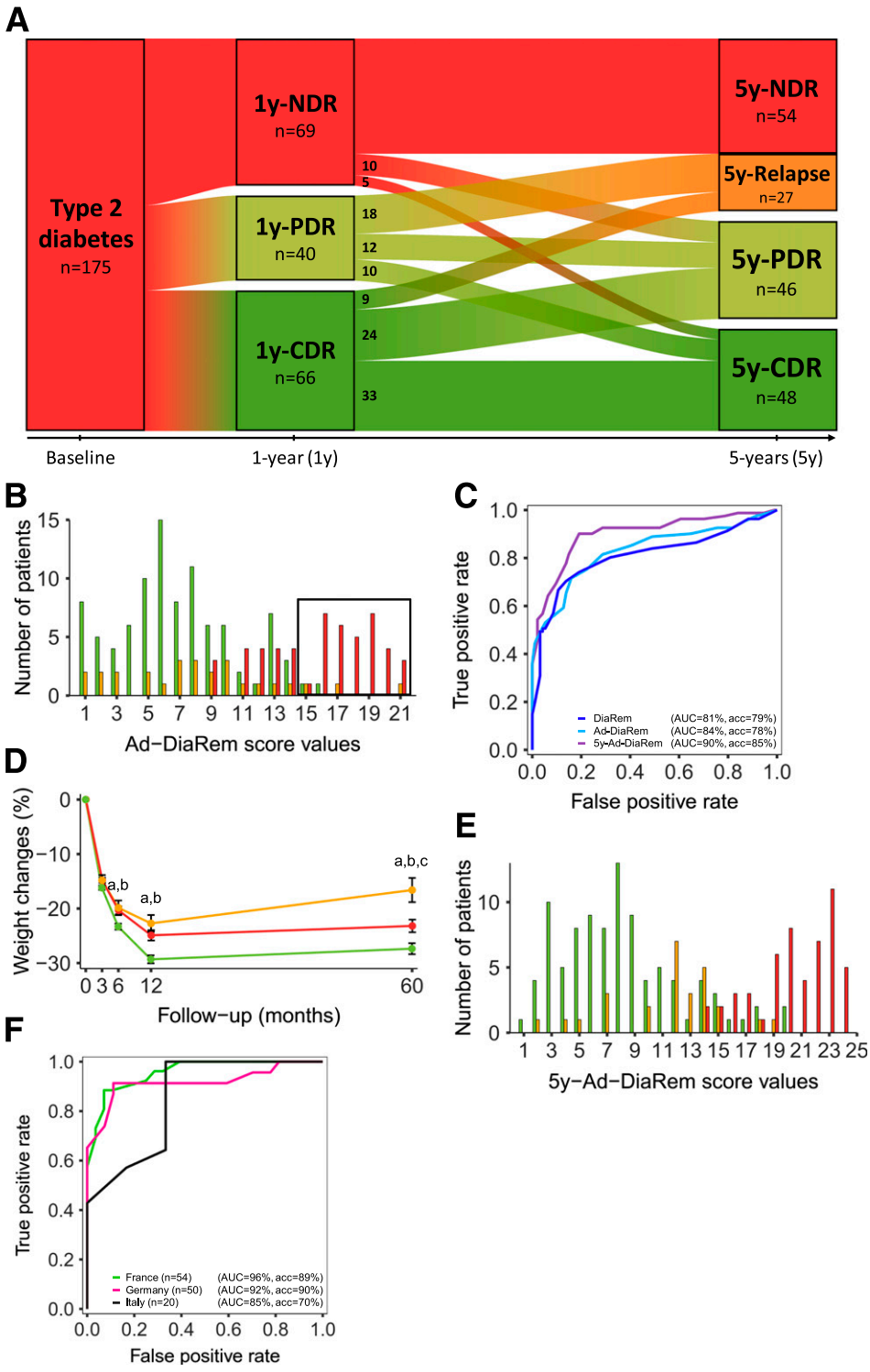

Figure 1—Evolution of T2D status throughout the follow-up in the test cohort, Ad-DiaRem patients distribution, and development of the 5y-Ad-DiaRem scores in the test cohort (n = 175) and three validation cohorts from France (n = 54), Italy (n = 20), and Germany (n = 50. *A*: Evolution of the T2D status in the 175 patients from the test cohort, before, 1 year, and 5 years after RYGB. DR was defined according to American Diabetes Association criteria (5). Patients were initially considered exhibiting T2D if they had HbA_{1c} ≥6.5% (≥48 mmol/mol), FPG ≥126 mg/dL (7.0 mmol/L) or ≥200 mg/dL (11.1 mmol/L) 2 h after ingesting 75 g of glucose during an oral glucose tolerance test, or if they were taking any anti-T2D medication. After RYGB, PDR was defined as HbA_{1c} <6.5% (<48 mmol/mol), FPG <7.0 mmol/L without the need of glucose-lowering agents at 1 year; CDR as HbA_{1c} <6.0% (<42 mmol/mol), FPG <5.6 mmol/L without glucose-lowering agents at 1 year. Patients who did not fit in either PDR or CDR were considered in NDR. *B*: Distribution of the 175 patients in the test cohort according to their Ad-DiaRem scores. The black border represents the zone where the Ad-DiaRem is ≥15, in which most patients are accurately predicted to be in 5y-NDR. *C*: ROC curves evaluating the performance of the DiaRem, the Ad-DiaRem and the 5y-Ad-DiaRem in the test cohort, to separate patients in 5y-DR from those in nonremission 5 years after RYGB. *D*: Weight loss dynamics during the follow-up. *E*: Distribution of the 175 patients in the test cohort according to their 5y-Ad-DiaRem score values. *F*: ROC curves evaluating the performance of the 5y-Ad-DiaRem in the three validation cohorts to separate patients in 5y-DR from those in NDR 5 years after RYGB. acc, accuracy; AUC, area under the curve. In panels *A*, *B*, *D*,

Table 2—Standardized ORs evaluating the risk of undergoing 5y-Relapse and/or remain in nonremission

	Risk of 5y-Relapse compared with 5y-DR*			Risk of 5y-NDR compared with 5y-Relapse*			Risk of 5y-NDR compared with 5y-DR*		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Baseline variables									
Fasting glucose (mmol/L)	1.16	0.75–1.74	0.61	1.41	0.83–2.55	0.31	1.95	1.34–2.95	0.002
HbA_{1c} (%)	1.19	0.78–1.79	0.53	4.88	2.09–13.79	0.004	6.69	3.5–14.44	<0.001
Number of anti-T2D treatments	1.85	1.19–2.96	0.04	3.51	1.85–7.65	0.002	4.98	2.98–9.13	<0.001
Insulin usage (yes/no)†	2.57	0.61–9.85	0.30	13.69	4.00–61.98	<0.001	47.81	15.57–187.96	<0.001
Age (years)	0.97	0.63–1.50	0.96	2.06	1.26–3.58	0.02	1.89	1.30–2.85	0.004
T2D duration (years)	1.48	0.94–2.35	0.18	5.32	2.32–15.24	0.002	6.73	3.66–13.93	<0.001
Sex (male/female)†	1.39	0.49–3.70	0.62	0.79	0.26–2.48	0.81	1.22	0.52–2.80	0.70
Kinetic variables during the 1st year‡									
Weight lost (% baseline)	2.66	1.62–4.66	0.01	0.63	0.37–1.03	0.13	1.72	1.18–2.60	0.01
Fat mass lost (% baseline)	2.23	1.25–4.33	0.04	0.61	0.33–1.06	0.15	1.31	0.89–1.97	0.23
Fat-free mass lost (% baseline)	0.42	0.21–0.76	0.04	1.48	0.87–2.65	0.24	0.64	0.42–0.95	0.05
Trunk fat mass lost (% baseline)	0.75	0.45–1.23	0.37	1.03	0.59–1.80	0.97	0.77	0.51–1.14	0.24
1-year variables									
Fasting glycemia (mmol/L)	1.28	0.82–1.97	0.37	2.17	1.16–4.75	0.07	2.40	1.60–3.83	<0.001
HbA_{1c} (%)	1.01	0.64–1.56	1.00	5.64	2.40–16.87	0.002	3.63	2.25–6.31	<0.001
Number of anti-T2D treatments	—	—	—	—	—	—	20.50	(8.1–72.04)	<0.001
Scores†									
DiaRem (20)	1.11	1.01–1.22	0.06	1.26	1.14–1.43	<0.001	1.54	1.36–1.81	<0.001
Ad-DiaRem (21)	1.12	1–1.27	0.12	1.51	1.28–1.87	<0.001	1.84	1.55–2.32	<0.001
5y-Ad-DiaRem	1.21	1.09–1.35	0.01	3.21	1.89–8.53	<0.001	1.94	1.57–2.63	<0.001

The variables were standardized using the following formula: $z_i = (x_i - \mu)/\sigma$ where μ represents the variable's mean and σ its SD. Sex and age were included in the regression model. See Supplementary Table 3 for the nonstandardized version of these ORs. *The group of patients was used as the reference. †Nonstandardized ORs. ‡Evolutions during the 1st year were calculated using the following formula: [(1-year value) − (baseline value)]/(baseline value) × 100.

in 5y-DR (Supplementary Fig. 4), the most important of which were diabetes duration and weight loss amount.

We then applied machine learning methods to optimize the score (31). As previously described (21), we applied the Fully Corrective Binning approach to attribute the optimal intervals and weight for each variable. This approach led us to identify the optimal score for predicting 5y-DR, called "5y-Ad-DiaRem" that is to be calculated at 1-year postsurgery (Table 3). An online tool allowing easy calculation of the score can be found at http://5y-Ad-DiaRem.nutriomics.org. Patients' repartition according to their scoring is shown in Fig. 1*E*. The 5y-Ad-DiaRem displayed a better negative predictive value (90% vs. 82%) and positive predictive value (80% vs. 67%) than the DiaRem and reassigned 13 of 39 patients misclassified with the DiaRem (i.e., score ≥7 while undergoing 5y-DR, or a <7 while being in 5y-NDR). Thus, the 5y-Ad-DiaRem displayed increased accuracy (85% vs. 79%) and sensitivity (90% vs. 72%), but the specificity remained unchanged compared with the DiaRem (Supplementary Table 2). Importantly, the 5y-Ad-DiaRem had very good accuracy (>90%) for scores ≤11 to predict long-term remission and >18 to predict long-term nonremission.

To evaluate the relevance of the 5y-Ad-DiaRem in a wide range of patients reflecting routine clinical care in different European countries, we tested the score's validity in three independent cohorts whose characteristics are summarized in Supplementary Tables 4–6. Whereas, the French cohort was similar to the original BARICAN cohort, the German cohort was older and more obese, and the Italian cohort was younger yet consisted of patients with more severe T2D who were mostly men. In the French confirmation cohort, the 5y-Ad-DiaRem performed better than the DiaRem and Ad-DiaRem in predicting 5y-DR (accuracy 89%, specificity 88%, sensitivity 89%, and AUROC 90%) (Fig. 1*F*, Supplementary Fig. 5*A*, and Supplementary Table 2). In the other two independent cohorts, the accuracy and AUROC (70% and 85% in the Italian cohort and 90% and 91% in the German cohort, respectively) to predict long-term remission were excellent and confirmed the robustness of our new score in a wide range of BMI and T2D severity stages (Supplementary Fig. 5*B* and *C* and Supplementary Table 2).

Clinical Relevance of the Scoring System for Relapse and Nonremission Patients

Whereas the 5y-Ad-DiaRem accurately predicts longer-term DR post-RYGB, we examined its clinical relevance for patients predicted to remain T2D or to relapse at 5 years postsurgery. As displayed in Fig. 1*E*, most of the 5y-Relapse patients were correctly classified, with a score >11 (i.e., the fixed 5y-DR threshold). Yet, eight patients who further

and *E*, green represents patients in 5y-DR; orange, those who relapsed after a transient remission; and red, those who remained with T2D during the post-RYGB follow-up. Panels *A* and *E* represent the number of patients for each value of the score (Ad-DiaRem in *A* and 5y-Ad-DiaRem in *E*). In panel *D*, the letter a means statistical difference ($P < 0.05$) between 5y-DR and 5y-NDR, b between 5y-DR and 5y-Relapse, and c between 5y-NDR and 5y-Relapse.

Table 3—5y-Ad-DiaRem scoring system

	Values
Preoperative prediction factors	
T2D duration (years)	
<1	0
[1; 3[	1
[3; 5[	2
[5; 7[	3
≥7	4
Number of antidiabetic medications*	
0	0
1	1
2	3
≥3	4
HbA_{1c} (%)†	
<6.3	0
[6.3; 6.9[	1
≥6.9	3
Postoperative (1-year) prediction factors	
Number of antidiabetic medication*	
0	0
1	1
≥2	4
Fasting blood glucose (mmol/L)	
<4.8	0
[4.8; 5.3[	1
[5.3; 5.8[	2
≥5.8	3
Body weight lost from baseline (%)‡	
< −34%	0
[−34; −25[%	1
[−25; −20[%	2
≥ −20%	3
1-year remission status§	
DR	0
PDR	3
NDR	5
Overall score (sum of the 7 factors)	0–26
≤11 predicts long-term remission	
≥18 predicts long-term nonremission	

The 5y-Ad-DiaRem can be easily computed using an online tool accessible on our website (http://5y-Ad-DiaRem.nutriomics.org). Based on clinical values, the tool determines the score and gives information about the predicted outcome. "[ ]" includes the value, whereas "[[" does not. *Includes all antidiabetic treatments, regardless of pharmacological class (insulin included). †HbA_{1c} values in mmol/mol are as follows: 6.3% is equal to 45 mmol/mol, [6.3; 6.9[% = [45; 52[, and 6.9% represents 52 mmol/mol. ‡The weight loss during the 1st year is calculated using the following formula: [(1-year body weight) − (baseline body weight)]/(baseline body weight) × 100. §DR was defined according to American Diabetes Association criteria (5).

relapsed had a score <11 and thus were misclassified. Interestingly, compared with 5y-DR patients, these eight patients had a well-controlled diabetes at baseline (i.e., 100% with HbA_{1c} levels on target at <7% [<53 mmol/mol] vs. 65% for the 5y-DR), but they lost less weight than 5y-DR patients during the 1st year (−25% vs. −30%), approaching statistical significance (P = 0.09). Although classified as 5y-Relapse based on biological threshold, five of these eight patients (62%) were free of antidiabetic medications at 5 years post-RYGB. By contrast, the 19 well-classified 5y-Relapse patients (5y-Ad-DiaRem >11) displayed more severe diabetes at baseline (i.e., mean Ad-DiaRem value [9.4 vs. 3.9], $P < 0.001$) and a reduced, but statistically nonsignificant, weight loss (−21% vs. −25%) compared with the 8 relapse patients with a score <11. At 1 year, those 19 patients were mostly PDR (84%), thus with higher fasting glucose and HbA_{1c} compared with relapse patients with a score ≤11 who were mostly (75%) in complete DR. Importantly, although they experienced relapse, most patients received oral glucose-lowering agents compared with their previous regimens involving insulin therapy, showing the beneficial effects of RYGB. However, insulin therapy was restarted in two patients in this group.

Examining the 5y-NDR group (n = 54), 81% of the patients were well classified with a 5y-Ad-DiaRem score ≥18, and 100% were >11 (i.e., the fixed 5y-DR threshold) (Fig. 1*E*). T2D worsened in 30% (n = 16) of the 5y-NDR group at 5 years compared with baseline (as documented with higher HbA_{1c} values). These patients had a high mean 5y-Ad-DiaRem of 20. Importantly, the other patients of the NDR group (n = 38) improved their metabolic condition, although they remained obese and with T2D (Supplementary Table 3). Their BMI decreased by 10 kg/m^2 along with improved body composition at 1 year. They subsequently regained a nonsignificant amount of fat mass during the rest of the follow-up. Their diabetes control improved, as seen by reaching a mean HbA_{1c} of 7.6% (60 mmol/mol) concomitantly with a significant reduction in the number of glucose-lowering agents and a reduction in insulin therapy (i.e., 35 patients were on insulin therapy at baseline vs. 19 at 1 year and 15 at 5 years). Interestingly, the type and number of glucose-lowering agents was not significantly different from 1 to 5 years post-RYGB, suggesting that improvement occurred early and further stabilized. The HbA_{1c} goal of <7% (53 mmol/mol) was achieved in 34 of 54 patients 1 year post-RYGB, which later decreased to 18 patients at 5 years. These NDR patients also improved their liver functions (alanine aminotransferase and γ-glutamyl transferase), lipid values (triglycerides and HDL-cholesterol), despite a reduction in antilipid drugs, and improved their blood pressure as seen by a reduction in antihypertensive drugs.

Interestingly, 15 patients (21%) classified as NDR at 1 year experienced DR at 5 years. These patients were well classified by the Ad-DiaRem, with a score of 8 (thus, below the cutoff of 10 predicting 1y-DR) (21). They exhibited a remarkable weight loss response, because they lost the same amount as 5y-DR patients both at 1 and 5 years.

CONCLUSIONS

Here, we propose the 5y-Ad-DiaRem, a new score easily usable in routine care, to predict longer-term (5-year) diabetes status post-RYGB. This score displays

a 90% accuracy to predict 5y-DR (threshold ≤11). The 5y-Ad-DiaRem accurately reclassified 13 patients compared with the DiaRem (out of 39 errors) and 12 compared with the Ad-DiaRem (out of 38). The 5y-Ad-DiaRem predictive relevance was confirmed in three independent cohorts from different countries, including a wide range of age and stages of T2D severity before RYGB, thus suggesting its robustness. The use of machine learning methods together with the selection of features by physicians has again (21) displayed its superiority compared with clinical experience (20). Although RYGB enables long-term T2D improvement in most patients, some undergo T2D relapse after 1 year, which is associated with lower weight loss during the 1st year and weight regain afterward, a clinical condition that could be targeted for intervention.

Whereas an abundant literature (8,10,11) demonstrates the efficiency of BS in inducing 1y-DR, studies now mention T2D relapse (8,13,32–34) afterward. Therefore, it becomes crucial to provide accurate mid- to long-term predictors to precisely adapt personalized patient pathways (35). As such, patients predicted to remain T2D would probably benefit from a rigorous follow-up with a specialized endocrinologist or nutritionist. Alternatively, patients with predicted remission could benefit from general practitioner or specialized nurse counseling (36). This personalized strategy might impact health care costs and patients' quality of life. Previous studies examining DR and relapse mostly focused on bariatric cohorts with a relatively small sample size in RCTs (<30 operated-on patients) (8,37) or similar sample sizes to ours but on specific subgroups (13). For instance, Arterburn et al. (38) focused on a population of veterans who were mostly males with a higher prevalence of poor glycemic control than the usual bariatric population. Population characteristic differences could eventually explain the wide range of observed relapse rates, going from 17% (13) to 35% of patients undergoing 1y-DR (8,33). Another recent study with 2–12 years post-RYGB follow-up assessed T2D remission rates and showed a decrease from 75 to 51% between years 2 and 12, thus showing decreased beneficial effects over time (39).

Our interest in developing this new 5y-DR prediction score lies in the modest accuracy to predict longer-term DR with previously described scores (15,20), which were constructed to predict 1y-DR (0.78 for both the DiaRem and the Ad-DiaRem) (20,21). Indeed, whereas DiaRem correctly predicted 5y-DR, patients with the higher scores still underwent 5y-DR, suggesting a poor specificity (22). In another cohort examined at 2 and 10 years post-RYGB, low DiaRem scores reasonably predicted 5y-DR. However, a third of their patients fell into the score middle zone (8–17) where the DiaRem displays its poorest accuracy. This results in a 50% chance of patients being misclassified (24). Our current study is in agreement with this limited accuracy of the DiaRem for 5-year prediction.

The ABCD score proved interesting to predict 5y-DR (40), although the predictive accuracy was not calculated. In addition, C-peptide measurements used in this algorithm are expensive and not widely performed in routine care, preventing its generalization. Compared with our 5y-Ad-DiaRem, the lack of accuracy of the DiaRem might originate from the weights that were optimized locally and separately for each variable, whereas here, machine learning methods found a global optimum weighting (29).

Interestingly, the Ad-DiaRem (21) precisely predicted 5y-NDR (i.e., all patients with a score ≥15), yet did not perform well to predict 5y-Relapse. By contrast, the 5y-Ad-DiaRem provided an optimal separation between patients with 5y-DR, 5y-NDR, and 5y-Relapse. The 5y-Ad-DiaRem partly relies on well-known presurgical parameters associated with DR. It is confirmed that the severity of T2D (i.e., HbA_{1c} [33], the number and type of glucose-lowering agents) and its duration (15,21,33), which are key components of the DiaRem (20), ABCD score (15), Ad-DiaRem (21), and DiaBetter (41), are critical to predict 1y-DR. Diabetes duration is also associated with 2-year DR (15,40,41). However, the use of weight loss and remission status at 1 year improved the predictive value of 5y-DR.

The importance of weight loss during the 1st year has already been associated with 1y-DR (42) and, interestingly, with 5y-DR (22,32,33,41), yet was never included in a predictive score. Furthermore, our current random forest analysis emphasizes the importance of weight loss in long-term remission (Supplementary Fig. 4). A previous study (13) found a 17% prevalence of relapse in a cohort similar to ours. However, their patients lost more weight (despite having similar baseline BMI), which could eventually explain their lower rate of diabetes relapse than that observed in our study. Here, we found not only that 1-year weight loss was significantly different among our three trajectory groups but also that the long-term weight regain between 1 and 5 years (+8%) was associated with higher risk of relapse, as previously seen (13,22,33). Patients who had stable weight in the long-term remained in their original status (i.e., 5y-DR or 5y-NDR), and relapse was associated with increased fat mass at 5 years compared with both 5y-DR and 5y-NDR. These observations underline that weight management is key to maintaining T2D remission.

Noteworthy, our results are in line with several studies that observed a weight regain in their cohort (39,43), yet the link with diabetes relapse was not assessed in those studies. By contrast, another RCT (44) monitoring patients for 2 years post-RYGB confirmed that weight stabilization after the 1-year mark enabled the maintenance of the proportion of patients achieving DR. Importantly, diabetes control (HbA_{1c}, DR status, and the number of antidiabetic drugs) at 1 year was a major predictive factor of longer-term outcomes in our study. Patients who further relapsed mostly exhibited partial DR at 1 year, confirming previous results (33) and suggesting the need to optimize T2D control during the 1st year.

Using the Youden method (30), the 5y-Ad-DiaRem threshold for 5y-DR was determined as a score of ≤11, whereas the cutoff for persistent T2D in the longer-term was ≥18. Importantly, 96% of patients with a score ≤11 were free of antidiabetic medication at 5 years compared with only 47% of patients with a score >11 ($P < 0.001$). Whereas some patients remained with T2D, we show that they generally improved further diabetes control post-RYGB (8,13). However, a small portion of our cohort only exhibited relatively little improvement or even worsened after RYGB.

The strength of our study lies in the development of this new score evaluated in obese T2D patients, representative

of usual bariatric cohorts with a myriad of phenotypes, whom were monitored for 5 years. The relevance of the 5y-Ad-DiaRem was confirmed in three independent RYGB cohorts from different countries and, most importantly, with different stages of T2D severity, yet all operated on with RYGB, suggesting its robustness in every clinical setting. Although the number of patients exhibiting diabetes relapse is low, it is concordant with published data (8,13,32–34). The 5y-Ad-DiaRem should now be validated in patients with lower BMI (30–35 kg/m^2), because literature demonstrates that BS also enables DR in this population and is associated with weight loss (45).

We acknowledge a few limitations. For score development purposes, the test cohort included 175 patients who had not missed any of the follow-up time points during the 1st year. The 5y-Ad-DiaRem should be further evaluated in an increased number of patients lacking a full 1-year follow-up. Loss of patients to follow-up remains a major issue in the bariatric setting, which can reach 50% of patients at 5 years (46), and has been associated with poor weight loss outcomes. Despite this limitation, the 5y-Ad-DiaRem appeared robust when tested in three independent cohorts from different European countries, yet these were all Caucasian populations. Further validation in other ethnic groups will be of interest. Despite this, the current literature, including Africans Americans, Caucasians, or different Asian ethnic groups, displays no general effect of ethnicity in T2D remission after BS (47,48).

Conclusion

The 5y-Ad-DiaRem, which combines preoperative data with weight loss trajectory and diabetes reoccurrence variables obtained 1 year post-RYGB, is relevant to predict 5y-DR in routine care. Although some patients remained in NDR, they still improved their clinical conditions, as previously seen (8,13). We propose to use the 5y-Ad-DiaRem score as an easily integrated tool to identify patients at risk for longer-term relapse during their 1-year follow-up assessments to propose strategies targeting optimized weight reduction and maintenance to maximize the length of their remission. For example, increasing physical activity should be tested to evaluate whether it could reduce T2D relapse as already seen in the reduced incidence of T2D in glucose-intolerant patients (49). Eventually, patients identified with the 5y-Ad-DiaRem to remain in long-term NDR could also be proposed add-on strategies to further improve their diabetes control and prevent long-term complications. For example, restrictive dietary interventions could be proposed because they were shown to induce T2D remission along with antidiabetic drugs cessation outside the bariatric setting (50). These add-on therapies should be evaluated in future studies, and in this context, dedicated prospective lifestyle interventions should test patient metabolic benefits.

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References

1. Angrisani L, Formisano G, Santonicola A, Hasani A, Vitiello A. Bariatric surgery worldwide. In *Bariatric and Metabolic Surgery* [Internet]. Milano, Italy, Springer, 2017. p. 19–24. Available from https://link.springer.com/chapter/10.1007/978-88-470-3944-5_3. Accessed 28 November 2017

2. Courcoulas AP, Christian NJ, Belle SH, et al.; Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. JAMA 2013;310:2416–2425

3. Sjöström L, Narbro K, Sjöström CD, et al.; Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007;357:741–752

4. Pournaras DJ, Aasheim ET, Søvik TT, et al. Effect of the definition of type II diabetes remission in the evaluation of bariatric surgery for metabolic disorders. Br J Surg 2012;99:100–103

5. Buse JB, Caprio S, Cefalu WT, et al. How do we define cure of diabetes? Diabetes Care 2009;32:2133–2135

6. Cummings DE, Arterburn DE, Westbrook EO, et al. Gastric bypass surgery vs intensive lifestyle and medical intervention for type 2 diabetes: the CROSSROADS randomised controlled trial. Diabetologia 2016;59:945–953

7. Halperin F, Ding S-A, Simonson DC, et al. Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. JAMA Surg 2014;149:716–726

8. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 2015;386:964–973

9. Rubino F, Nathan DM, Eckel RH, et al.; Delegates of the 2nd Diabetes Surgery Summit. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care 2016;39:861–877

10. Schauer PR, Mingrone G, Ikramuddin S, Wolfe B. Clinical outcomes of metabolic surgery:

efficacy of glycemic control, weight loss, and remission of diabetes. Diabetes Care 2016;39:902–911
11. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. N Engl J Med 2017;376:641–651
12. Courcoulas AP, Belle SH, Neiberg RH, et al. Three-year outcomes of bariatric surgery vs lifestyle intervention for type 2 diabetes mellitus treatment: a randomized clinical trial. JAMA Surg 2015;150:931–940
13. Brethauer SA, Aminian A, Romero-Talamás H, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. Ann Surg 2013;258:628–636; discussion 636–637
14. Hayes MT, Hunt LA, Foo J, Tychinskaya Y, Stubbs RS. A model for predicting the resolution of type 2 diabetes in severely obese subjects following Roux-en Y gastric bypass surgery. Obes Surg 2011;21:910–916
15. Lee W-J, Hur KY, Lakadawala M, et al. Predicting success of metabolic surgery: age, body mass index, C-peptide, and duration score. Surg Obes Relat Dis 2013;9:379–384
16. Ramos-Levi AM, Matia P, Cabrerizo L, et al. Statistical models to predict type 2 diabetes remission after bariatric surgery. J Diabetes 2014;6:472–477
17. Still CD, Wood GC, Argyropoulos G. DiaRem score: external validation–authors' reply. Lancet Diabetes Endocrinol 2014;2:13
18. Lee W-J, Chong K, Chen S-C, et al. Preoperative prediction of type 2 diabetes remission after gastric bypass surgery: a comparison of DiaRem scores and ABCD scores. Obes Surg 2016;26:2418–2424
19. Cotillard A, Poitou C, Duchâteau-Nguyen G, et al. Type 2 diabetes remission after gastric bypass: what is the best prediction tool for clinicians? Obes Surg 2015;25:1128–1132
20. Still CD, Wood GC, Benotti P, et al. A probability score for preoperative prediction of type 2 diabetes remission following RYGB surgery. Lancet Diabetes Endocrinol 2014;2:38–45
21. Aron-Wisnewsky J, Sokolovska N, Liu Y, et al. The advanced-DiaRem score improves prediction of diabetes remission 1 year post-Roux-en-Y gastric bypass. Diabetologia 2017;60:1892–1902
22. Aminian A, Brethauer SA, Kashyap SR, Kirwan JP, Schauer PR. DiaRem score: external validation. Lancet Diabetes Endocrinol 2014;2:12–13
23. Wood GC, Mirshahi T, Still CD, Hirsch AG. Association of DiaRem score with cure of type 2 diabetes following bariatric surgery. JAMA Surg 2016;151:779–781
24. Mehaffey JH, Mullen MG, Mehaffey RL, et al. Type 2 diabetes remission following gastric bypass: does diarem stand the test of time? Surg Endosc 2017;31:538–542
25. Fried M, Yumuk V, Oppert JM, et al.; European Association for the Study of Obesity; International Federation for the Surgery of Obesity - European Chapter. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Facts 2013;6:449–468
26. Bel Lassen P, Charlotte F, Liu Y, et al. The FAT score, a fibrosis score of adipose tissue: predicting weight-loss outcome after gastric bypass. J Clin Endocrinol Metab 2017;102:2443–2453
27. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression scale. Acta Psychiatr Scand 1983;67:361–370
28. Richter P, Werner J, Heerlein A, Kraus A, Sauer H. On the validity of the Beck Depression Inventory. A review. Psychopathology 1998;31:160–168
29. Sokolovska N, Chevaleyre Y, Zucker J-D. A provable algorithm for learning interpretable scoring systems. Presented at: 21st International Conference on Artificial Intelligence and Statistics (AISTATS), Lanzarote, Canary Islands, 9–11 April 2018
30. Youden WJ. Index for rating diagnostic tests. Cancer 1950;3:32–35
31. Beam AL, Kohane IS. Big data and machine learning in health care. JAMA 2018;319:1317–1318
32. Aminian A, Brethauer SA, Andalib A, et al. Can sleeve gastrectomy "cure" diabetes? Long-term metabolic effects of sleeve gastrectomy in patients with type 2 diabetes. Ann Surg 2016;264:674–681
33. Arterburn DE, Bogart A, Sherwood NE, et al. A multisite study of long-term remission and relapse of type 2 diabetes mellitus following gastric bypass. Obes Surg 2013;23:93–102
34. Gonzalez AG, Canner JK, Alsulaim HA, Steele KE. Remission and relapse of type 2 diabetes mellitus after bariatric surgery: vertical sleeve gastrectomy vs Roux-en-Y gastric bypass. J Am Coll Surg 2017;225(Suppl. 1):S18
35. Gloyn AL, Drucker DJ. Precision medicine in the management of type 2 diabetes. Lancet Diabetes Endocrinol. 23 April 2018 [Epub ahead of print]. DOI: 10.1016/S2213-8587(18)30052-4
36. Barbelanne A, Wolf S, Foiry A-F, Guillot C, Aron Wisnewsky J. A cooperation protocol for the follow-up of patients after bariatric surgery. Soins Rev Ref Infirm 2016;61:55–57 [in French]
37. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med 2012;366:1577–1585
38. Arterburn DE, Olsen MK, Smith VA, et al. Association between bariatric surgery and long-term survival. JAMA 2015;313:62–70
39. Adams TD, Davidson LE, Litwin SE, et al. Weight and metabolic outcomes 12 years after gastric bypass. N Engl J Med 2017;377:1143–1155
40. Lee MH, Lee WJ, Chong K, et al. Predictors of long-term diabetes remission after metabolic surgery. J Gastrointest Surg 2015;19:1015–1021
41. Pucci A, Tymoszuk U, Cheung WH, et al. Type 2 diabetes remission 2 years post Roux-en-Y gastric bypass and sleeve gastrectomy: the role of the weight loss and comparison of DiaRem and DiaBetter scores. Diabet Med 2018;35:360–367
42. Ikramuddin S, Korner J, Lee WJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. JAMA 2013;309:2240–2249
43. Courcoulas AP, King WC, Belle SH, et al. Seven-year weight trajectories and health outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) study. JAMA Surg 2017;153:427–434
44. Ikramuddin S, Billington CJ, Lee W-J, et al. Roux-en-Y gastric bypass for diabetes (the Diabetes Surgery Study): 2-year outcomes of a 5-year, randomised, controlled trial. Lancet Diabetes Endocrinol 2015;3:413–422
45. Parikh M, Chung M, Sheth S, et al. Randomized pilot trial of bariatric surgery versus intensive medical weight management on diabetes remission in type 2 diabetic patients who do NOT meet NIH criteria for surgery and the role of soluble RAGE as a novel biomarker of success. Ann Surg 2014;260:617–622; discussion 622–624
46. Thereaux J, Lesuffleur T, Païta M, et al. Long-term follow-up after bariatric surgery in a national cohort. Br J Surg 2017;104:1362–1371
47. Admiraal WM, Celik F, Gerdes VE, Dallal RM, Hoekstra JB, Holleman F. Ethnic differences in weight loss and diabetes remission after bariatric surgery: a meta-analysis. Diabetes Care 2012;35:1951–1958
48. Toh BC, Chan WH, Eng AKH, et al. Five-year long-term clinical outcome after bariatric metabolic surgery: a multi-ethnic Asian population in Singapore. Diabetes Obes Metab 2018;20:1762–1765
49. Laaksonen DE, Lindström J, Lakka TA, et al.; Finnish Diabetes Prevention Study. Physical activity in the prevention of type 2 diabetes: the Finnish Diabetes Prevention Study. Diabetes 2005;54:158–165
50. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet Lond Engl 2018;391:541–551