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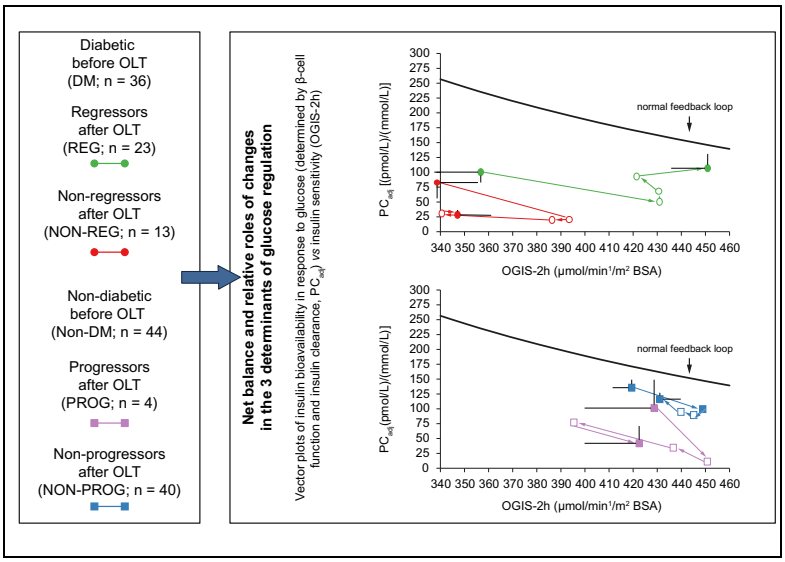
Central role of the β-cell in driving regression of diabetes after liver transplantation in cirrhotic patients

Graphical abstract



Highlights

- The mechanisms underlying diabetes regression after liver transplantation are unclear.
- Diabetes regressed in ~2/3 of diabetic patients and developed in <10% of non-diabetic individuals.
- Only baseline HbA_{1c} and a family history of diabetes independently predicted regression.
- β-cell function governed changes in glucose regulation after liver transplantation.
- A sustained improvement of insulin sensitivity accompanied rescue of β-cell function.

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Lay summary

Diabetes occurring in cirrhosis as a direct consequence of loss of liver function should regress after transplantation of a new functioning liver, though the pathophysiological mechanisms are unclear. This is the first study evaluating the contribution of all 3 direct determinants of insulin-dependent glucose regulation using a sophisticated mathematical model. Results show that β-cell function is the key process governing favourable or detrimental changes in glucose regulation in cirrhotic patients undergoing transplantation, pointing to the need to develop therapies to sustain β-cell function in these individuals.

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Central role of the β-cell in driving regression of diabetes after liver transplantation in cirrhotic patients

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Background & Aims: Diabetes occurring as a direct consequence of loss of liver function is usually characterized by non-diabetic fasting plasma glucose (FPG) and haemoglobin A_{1c} (HbA_{1c}) levels and should regress after orthotopic liver transplantation (OLT). This observational, longitudinal study investigated the relationship between the time-courses of changes in all 3 direct determinants of glucose regulation, *i.e.*, β-cell function, insulin clearance and insulin sensitivity, and diabetes regression after OLT.

Methods: Eighty cirrhotic patients with non-diabetic FPG and HbA_{1c} levels underwent an extended oral glucose tolerance test (OGTT) before and 3, 6, 12 and 24 months after OLT. The OGTT data were analysed with a mathematical model to estimate derivative control (DC) and proportional control (PC) of β-cell function and insulin clearance (which determine insulin bioavailability), and with the Oral Glucose Insulin Sensitivity (OGIS)-2 h index to estimate insulin sensitivity.

Results: At baseline, 36 patients were diabetic (45%) and 44 were non-diabetic (55%). Over the 2-year follow-up, 23 diabetic patients (63.9%) regressed to non-diabetic glucose regulation, whereas 13 did not (36.1%); moreover, 4 non-diabetic individuals progressed to diabetes (9.1%), whereas 40 did not (90.9%). Both DC and PC increased in regressors (from month 3 and 24, respectively) and decreased in progressors, whereas they remained stable in non-regressors and only PC decreased in non-progressors. Insulin clearance increased in all groups, apart from progressors. Likewise, OGIS-2 h improved at month 3 in all groups, but thereafter it continued to improve only in regressors, whereas it returned to baseline values in the other groups.

Conclusions: Increased insulin bioavailability driven by improved β-cell function plays a central role in favouring diabetes regression after OLT, in the presence of a sustained improvement of insulin sensitivity.

Lay summary: Diabetes occurring in cirrhosis as a direct consequence of loss of liver function should regress after transplantation of a new functioning liver, though the pathophysiological mechanisms are unclear. This is the first study evaluating the contribution of all 3 direct determinants of insulin-dependent glucose regulation using a sophisticated mathematical model. Results show that β-cell function is the key process governing favourable or detrimental changes in glucose regulation in cirrhotic patients undergoing transplantation, pointing to the need to develop therapies to sustain β-cell function in these individuals.

Trial registration: ClinicalTrials.gov, NCT02038517.

Introduction

Diabetes mellitus (DM) is a common feature in cirrhotic individuals, due to the bidirectional relationship between impaired glucose metabolism and chronic liver disease.[1] On the one hand, type 2 DM is a risk factor for non-alcoholic fatty liver disease (NAFLD)[2] and, though not included in the most widely used prognostic tools,[3] is a major predictor of adverse outcomes in cirrhotic individuals both before[4] and after[5] orthotopic liver transplantation (OLT). On the other hand, certain aetiological agents of liver disease, including HCV and NAFLD, may cause β-cell dysfunction and/or insulin resistance, thus favouring development of DM even prior to the onset of cirrhosis.[1] Moreover, DM may be a direct consequence of loss of liver function, which impairs insulin secretion and sensitivity via several, partly unrecognized, mechanisms.[6] This is the so-called hepatogenous DM, which is not considered a separate clinical entity, despite distinguishing pathophysiological and clinical features.[7] We have previously shown that, compared with non-DM cirrhotic individuals, those with hepatogenous DM are characterized by worse β-cell function, which deteriorates

Keywords: Liver cirrhosis; Hepatogenous diabetes; Orthotopic liver transplantation; β-cell dysfunction; Insulin resistance.
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in parallel with severity of liver disease.[8] In addition, they present with fasting plasma glucose (FPG) and haemoglobin A_{1c} (HbA_{1c}) levels not in the DM range, due to impaired glucose metabolism and reduced lifespan of erythrocytes, respectively.[6,7] This "subclinical" presentation implies that, in cirrhotic patients, an oral glucose tolerance test (OGTT) is required for DM diagnosis[6,9] and explains the differences in prevalence estimates of DM according to the method(s) of assessment.[9]

By definition, hepatogenous DM should benefit from OLT, the first-choice treatment for end-stage liver disease, as restoration of liver function would remove the local and systemic factors detrimentally affecting insulin secretion and sensitivity, thereby leading to improvement or even regression of DM.[9] However, like other solid organ transplants, OLT is often associated with development of post-transplant DM,[10] which is predicted by prior DM[11] and is favoured by immunosuppressant treatment[12] and changes in nutritional habits[13]. Previous studies in patients with overt DM provided conflicting results. Perseghin *et al.* reported that transplantation was successful in curing DM in two-thirds of cases[14]. Conversely, Lunati *et al.* showed that DM prevalence remained unchanged over a 1-year follow-up, with DM regressing or developing as new-onset DM in a few patients.[13] Likewise, even in cirrhotic patients with normal FPG (*i.e.* those likely suffering from hepatogenous DM), abnormalities of glucose tolerance persisted despite restoration of liver function.[15]

The pathophysiological mechanisms underlying regression *vs.* non-regression are largely unknown, though failure to cure DM was found to be associated with persistence of β-cell dysfunction.[14] Surprisingly, so far, no study has evaluated the contribution of all 3 direct determinants of insulin-dependent glucose regulation, *i.e.*, insulin secretion and catabolism, which together determine insulin bioavailability and insulin sensitivity. Therefore, this is the first study aimed at monitoring changes in β-cell function, insulin clearance, and insulin sensitivity occurring over a 2-year period after OLT in cirrhotic patients with non-DM FPG and HbA_{1c} levels, using a frequently sampled, extended OGTT analysed with established models.

Patients and methods

Design

The Cirrhosis, Effects of TRAnsplantation and diabetes (CETRA) Study is an observational, prospective survey aimed at assessing the relationship of insulin secretion and sensitivity with changes in glucose regulation occurring after OLT in cirrhotic individuals with non-DM FPG and HbA_{1c} levels.

The study complies with the Declaration of Helsinki. The research protocol was approved by the Ethics Committee of the IRCCS Cà Granda – Ospedale Maggiore Policlinico Foundation (Prot. n. 516) and written informed consent was provided by each participant.

Patients

From January 2010 to December 2016, 187 consecutive patients with biopsy-proven liver cirrhosis, who were candidates for liver transplantation, were evaluated for eligibility. The baseline data from 143 of these individuals were included in a previous publication, together with those of 17 cirrhotic patients not on the waitlist.[8] After excluding 65 patients with FPG and HbA_{1c} values in the DM range, 117 of the remaining 122 patients were enrolled in the CETRA study. Finally, 98 of these individuals underwent transplantation and 80 of them completed a 2-year follow-up and were included in this analysis. The reason for analysing only patients who had completed a 2-year follow-up was that glucose homeostasis usually fluctuated during the first year and stabilized thereafter.

Measurements

At enrolment, all patients underwent a structured interview to collect a complete medical history and were classified according to Child-Pugh class.[3]

Before and 3, 6, 12, and 24 months after transplantation all patients underwent measurement of anthropometric and clinical parameters; moreover, fasting blood samples were taken to assess glucose and lipid metabolism and liver and renal function.

At the same time points, patients underwent a 75 g OGTT, with measurement of glucose, insulin and C-peptide levels at time 0, and 15, 30, 45, 60, 90, 120, 150, and 180 min after glucose challenge, and were classified as normal (normal fasting glucose [NFG]/normal glucose tolerance [NGT]), pre-diabetic (impaired fasting glucose [IFG] and/or impaired glucose tolerance [IGT]), or DM according to the American Diabetes Association criteria.[16] Based on the OGTT results at baseline and month 24, patients were retrospectively assigned to one of the following outcomes groups: (1) non-progressors (NON-PROG): non-DM both before and 24 months after OLT; (2) progressors (PROG): non-DM before OLT and DM 24 months after OLT; (3) non-regressors (NON-REG): DM both before and 24 months after OLT; and (4) regressors (REG): DM before OLT and non-DM 24 months after OLT. The OGTT data were further analysed to assess β-cell function, insulin clearance and insulin sensitivity.

Both β-cell function and insulin clearance were estimated using an established mathematical model.[17,18] β-cell function is described as the sum of 2 components: derivative (or dynamic) control (DC) and proportional (or static) control (PC). DC is the response of β-cells to the rate of glucose increase, *i.e.*, the sensitivity of β-cells to glucose increase, and reflects the first phase of insulin secretion. PC is the response of β-cells to glucose concentrations (*i.e.*, the sensitivity of β-cells to glucose *per se*) and reflects the second phase of insulin secretion. To track changes over time in PC, it is presented with a compact descriptor, *i.e.*, the slope of the curve relating glucose to insulin secretion rate (ISR) ($\sigma 2$). Insulin clearance index (InsClear) was calculated as in.[18] Insulin sensitivity was estimated by calculating the Oral Glucose Insulin Sensitivity index at 2-hours of the OGTT (OGIS-2 h).[19]

Insulin sensitivity and bioavailability of insulin in response to glucose form a physiological feedback loop which determines the status of glucose regulation.[20–22] As β-cell function and insulin clearance determine insulin bioavailability and PC accounts for the greater amount of insulin released by the β-cells in response to OGTT, we computed insulin bioavailability as adjusted PC (PC_{adj}), *i.e.*, the increment in insulin concentration caused by an increment in glucose concentration of 1 mmol/L according to the formula: $PC_{adj} = \sigma 2/InsClear$. Then, we plotted the concomitant changes over time of joint PC_{adj} and OGIS-2 h by outcome group.[22] Points represent the joint action of insulin bioavailability and insulin sensitivity, while trajectories are the changes over time, *i.e.* the time vectors; hence, these plots are named "vector plots".[22,23] The concave line in the vector plots is the physiological inverse (hyperbolic)

relationship between insulin bioavailability (PC_{adj}) and insulin sensitivity (OGIS-2 h) found in the individuals with normal glucose homeostasis (NFG/NGT) from our cohort. The area below the concave line houses the less than normal adaptation to insulin sensitivity. The greater is the distance between a point in this area and the concave line, the worse is the body's adaptation, and the worse is glucose regulation. Theoretically, the return to the normal feedback loop may occur through changes in insulin bioavailability (upward vertical vector), insulin sensitivity (rightward horizontal vector) or, most commonly, both (oblique vector).[22]

Statistical analysis

Results are presented as mean ± SD in the tables and plotted as mean ± SEM in the figures. Baseline-to-year-2 changes are expressed as mean difference and 95% CIs.

Between-group differences for baseline values and baseline-to-year-2 changes were analysed using the unpaired Student's *t* test or the 1-way ANOVA, followed by Bonferroni test for *post hoc* multiple comparisons. The Mann-Whitney *U* or the Kruskal-Wallis test were used for variables with non-Gaussian distribution. Within-group differences for baseline-to-year-2 changes for anthropometric, metabolic, and liver and renal function parameters were evaluated using the paired Student's *t* test or the Wilcoxon signed ranks test. The χ^2 was used for continuous variables.

A hierarchical general linear model (GLM) was applied to assess changes over time in β-cell function, InsClear and OGIS-2 h, after normalization of data, if needed, by logarithmic or square root transformation, as appropriate. When a significant group-by-time interaction was detected, the GLM analysis was repeated within each group to assess differences between after and before OLT. The ISR-glucose response of PC was analysed by GLM for repeated measures. Since no transformation could normalize the distribution of DC values, the non-parametric Friedman test was used, followed by the Wilcoxon test for comparison of each post-OLT time-point to baseline values.

Multiple regression analysis with backward variable selection was performed to assess independent correlates of DM regression *vs.* non-regression.

A *p* value of less than 0.05 was considered statistically significant.

Statistical analyses were performed using SPSS version 13·0 (SPSS Inc., Chicago, Illinois, USA).

For further details regarding the materials used, please refer to the supplementary information.

Results

The main characteristics of study participants are presented in Table S1. At baseline, 36 had DM and 44 were non-DM (15 NFG/NGT, 5 IFG, 20 IGT, and 4 IFG + IGT). Compared to non-DM patients, those with DM were older and had higher HbA_{1c}, glucose, C-peptide, and aminotransferase levels, similar InsClear, and lower DC, PC (σ2) and OGIS-2 h (Table 1).

Over the 2-year follow-up, 23 DM patients (63.8%) regressed to non-diabetic glucose regulation (13, 56.5%, to normal and 10, 43.5%, to pre-diabetic state), whereas 13 did not regress (36.2%). Among the non-DM patients, 4 progressed to DM (9.1%), whereas 40 did not (91.1%). At baseline, REG had lower HbA_{1c} ($p = 0.029$), FPG ($p = 0.046$), and 2 h glucose ($p = 0.030$) than NON-REG, whereas no differences were detected in all the other parameters, including aetiology and severity of liver disease, body mass index, and measures of insulin secretion, catabolism, and sensitivity (Table 2). Likewise, among the baseline variables, only HbA_{1c} ($\beta = -1.772$; $p = 0.030$) and family history of DM ($\beta = -2.942$; $p = 0.019$) were independent predictors of DM regression. No differences were observed between PROG and NON-PROG (Table 2).

Table 3 shows baseline-to-year-2 changes in the 4 outcome groups. Though HbA_{1c} values increased in all groups, as expected,[6,7] increments were significantly greater in PROG than in REG ($p = 0.025$), NON-REG ($p = 0.021$) and NON-PROG ($p = 0.010$), reflecting the deterioration of glucose homeostasis in patients who developed DM. Only minor changes in FPG were detected, but both REG and PROG showed marked reductions and rises, respectively, in 2 h glucose. No differences were observed among groups in change in body weight. In all groups, lipid and BP levels increased, liver function improved, and eGFR slightly declined because of immunosuppressant treatment. Immunosuppressant therapy and OLT complications did not differ significantly among groups (Table S2) and, like change in body weight, were not associated with DM regression in the multiple logistic regression analysis (data not shown).

After OLT, InsClear increased in all groups apart from PROG (Fig. 1A). The OGIS-2 h also increased in all groups 3 months after OLT, although the change was not statistically significant in PROG. Subsequently, it kept rising in REG, whereas it declined towards the baseline values in the other groups (Fig. 1B). Both DC (Fig. 2A) and PC (Fig. 2B) significantly increased in REG and decreased in PROG, whereas they stayed stable in NON-PROG and only PC decreased in NON-REG. Interestingly, in REG, an increase in DC was already observed at month 3 and preceded the increment in PC, which occurred at year 1 and 2. The worsening in OGIS-2 h, DC, and PC with deterioration of glucose regulation was confirmed by analysing all non-DM patients who worsened their glucose regulation status, *i.e.*, the 4 PROG patients and the 4 NON-PROG individuals who did not develop DM but progressed from NFG/NGT to IGT (±IFG) (Fig. S1).

The NON-REG vector starts from a position far from the normal curve and, at month 3, its distance does not decrease owing to a downward shift (worsening of PC_{adj}) which matches the rightward shift (improved OGIS-2 h). Subsequently, insulin sensitivity falls back (leftward shift) to baseline values, but, since no significant improvements in PC_{adj} occur, at the end of the 2-year follow-up the distance of the NON-REG vector from the normal curve is, if anything, increased (Fig. 3A). The REG vector shows a similar behaviour over the first 6 months after OLT, with little reduction in the distance from the normal curve, because the rightward shift (improved OGIS-2 h) is almost matched by a downward shift (worsening of PC_{adj}). However, at month 12 and, especially, 24, the REG vector almost entirely closes the distance from the normal curve, primarily because of an upward shift (improved PC_{adj}) (Fig. 3A).

The NON-PROG vector starts close to the normal curve. After OLT, the vector travels back and forth to points which lie at approximately the same distance from, and seem to draw a line approximately parallel to, the normal feedback loop, although they are located slightly below it, *i.e.*, the shifts in PC_{adj} and OGIS-2 h compensate each other (Fig. 3B). In contrast, already 3 months after OLT, the PROG vector relocates to a greater distance from the normal curve than before OLT, essentially because of a downward shift (worsening of PC_{adj}) which exceeds

Table 1. Clinical features and measures of insulin secretion, catabolism, and sensitivity according to the presence or absence of DM at baseline.

	No DM	DM	*p* value
N	44	36	
Age, yr	50.4 ± 9.6	55.9 ± 7.0	0.006
Male gender, n (%)	34 (77.3)	23 (63.9)	0.188
Child-Pugh score	8.68 ± 2.44	8.86 ± 1.42	0.697
HCV, n (%)	18 (40.9)	20 (55.6)	0.192
HCC, n (%)	13 (29.5)	12 (33.3)	0.716
Family history of DM, n (%)	20 (45.5)	14 (38.9)	0.555
HbA_{1c}, %	4.53 ± 0.72	4.95 ± 0.82	0.018
Glucose, mmol/L	5.02 ± 0.86	5.58 ± 1.59	0.047
Glucose-2 h, mmol/L	8.22 ± 1.73	14.53 ± 3.02	<0.0001
Insulin, pmol/L	95.4 ± 58.5	94.9 ± 68.0	0.813
C-peptide, nmol/L	1.13 ± 0.41	1.41 ± 0.61	0.020
BMI, kg/m^2	25.6 ± 3.3	26.3 ± 4.6	0.452
Waist circumference, cm	98.6 ± 12.5	98.4 ± 11.0	0.953
Hip circumference, cm	100.5 ± 8.1	102.0 ± 7.8	0.769
Triglycerides, mmol/L	0.94 ± 0.56	0.91 ± 0.23	0.118
Total cholesterol, mmol/L	3.62 ± 1.26	3.43 ± 1.13	0.726
HDL cholesterol, mmol/L	1.31 ± 0.57	1.27 ± 0.49	0.763
LDL cholesterol, mmol/L	1.86 ± 1.08	1.76 ± 0.91	0.851
Systolic BP, mmHg	113.2 ± 14.3	111.1 ± 13.9	0.510
Diastolic BP, mmHg	69.6 ± 9.3	68.4 ± 8.4	0.575
Total proteins, g/L	6.92 ± 0.94	6.94 ± 0.74	0.897
Albumin, g/L	3.56 ± 0.51	3.21 ± 0.39	0.001
Total bilirubin, μmol/L	63.1 ± 68.6	49.8 ± 26.0	0.871
Direct bilirubin, μmol/L	37.2 ± 61.2	29.0 ± 18.3	0.318
AST, U/L	65.1 ± 43.0	94.5 ± 66.1	0.008
ALT, U/L	44.5 ± 41.3	58.3 ± 36.5	0.011
GGT, U/L	89.7 ± 81.6	76.5 ± 62.9	0.657
ALP, U/L	148.2 ± 66.6	137.3 ± 61.9	0.549
Pseudocholinesterase, U/L	3,277 ± 2,067	2,326 ± 858	0.160
eGFR, ml/min/1.73 m^2	94.1 ± 23.6	86.4 ± 19.6	0.124
DC, pmol/m^2 BSA/mmol/min	1,550 ± 1,624	522.9 ± 846	<0.0001
PC (σ2), pmol/min/m^2 BSA/mmol/L	129.9 ± 62.3	89.4 ± 53.1	0.002
PC (ISR), pmol/min/m^2 BSA			
4.0 mmol/L glucose	174.1 ± 73.7	241.0 ± 122.8	0.012
5.5 mmol/L glucose	219.8 ± 82.5	269.4 ± 147.1	0.204
8.0 mmol/L glucose	497.0 ± 172.6	380.0 ± 228.2	0.002
11.0 mmol/L glucose	887.0 ± 321.9	585.9 ± 315.6	<0.001
15.0 mmol/L glucose	1,406.9 ± 549.7	936.6 ± 483.6	<0.001
InsClear, L/min/m^2 BSA	1,224 ± 1,473	1,338 ± 2,007	0.462
OGIS-2 h, ml/min/m^2 BSA	419.9 ± 69.6	353.5 ± 82.5	<0.001

Data are mean ± SD, where not otherwise indicated. Unpaired Student's *t* test, Mann-Whitney test, and χ^2 test for parametric continuous variables, non-parametric continuous variables, and categorical variables, respectively. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; BSA, body surface area; DC, derivative control; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyltransferase; HbA_{1c}, haemoglobin A_{1c}; HCC, hepatocellular carcinoma; InsClear, insulin clearance; ISR, insulin secretion rate; OGIS, Oral Glucose Insulin Sensitivity; PC, proportional control.

the rightward shift (improved OGIS-2 h). All the subsequent changes in PROG maintain an almost constant distance with the normal curve, and the vector apparently travels back and forth on a line which is parallel to, but much farther from the line of the normal feedback loop, when compared to before OLT (Fig. 3B).

Discussion

In this study, we sought to determine the pathophysiological determinant(s) of changes in glucose regulation occurring in cirrhotic individuals after OLT. To this end, we followed longitudinally a cohort of patients undergoing OLT by assessing their glucose tolerance and its main determinants at predetermined time intervals. We then retrospectively identified 4 outcome groups according to the glucose regulation status achieved 2 years after surgery *vs.* baseline.

The proportion of REG patients (64%) over the total number of DM individuals before OLT is remarkably similar to that reported by Perseghin *et al.*[14] and, on purely theoretical grounds, should be an approximate estimate of the cases with genuine hepatogenous DM.

Another relevant finding is that only pre-OLT HbA_{1c} was a negative independent predictor of DM regression, together with family history of DM. This finding suggests that, within this population, HbA_{1c} still reflects the severity (and duration?) of metabolic derangements despite the confounding effect of altered erythrocyte lifespan. It is perhaps surprising that no other factor, including baseline and post-OLT changes in body weight, immunosuppressant therapy, and HCV infection, turned out to be a significant predictor of DM regression, but this finding might be related to the relatively small sample size.

The novelty of our study is the simultaneous assessment of β-cell function, insulin catabolism and insulin sensitivity, which

Table 2. Baseline clinical features and measures of insulin secretion, catabolism, and sensitivity according to the outcome.

	REG	NON-REG	PROG	NON-PROG	*p* value
N	23	13	4	40	
Age, yr	57.0 ± 7.4	54.1 ± 6.1	57.0 ± 5.9	49.8 ± 9.7	0.011
Male gender, n (%)	12 (52.2)	11 (84.6)	2 (50.0)	32 (80.0)	0.055
Child-Pugh score	8.87 ± 1.42	8.85 ± 1.46	8.75 ± 1.71	8.68 ± 2.52	0.984
HCV, n (%)	12 (52.2)	8 (61.5)	1 (25.0)	17 (42.5)	0.486
HCC, n (%)	6 (26.1)	6 (46.2)	1 (25.0)	12 (30.0)	0.630
Family history of DM, n (%)	6 (26.1)	8 (61.5)	3 (75.0)	17 (42.5)	0.103
HbA_{1c}, %	4.68 ± 0.57	5.42 ± 1.00	4.33 ± 0.84	4.56 ± 0.71	0.003
Glucose, mmol/L	5.17 ± 1.04	6.31 ± 2.12	4.75 ± 0.41	5.05 ± 0.89	0.010
Glucose-2 h, mmol/L	13.70 ± 2.19	16.00 ± 3.77	9.19 ± 1.47	8.13 ± 1.74	<0.0001
Insulin, pmol/L	87.5 ± 64.8	109.3 ± 74.4	81.0 ± 25.8	96.8 ± 60.8	0.827
C-peptide, nmol/L	1.34 ± 0.49	1.55 ± 0.78	0.94 ± 0.21	1.15 ± 0.42	0.092
Body weight, kg	71.5 ± 14.3	80.5 ± 17.5	71.9 ± 15.6	73.6 ± 12.9	0.292
BMI, kg/m^2	26.1 ± 4.4	26.5 ± 5.1	25.8 ± 2.3	25.6 ± 3.4	0.885
Waist circumference, cm	96.1 ± 10.0	102.4 ± 11.9	97.8 ± 12.5	98.6 ± 12.6	0.505
Hip circumference, cm	101.8 ± 7.9	102.3 ± 8.1	100.8 ± 12.5	102.7 ± 7.7	0.954
Triglycerides, mmol/L	0.91 ± 0.26	0.91 ± 0.20	0.78 ± 0.20	0.95 ± 0.59	0.458
Total cholesterol, mmol/L	3.54 ± 1.26	3.24 ± 0.85	3.70 ± 0.99	3.61 ± 1.29	0.892
HDL cholesterol, mmol/L	1.31 ± 0.52	1.18 ± 0.42	1.51 ± 0.52	1.30 ± 0.57	0.670
LDL cholesterol, mmol/L	1.83 ± 0.98	1.64 ± 0.80	1.84 ± 0.69	1.87 ± 1.12	0.944
Systolic BP, mmHg	110.9 ± 15.4	111.4 ± 11.3	101.3 ± 20.2	114.4 ± 13.3	0.309
Diastolic BP, mmHg	69.1 ± 8.3	67.2 ± 8.8	65.0 ± 10.0	70.0 ± 9.3	0.606
Total proteins, g/L	7.00 ± 0.77	6.83 ± 0.70	7.25 ± 1.76	6.88 ± 0.85	0.809
Albumin, g/L	3.24 ± 0.39	3.14 ± 0.39	3.15 ± 0.49	3.60 ± 0.50	0.003
Total bilirubin, μmol/L	51.2 ± 27.9	47.0 ± 22.7	38.9 ± 7.5	65.6 ± 71.5	0.898
Direct bilirubin, μmol/L	29.9 ± 20.1	27.4 ± 14.9	20.6 ± 5.3	38.9 ± 64.0	0.785
AST, U/L	91.2 ± 74.5	100.5 ± 49.2	52.5 ± 19.7	66.4 ± 44.7	0.045
ALT, U/L	57.3 ± 41.4	60.2 ± 26.9	34.0 ± 15.1	45.5 ± 43.0	0.072
GGT, U/L	80.5 ± 70.9	69.2 ± 46.7	128.8 ± 105.9	85.8 ± 79.4	0.826
ALP, U/L	137.3 ± 70.2	137.3 ± 44.4	158.0 ± 125.1	147.2 ± 60.3	0.813
Pseudocholinesterase, U/L	2,459 ± 885	2,095 ± 790	2,739 ± 593	3,325 ± 2147	0.392
eGFR, ml/min/1.73 m^2	83.4 ± 17.7	92.1 ± 22.4	81.5 ± 19.8	95.4 ± 23.8	0.170
DC, pmol/m^2 BSA/mmol/min	466 ± 613	632 ± 1,201	1,261 ± 972	1579 ± 1682	0.002
PC (σ2), pmol/min/m^2 BSA/mmol/L	90.5 ± 50.7	148.2 ± 239.9	124.5 ± 28.3	130.5 ± 60.9	0.023
PC (ISR), pmol/min/m^2 BSA					
4.0 mmol/L glucose	244.4 ± 100.5	234.5 ± 162.2	163.7 ± 41.8	175.1 ± 76.5	0.039
5.5 mmol/L glucose	279.8 ± 114.5	249.4 ± 200.1	194.0 ± 70.9	222.5 ± 84.0	0.164
8.0 mmol/L glucose	400.8 ± 190.7	340.1 ± 292.5	396.7 ± 136.5	507.2 ± 174.0	0.004
11.0 mmol/L glucose	636.5 ± 245.8	488.9 ± 413.9	759.8 ± 131.5	900.0 ± 333.6	<0.001
15.0 mmol/L glucose	999.3 ± 376.4	816.4 ± 644.6	1,243.9 ± 203.0	1,423.7 ± 572.4	0.002
InsClear, L/min/m^2 BSA	0.846 ± 0.434	0.898 ± 0.354	1.721 ± 1.808	1.089 ± 1.289	0.320
OGIS-2 h, ml/min/m^2 BSA	360.1 ± 89.7	341.8 ± 69.8	403.7 ± 76.8	421.5 ± 69.7	0.003

Data are mean ± SD, where not otherwise indicated. One-way ANOVA, Kruskal-Wallis test, and χ^2 test for parametric continuous variables, non-parametric continuous variables, and categorical variables, respectively. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; BSA, body surface area; DC, derivative control; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyltransferase; HbA_{1c}, haemoglobin A_{1c}; HCC, hepatocellular carcinoma; InsClear, insulin clearance; ISR, insulin secretion rate; NON-PROG, non-progressors; NON-REG, non-regressors; OGIS, Oral Glucose Insulin Sensitivity; PROG, progressors; PC, proportional control; REG, regressors.

are the key immediate determinants of glucose regulation and are expected to change sensibly as a direct consequence of OLT. In fact, the new functioning organ should increase both liver insulin sensitivity and insulin catabolism, 2 processes working in opposite directions by enhancing whole body insulin sensitivity and reducing insulin bioavailability, respectively. Moreover, OLT might improve β-cell function, consistent with our observation that the failing liver exerts an independent "toxic" effect on β-cells, thus driving transition to DM.[8] Additional confounding roles may be played by immunosuppressant therapy.

Our data demonstrate that, 3 months after OLT, the expected metabolic changes, *i.e.* improvement in insulin sensitivity and increase in insulin clearance, were detectable in all groups. As for β-cell function, PC was unchanged, whereas DC showed an increase in the REG group and a nonsignificant decrease in the PROG group. Subsequently, there was a stepwise increase in PC in the REG group. This change, together with the mirror decrease observed in the PROG group, point to β-cell function as the key determinant of the regression from and, with all the caveats due to the small number of patients in the PROG group, progression to DM after OLT. However, changes in the other 2 factors, *i.e.* insulin clearance and insulin sensitivity, confound the interpretation of the evolution of glucose regulation in both REG and PROG.

The vector plots show that, after 3 months, the net average result of changes in the 3 determinants of glucose regulation did not appreciably modify the distance of each group from the line of normal glucose regulation, with the possible relevant exception of PROG, who sensibly increased their distance from

Table 3. Change in anthropometric and clinical parameters at year 2 after liver transplantation *vs.* baseline according to the outcome group.

	REG		NON-REG		PROG		NON-PROG	
	Mean (95% CI)	*p* value	Mean (95% CI)	*p* value	Mean (95% CI)	*p* value	Mean (95% CI)	*p* value
HbA_{1c}, %	0.53 (0.15; 0.92)	0.009	0.41 (−0.44; 1.25)	0.313	2.13 (1.69; 2.56)	0.053	0.43 (0.13; 0.72)	0.006
Glucose, mmol/L	−0.05 (−0.40; 0.31)	0.791	0.18 (−1.07; 1.42)	0.764	1.53 (0.73; 2.32)	0.176	0.15 (−0.09; 0.39)	0.206
Glucose-2 h, mmol/L	−5.99 (−6.81; −5.16)	<0.0001	−1.62 (−3.99; 0.76)	0.164	3.76 (−0.72; 8.23)	0.973	−1.14 (−1.79; −0.49)	0.001
Insulin, pmol/L	−41.6 (−68.9; −14.3)	0.005	−34.32 (−83.6; 15.0)	0.154	−7.7 (−108.0; 92.6)	0.504	−36.0 (−55.4; −16.5)	0.001
C-peptide, nmol/L	−0.35 (−0.55; −0.16)	0.001	−0.28 (−0.71; 0.16)	0.190	0.49 (−1.80; 2.79)	0.170	−0.23 (−0.36; −0.10)	0.001
Body weight, kg	−1.71 (−4.86; 1.44)	0.273	0.11 (−8.19; 8.40)	0.978	3.38 (−19.7; 26.5)	0.273	2.69 (0.00; 5.39)	0.050
BMI, kg/m^2	−0.91 (−2.15; 0.33)	0.141	0.14 (−2.61; 2.89)	0.916	2.11 (−7.3; 11.5)	0.869	0.80 (−0.16; 1.76)	0.101
Waist circumference, cm	0.57 (−2.85; 3.98)	0.735	−1.77 (−8.71; 5.17)	0.589	1.25 (−25.9; 28.4)	0.366	2.78 (−0.57; 6.12)	0.102
Hip circumference, cm	−1.04 (−3.95; 1.86)	0.464	−0.92 (−5.62; 3.77)	0.676	1.00 (−15.6; 17.6)	0.327	1.43 (−1.10; 3.95)	0.260
Triglycerides, mmol/L	0.36 (0.14; 0.58)	0.002	0.40 (0.20; 0.61)	0.001	0.94 (−0.11; 2.00)	0.706	0.40 (0.14; 0.66)	0.003
Total cholesterol, mmol/L	0.85 (0.28; 1.42)	0.005	0.58 (−0.43; 1.59)	0.234	1.26 (−0.46; 2.97)	0.905	0.76 (0.21; 1.30)	0.008
HDL cholesterol, mmol/L	0.17 (−0.12; 0.46)	0.230	−0.13 (−0.46; 0.21)	0.427	−0.25 (−1.08; 0.58)	0.783	−0.08 (−0.28; 0.12)	0.410
LDL cholesterol, mmol/L	0.52 (−0.01; 1.05)	0.055	0.52 (−0.26; 1.30)	0.171	1.08 (−0.27; 2.43)	0.996	0.67 (0.21; 1.13)	0.005
Systolic BP, mmHg	13.7 (6.9; 20.5)	<0.0001	11.7 (2.9; 20.5)	0.014	20.0 (−8.3; 48.3)	0.528	9.25 (4.81; 13.69)	0.000
Diastolic BP, mmHg	9.13 (4.92; 13.34)	<0.0001	11.3 (4.0; 18.6)	0.005	12.5 (−12.2; 37.2)	0.225	6.13 (2.79; 9.46)	0.001
Total proteins, g/L	−0.38 (−0.72; −0.04)	0.030	−0.25 (−1.05; 0.55)	0.504	−0.97 (−3.92; 1.97)	0.775	0.03 (−0.30; 0.37)	0.835
Albumin, g/L	1.14 (0.90; 1.38)	<0.0001	1.08 (0.75; 1.41)	<0.0001	0.93 (0.16; 1.69)	0.659	0.84 (0.64; 1.04)	0.000
Total bilirubin, µmol/L	−35.7 (−50.8; −20.5)	<0.0001	−25.9 (−41.5; −10.4)	0.004	−22.9 (−47.5; 1.7)	0.885	−52.3 (−75.2; −29.4)	0.000
Direct bilirubin, µmol/L	−22.8 (−32.4; −13.2)	<0.0001	−16.6 (−27.4; −5.8)	0.006	−12.1 (−31.3; 7.0)	0.572	−31.5 (−52.3; −10.8)	0.004
AST, U/L	−65.1 (−96.0; −34.1)	<0.0001	−44.6 (−81.2; −8.0)	0.021	−28.8 (−64.8; 7.3)	0.888	−40.5 (−54.8; −26.2)	0.000
ALT, U/L	−31.2 (−48.8; −13.5)	0.001	−0.75 (−34.6; 33.1)	0.962	−6.5 (−30.9; 17.9)	0.331	−22.8 (−36.7; −8.9)	0.002
GGT, U/L	16.6 (−56.8; 89.9)	0.644	49.0 (−43.0; 141.0)	0.266	1.50 (−360.7; 363.7)	0.145	−22.7 (−59.1; 13.7)	0.214
ALP, U/L	−32.0 (−76.8; 12.8)	0.152	−37.0 (−86.8; 12.8)	0.130	−81.5 (−258.3; 95.3)	0.177	−48.8 (−77.4; −20.2)	0.001
Pseudocholinesterase, U/L	4,777 (3,836; 5,718)	<0.0001	4,334 (3,222; 5,445)	<0.0001	3,283 (−2,687; 9,254)	0.158	3,631 (2,598; 4,663)	0.000
eGFR, ml/min/1.73 m^2	−18.0 (−25.1; −10.8)	<0.0001	−18.3 (−31.6; −4.9)	0.012	−20.3 (−50.8; 10.3)	0.278	−11.4 (−18.5; −4.3)	0.002

Values are mean difference (95% CI). Paired Student's *t* test and Wilcoxon signed ranks test for parametric and non-parametric variables, respectively. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyltransferase; HbA_{1c}, haemoglobin A_{1c}; NON-PROG, non-progressors; NON-REG, non-regressors; PROG, progressors; REG, regressors.

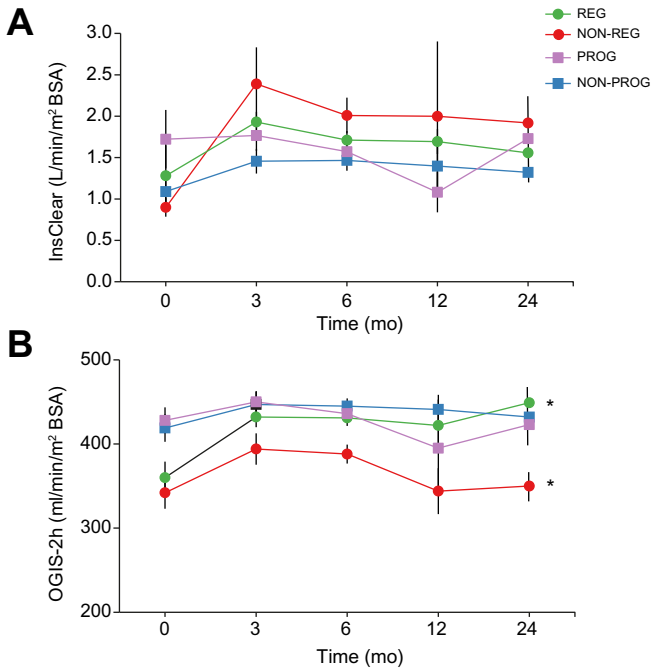

Fig. 1. Time course of InsClear and OGIS-2 h. Changes in (A) InsClear and (B) OGIS-2 h over the 2-year follow-up in REG, NON-REG, PROG and NON-PROG patients. Data are mean ± SEM. *p <0.05: OGIS-2 h for REG, overall and at all post-OLT time points *vs.* baseline; and for NON-REG, overall and at month 3 and 6 post-OLT *vs.* baseline (hierarchical general linear model). InsClear, insulin clearance index; NON-PROG, non-progressors; NON-REG, non-regressors; OGIS-2 h, Oral Glucose Insulin Sensitivity index at 2 hours after the OGTT; OGTT, oral glucose tolerance test; OLT, orthotopic liver transplantation; PROG, progressors; REG, regressors.

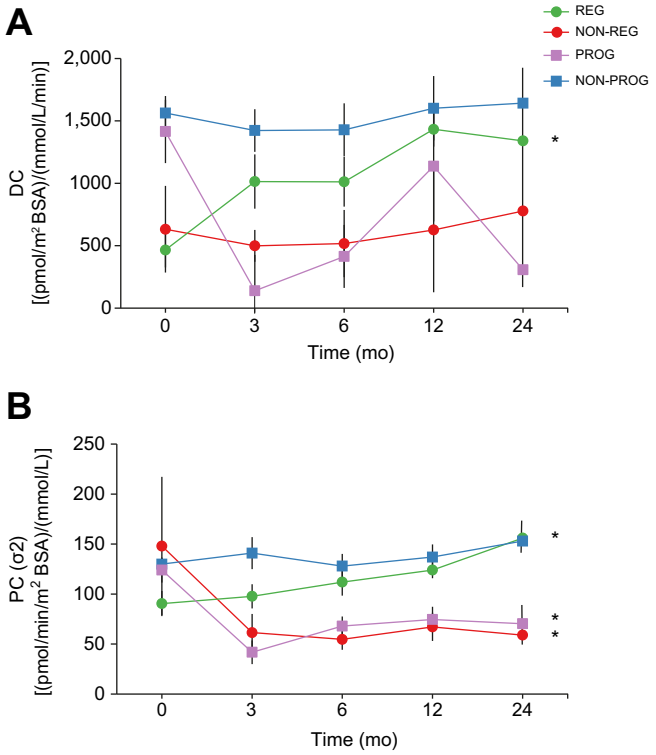

Fig. 2. Time course of β-cell function. Changes in (A) DC and (B) PC (σ2) over the 2-year follow-up in REG, NON-REG, PROG and NON-PROG patients. Data are mean ± SEM. *p <0.05: DC for REG, overall and at all post-OLT time points *vs.* baseline; and for PROG, overall (Friedman test followed by Wilcoxon test); PC for NON-REG, overall and at month 3 post-OLT *vs.* baseline; REG, overall and at month 12 and 24 post-OLT *vs.* baseline; and PROG, overall and at month 3 and 24 post-OLT *vs.* baseline (hierarchical general linear model). DC, derivative control; NON-PROG, non-progressors; NON-REG, non-regressors; OLT, orthotopic liver transplantation; PC (σ2), glucose sensitivity of proportional control; PROG, progressors; REG, regressors.

normalcy, suggesting that the pathophysiological disruption responsible for progression to DM is a process which takes place almost entirely within 3 months after OLT.

Importantly, 3 months after OLT, no statistically significant changes occurred in β-cell function in any group, but for the improvement in DC seen in REG. Though only a relatively small fraction of total insulin secretion is accounted for by DC during an OGTT, it is possible that the amelioration of DC is a biomarker and/or a causal factor of the subsequent improvement in glucose regulation occurring in these patients. While β-cell DCs during OGTT and intravenous glucose tolerance test (IVGTT) cannot be considered pathophysiologically superimposable to each other, β-cell DCs during the IVGTT[24] or the hyperglycaemic clamp[25] account for the first phase of insulin secretion, the most sensitive β-cell derived indicator of the glucose regulation status[26] and its future change.[23]

The vector plots show that the distance from the normal curve remained stable in NON-PROG, and possibly increased in NON-REG. In both groups, the increase in insulin clearance was still detectable at year 2, whereas the improvement in insulin sensitivity faded over time. Though the interpretation of changes in insulin sensitivity is unclear, as they can be affected by a number of factors (lifestyle, adiposity, drugs, *etc.*), failure to maintain the initial improvement brought about by OLT is detrimental for glucose regulation.

While the net impact of changes observed in NON-REG and NON-PROG is negligible, in the paths of PROG and REG to worse and better glucose regulation, respectively, the predominant pathogenic factor appears to be the bioavailability of insulin in response to glucose. Thus, the β-cell appears to play a central role both in the development of pre-transplant DM[8] and its regression after OLT, though baseline β-cell function did not predict outcome. These findings are consistent with those of Perseghin *et al.*[14] however, in contrast to this previous report, we were able to demonstrate that, in REG individuals, the restoration of β-cell function started with an amelioration of DC, which was followed by an increase in PC, accompanied and possibly favoured by the maintenance of the initial improvement in insulin sensitivity.

The main strengths of this work are the simultaneous assessment of β-cell function, insulin clearance, and insulin sensitivity and the monitoring of their dynamic interplay over a 2-year period post-OLT. Limitations include the heterogeneity of aetiologies of liver disease. In addition, though none of the known risk factors for the occurrence or persistence of DM after OLT (*i.e.*, changes in body weight, immunosuppressant treatment, and possibly the aetiology of liver disease) were found to differ among groups or to independently predict outcome, the relatively small size of the cohort may have hampered a thorough evaluation of their role in post-OLT changes in glucose regulation and its determinants. However, this analysis was beyond the scope of our investigation. Finally, the behaviour of PROG should be interpreted with much caution owing to the very small number of patients in this group, though data were

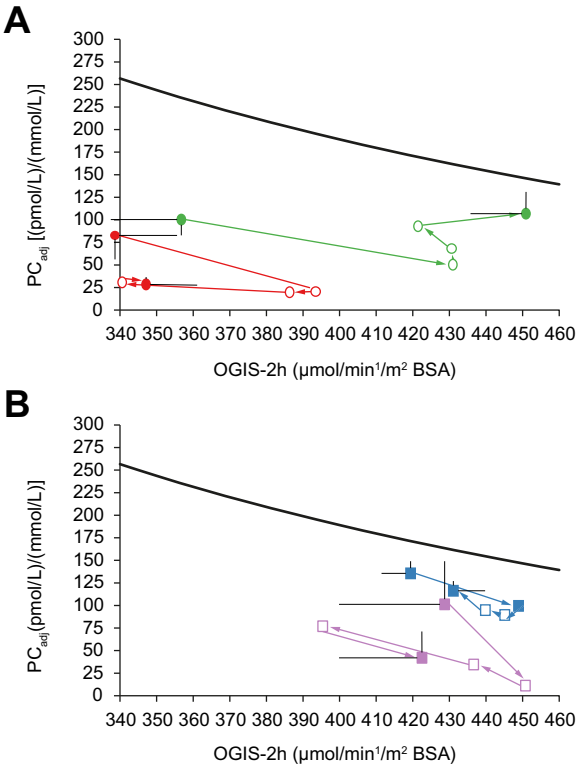

Fig. 3. Time course of the relationship between PC_{adj} and OGIS-2 h. Vector plots of the relationship between insulin bioavailability in response to glucose (PC_{adj}) and insulin sensitivity (OGIS-2 h) over the 2-year follow-up in (A) REG (green line and circles) and NON-REG (red line and circles) patients and in (B) PROG (purple line and squares) and NON-PROG (blue line and squares) patients. Data are mean ± SEM. The concave line represents the normal feedback loop between glucose and insulin. NON-PROG, non-progressors; NON-REG, non-regressors; OGIS-2 h, Oral Glucose Insulin Sensitivity index at 2 hours after the OGTT; OGTT, oral glucose tolerance test; OLT, orthotopic liver transplantation; PC_{adj} = insulin bioavailability; PROG, progressors; REG, regressors.

confirmed by including the 4 patients who became IGT in this group.

In conclusion, bioavailability of insulin in response to glucose, in which β-cell function appears to play a major role, is the key process governing favourable or detrimental changes in glucose regulation after OLT. In consideration of the negative prognostic impact of DM in cirrhotic patients undergoing OLT, therapies should be developed to sustain β-cell function in these individuals.

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Conflict of interest

Dr. Grancini reported lecture fees from Astra-Zeneca, Eli Lilly, Merck-Sharp&Dohme, Roche, Sanofi-Aventis, and consulting fees from Boehringer Ingelheim. Dr. Lunati Dr. Pugliese reported lecture fees from Merck-Sharp&Dohme. Dr. Palmieri reported lecture fees from Astra-Zeneca, Eli Lilly, Merck-Sharp&Dohme, and consulting fees from Boehringer Ingelheim, Novo Nordisk. Dr. Resi reported lecture fees from Eli-Lilly, Novartis, Novo Nordisk, Sanofi-Aventis, SigmaTau, Takeda, and consulting fees from Janssen-Cilag. Dr. Pugliese reported lecture fees from Astra-Zeneca, Eli-Lilly, Merck-Sharp&Dohme, Sigma-Tau, Takeda. Dr. Bonadonna reported lecture fees from Astra-Zeneca, Eli-Lilly, Sanofi-Aventis, and consulting fees from Astra-Zeneca, Boehringer Ingelheim, Eli-Lilly, Johnson&Johnson, Merck-Sharp&Dohme, Sanofi-Aventis. Dr. Orsi reported lecture fees from Abbot, Astra-Zeneca, Eli-Lilly, Lifescan, Sanofi-Aventis, Takeda, and consulting fees from Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, Sanofi-Aventis. No other disclosures were reported.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conception and design: VG, GP, RCB, and EO. Generation, collection, and assembly of data: VG, MEL, SG, MFD, EP, VR, and EO. Analysis and interpretation of data: VG, MT, MEL, MLB, SG, MFD, EP, VR, GP, RCB, and EO. Drafting the manuscript: VG, GP, RCB, and EO. Critical revision of the manuscript for important intellectual content: MT, MEL, MLB, SG, MFD, EP, and VR. Mathematical modelling: MLB and RCB. Statistical analysis: GP and RCB. Study supervision: RCB and EO.

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Supplementary data

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