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Cognitive Outcome After Islet Transplantation

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Background. Severe or repeated hypoglycemia events may favor memory complaints in type 1 diabetes (T1D). Pancreatic islet transplantation (IT) is an alternative option to exogenous insulin therapy in case of labile T1D, implying a maintenance immunosuppression regimen based on sirolimus or mycophenolate, associated with tacrolimus, that may also have neurological toxicity. The objective of this study was to compare a cognitive rating scale Mini-Mental State Examination (MMSE) between T1D patients with or without IT and to identify parameters influencing MMSE. **Methods.** This retrospective cross-sectional study compared MMSE and cognitive function tests between islet-transplanted T1D patients and nontransplanted T1D controls who were transplant candidates. Patients were excluded if they refused. **Results.** Forty-three T1D patients were included: 9 T1D patients before IT and 34 islet-transplanted patients (14 treated with mycophenolate and 20 treated with sirolimus). Neither MMSE score ($P=0.70$) nor higher cognitive function differed between islet versus non–islet-transplanted patients, whatever the type of immunosuppression. In the whole population (N=43), MMSE score was negatively correlated to glycated hemoglobin ($r=-0.30$; $P=0.048$) and the time spent in hypoglycemia on the continuous glucose monitoring ($r=-0.32$; $P=0.041$). MMSE score was not correlated to fasting C-peptide level, time spent in hyperglycemia, average blood glucose, time under immunosuppression, duration of diabetes, or beta-score (success score of IT). **Conclusions.** This first study evaluating cognitive disorders in islet-transplanted T1D patients argues for the importance of glucose balance on cognitive function rather than of immunosuppressive treatment, with a favorable effect of glucose balance improvement on MMSE score after IT.

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Type 1 diabetes (T1D) is a multifactorial autoimmune disease, leading to the destruction of the pancreatic insulin-secreting beta cells.[1] Exogenous insulin administration limits chronic hyperglycemia, which is responsible for micro- and macroangiopathic complications, at the cost of an increased risk of hypoglycemia,[2] associated with an enhanced risk of mortality.[3]

Severe or repeated hypoglycemia events may favor memory complaints, as demonstrated in different studies,[4-10] including a meta-analysis of 62 studies showing that childhood hypoglycemia complicated by seizures or coma was associated with impaired verbal and visual-spatial memory in adulthood.[11] In another analysis comparing T1D patients with nondiabetic control subjects, cognitive assessment, although performed during a period of glycemic control, showed impairment of several cognitive domains, including information processing speed, attention, mental flexibility, and visual perception, whereas other domains such as selective attention, language, or memory did not differ from control subjects in this study.[12]

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All data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

All authors participated in the research. A.M. and M.-C.V. performed data analysis and wrote the article. C.T. performed statistical analysis. A.J., M.L., B.C., K.L.M., F.D., M.M., M.C., and Fr.P. were deeply involved in the recruitment and follow-up of the patients. Fl.P., M.-A.M., and A.R. performed cognitive assessments.

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The link between diabetes and cognitive impairment is complex and multifactorial, underpinned by repeated episodes of hyperglycemia and hypoglycemia, microvascular and macrovascular complications, chronic inflammation, and mitochondrial dysfunction.[6,13]

Pancreatic islet transplantation is an alternative option to exogenous insulin therapy in the case of labile T1D.[14-16] It implies a maintenance immunosuppression based on tacrolimus, a calcineurin inhibitor, associated with either sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, or mycophenolate mofetil, an antimetabolite.

In organ transplant patients, the impact of immunosuppressive treatment on cognitive performance has been widely studied; an alteration in cognitive performance was shown among 37 heart transplant patients, mostly men aged 57 y old, on average 20 y after transplantation, mainly concerning the speed of information processing, executive functions, memory, and language.[17] Similar alterations in posttransplant cognitive abilities have been shown in lung transplant patients compared with the pretransplant assessment, especially in the eldest subjects and those with a lower education level.[18,19] Nevertheless, there was no control group, and the results were discordant with other studies. For instance, an improvement of certain cognitive performances in renal transplanted subjects compared with nontransplanted patients in end-stage renal disease was shown,[20-22] and a 2018 meta-analysis found an improvement of cognitive performances in transplanted subjects compared with their own cognitive assessment before renal transplantation whether they were on dialysis or conservative treatment.[23] In contrast, their abilities remained strictly inferior to those of healthy control subjects, particularly in verbal fluency, executive function, and language.

These alterations could be mediated through an increased level of oxidative stress;[24] a decreased level of cytokines, which play an important role in neuronal signaling and synaptic plasticity;[25] and decreased oxygen consumption with mitochondrial dysfunction.[26]

To our knowledge, no evaluation of the cognitive impact of islet transplantation has been published in the literature to date. However, the issue is important because islet-transplanted patients generally have a durable suppression of hypoglycemia related to the restoration of endogenous beta-cell function with a much better glucose balance, whereas they could have potential negative impact related to previous repeated severe hypoglycemia events, long-term immunosuppression, and micro- and macroangiopathic complications.

Therefore, this study aimed to characterize cognitive functions in T1D patients undergoing islet transplantation by comparison with nontransplanted T1D controls, with the objective to identify the determinants of this outcome, if any.

PATIENTS AND METHODS

Study Design

This monocentric cross-sectional study was conducted in a single university hospital from 2003 to 2016 in the framework of clinical trials of islet transplantation approved by an ethical committee (ClinicalTrials.gov; NCT01123187, NCT00446264, NCT01148680). The protocol of these trials has been detailed elsewhere.[14,15] The 2 first clinical trials began in 2003 and included patients who had been receiving sirolimus for a period that was probably the longest in literature because the drug was given in these trials before it was made commercially available in France.

The main objective of this work was to compare the results of a cognitive assessment scale using Mini-Mental State Examination (MMSE) between islet-transplanted T1D patients and nontransplanted T1D controls. Our secondary objectives were to characterize the type of impairment of higher cognitive functions in T1D patients with and without islet transplantation and to conduct a correlation study between the MMSE score and the main parameters of glucose balance using a continuous glucose monitoring system (CGMS) and islet transplantation.

Patients

Specialized cognitive assessment was offered to all T1D patients considering or having received islet transplantation because of T1D complicated with severe hypoglycemia events or impaired hypoglycemia awareness, or glycemic lability, or because of already receiving immunosuppression for kidney transplantation in a single university hospital. These investigations were proposed systematically to the patients after a few patients had reported memory disorders during the long-term post–islet transplantation follow-up. The exclusion criteria for the present study were the refusal of the patient to undergo a cognitive evaluation.

The control group (group 1) corresponded to T1D subjects referred to the department to evaluate the benefit–risk ratio of potential islet transplantation because of T1D complicated with severe hypoglycemia and/or impaired hypoglycemia awareness or glycemic lability.

The transplanted group (group 2) corresponded to patients who had underwent islet transplantation from 2014 onward. All transplanted patients received combined maintenance immunosuppression with a calcineurin inhibitor associated with either mycophenolate (group 2A) or sirolimus (group 2B). Note that the induction protocol was different in the 2 groups. Group 2A received induction with a unique bolus of steroids (1 mg/kg of body weight) just before antilymphocyte antibodies for the first islet injection, followed by anti–interleukin 2 receptor antibodies for the second and the third islet injection, each islet injection being associated with a course of etanercept and the 2 or 3 islet injections being done for a 3-mo period in mean. Group 2B (Edmonton protocol) only received anti–interleukin 2 receptor antibodies for each of the 2 or 3 islet injections without steroid or etanercept. We split the whole islet-transplanted group into those 2 subgroups to evaluate the potential impact of the type of immunosuppressive treatment received.

Data Collection

Data were collected through the patient's computerized medical record after informed consent. The following demographic and clinical characteristics were collected for all patients: gender, age at the time of cognitive assessment, educational level, duration of diabetes at the time of cognitive assessment, body mass index (BMI) in kilogram per meter square, smoking status, presence of macroangiopathic complications (stroke, hypertension, or treatment for high blood pressure, treated coronary artery disease, carotid artery disease, or lower extremity arterial disease confirmed by ultrasound screening), and presence of microangiopathic complications (retinopathy, nephropathy defined

by microalbuminuria >30 mg/g of urine creatinine, and neuropathy confirmed by electromyogram). For islet-transplanted patients, age and duration of diabetes at the time of islet transplantation; glycated hemoglobin (HbA1c) before transplantation, whole duration of immunosuppressive treatment (since the first transplantation of either kidney—for islet after kidney transplantation—or since islet transplantation—for islet transplantation alone), which corresponds to the time in years between the transplantation and the cognitive evaluation; and the duration of immunosuppression since islet transplantation were recorded.

The following metabolic parameters were also collected at the time of cognitive assessment: blood HbA1c, fasting and postprandial C-peptide and glucose levels, and lipid parameters; average blood glucose and time spent in hypoglycemia <70 mg/dL and in hyperglycemia >180 mg/dL on CGMS; cognitive complaints before the patient's cognitive evaluation; impaired higher executive functions among episodic memory, language, orientation, executive functions, attention, visual-constructive skills, gnosia, and working memory on the neuropsychological assessment; and score of the cognitive evaluation scale (MMSE) on 30 points.

The MMSE score is a 30-point questionnaire extensively used to estimate the severity and progression of cognitive impairment.[27] Administration of the test takes between 5 and 10 min and examines functions including registration (repeating named prompts), attention and calculation, recall, language, ability to follow simple commands, and orientation. Although MMSE scores should always be considered in relation to the age and education level of patients, an MMSE score of ≥27 is considered normal cognition, an MMSE score between 21 and 26 corresponds to mild cognitive impairment, and an MMSE score between 11 and 20 or <11 corresponds to moderate and to severe cognitive impairment, respectively. The MMSE score cannot be >30.

For transplanted patients, we calculated beta-score (score of success of islet transplantation between 0 and 8, 8 being the best success) and Igls score (a combined score assessing the functional status of transplanted islet between optimal, good, marginal, or failure).[28]

Statistical Analysis

Categorical variables were described in terms of numbers and percentages. Non-Gaussian quantitative variables were described in terms of median and interquartile range and Gaussian quantitative variables in terms of mean and standard deviation. The normality of the distributions was checked graphically and tested using the Shapiro-Wilk test. Correlations of quantitative variables with the MMSE were assessed using the Spearman correlation coefficient.

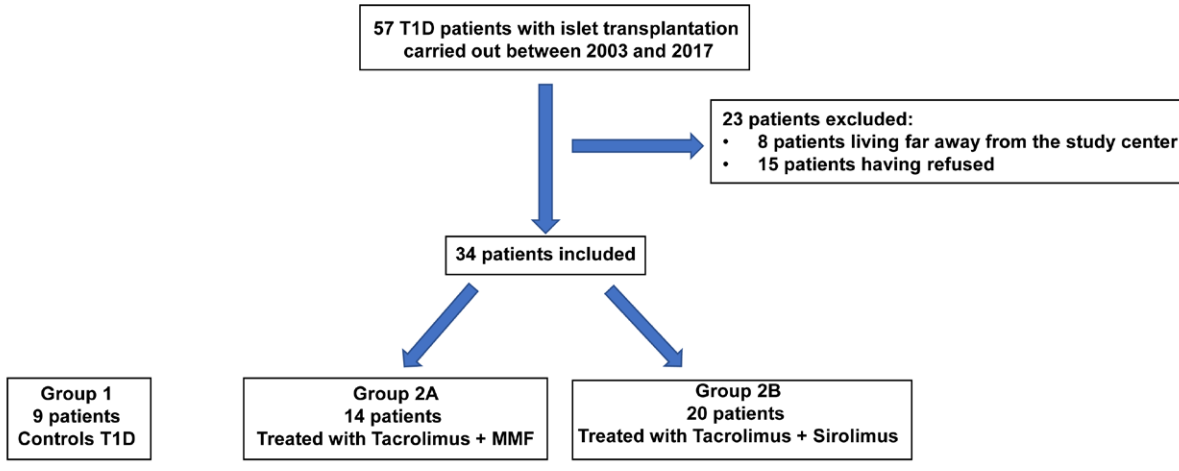
Comparison of MMSE between the 3 patient groups was performed using a Kruskal-Wallis test. Comparisons of the different types of cognitive impairment between the 3 patient groups were performed using chi-square tests. Two-tailed tests were performed at the 5% significance level. Statistical analyses were performed using SAS software (SAS Institute version 9.4).

RESULTS

Demographic and Clinical Characteristics of the Study Population

Fifty-seven T1D patients received islet transplantation between 2003 and 2016. Twenty-three patients were excluded from this study: 8 patients lived too far away from the study center, and 15 patients refused to participate. Besides, 9 T1D patients considering islet transplantation were included. Finally, 43 T1D patients, of whom 34 were islet-transplanted patients, were included in the study (Figure 1) and divided into 3 groups:

- Group 1: 9 T1D patients in the pretransplantation assessment (control)



Legend: T1D: Type 1 Diabetes; MMF: mycophenolate mofetil

FIGURE 1. Flowchart of the study. MMF, mycophenolate mofetil; T1D, type 1 diabetes.

- Group 2A: 14 T1D islet-transplanted patients receiving maintenance immunosuppression with tacrolimus and mycophenolate mofetil:
  - 3 islet-after-kidney transplantation
  - 11 islet-alone transplanted patients

- Group 2B: 20 T1D islet-transplanted patients receiving tacrolimus and sirolimus:
  - 2 islet-after-kidney transplantation
  - 18 islet-alone transplanted patients

The main demographic and clinical characteristics of the whole population and the 3 groups are detailed in Table 1. Briefly, the 43 patients included in the study had a mean age at cognitive evaluation of 54.4 ± 7.8 y with a balanced sex ratio (46.5% female patients).

The age at transplantation was grossly similar between the 2 groups defined by the type of immunosuppression (49.7 ± 8 y in the islet-transplanted patients treated with mycophenolate mofetil [group 2A] and 47.2 ± 8.5 y in those treated with sirolimus [group 2B]). The level of education was "high" in a little more than one-quarter of the whole cohort and tended to be higher (about one-third of "high level" education in the transplanted group versus 10% in the control group). The median duration of diabetes at the time of cognitive evaluation was 30 (27–40) y, with a mean BMI before transplantation of 24.3 ± 2.1 kg/m^2 in the T1D islet-transplanted group (2A + 2B) and a mean BMI at time of cognitive evaluation at 25.8 ± 4 kg/m^2 in the control group (group 1) and at 22.9 ± 2.5 kg/m^2 in the T1D islet-transplanted group (group 2A + 2B). The cognitive evaluation was performed 3.1 ± 2.6 y after transplantation for the 2A group and 6.9 ± 4 y for the 2B group. At the time of cognitive assessment, 64.3% of group 2A patients (tacrolimus + mycophenolate; n = 9/14) had a good or optimal islet function according to the Igls criteria (meaning HbA1c <7%, no severe hypoglycemia event, basal C-peptide level above pretransplant level and stimulated C-peptide level >0.5 ng/mL, and daily insulin need <50% as compared with pretransplantation level). In group 2B (sirolimus + tacrolimus), 50% of patients (10/20) had a good or optimal islet function.

Concerning macroangiopathic complications of the whole cohort at the time of cognitive assessment, no patient had a stroke; about half of them had hypertension; around one-quarter had coronary artery disease (the most heterogeneous frequency across groups: 15%–44%). Carotid artery disease or lower extremity arterial disease was present in 22% to 43% for both parameters across the 3 groups.

Concerning microangiopathic complications, nephropathy was present in 25% to 42.9% of the patients across the 3 groups, retinopathy in three-quarters of the patients, and neuropathy in about 55% of the patients, with the same distribution across the 3 groups for these 2 last complications.

TABLE 1.

Demographic and clinical characteristics of the population study

	All patients	Controls T1D	T1D islet-transplanted	T1D islet-transplanted treated by MMF	T1D islet-transplanted treated by sirolimus
	(N = 43)	Group 1 (n = 9)	Group 2A + 2B (n = 34)	Group 2A (n = 14)	Group 2B (n = 20)
Demographical characteristics					
Age at time of transplant, y	–	–	48.2 ± 8.3	49.7 ± 8	47.2 ± 8.5
Age at time of cognitive assessment, y	54.4 ± 7.8	55.3 ± 9	54.2 ± 7.6	53.5 ± 8.5	54.7 ± 7.1
Sex, female	20 (46.5)	4 (44.4)	16 (47.1)	6 (42.9)	10 (50)
Cognitive complaint at the time of assessment	24 (55.8)	6 (66.7)	18 (52.9)	9 (64.3)	9 (45)
Education level					
Primary without degree	4 (9.3)	2 (22.2)	2 (5.9)	2 (14.3)	0 (0)
Primary with degree	15 (34.9)	4 (44.4)	11 (32.4)	2 (14.3)	9 (45)
Secondary	12 (27.9)	2 (22.2)	10 (29.4)	5 (35.7)	5 (25)
High	12 (27.9)	1 (11.1)	11 (32.4)	5 (35.7)	6 (30)
Clinical characteristics					
Duration of diabetes at time of cognitive assessment, y	30 (27;40)	39 (32;44)	29.5 (26;35)	30.5 (27;42)	28 (25;31.5)
Time under immunosuppression, y	–	–	5.0 ± 3.8	3.0 ± 2.6	6.5 ± 4
BMI before transplantation, kg/m^2	–	–	24.3 ± 2.1	24.6 ± 2	24 ± 2.2
BMI at time of cognitive assessment, kg/m^2	23.5 ± 3.1	25.8 ± 4	22.9 ± 2.5	23.6 ± 3	22.4 ± 2.1
Macroangiopathic complications					
Hypertension	21 (48.8)	5 (55.6)	16 (47.1)	5 (35.7)	11 (55)
Stroke	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ischemic heart disease	11 (25.6)	4 (44.4)	7 (20.6)	4 (28.6)	3 (15)
Hypertensive cardiopathy	1 (2.3)	0 (0)	1 (2.9)	1 (7.1)	0 (0)
Carotid arteriopathy	13 (30.2)	2 (22.2)	11 (32.4)	6 (42.9)	5 (25)
Lower extremity arterial disease	14 (32.6)	2 (22.2)	12 (35.3)	6 (42.9)	6 (30)
Microangiopathic complications					
Nephropathy	14 (32.6)	3 (33.3)	11 (32.4)	6 (42.9)	5 (25)
Retinopathy	32 (74.4)	7 (77.8)	25 (73.5)	10 (71.4)	15 (75)
Neuropathy	24 (55.8)	5 (55.6)	19 (55.9)	8 (57.1)	11 (55)

Values are expressed as the number (%), mean ± standard deviation, or median (interquartile range).
BMI, body mass index; MMF, mycophenolate mofetil; T1D, type 1 diabetes.

Metabolic Characteristics at the Time of Cognitive Assessment

The metabolic characteristics of the 3 groups are detailed in Table 2. HbA1c levels at the time of the cognitive assessment were overtly higher (8.5% ± 1.6%) in the control group than in the islet-transplanted groups: 6.5% ± 1% in group 2A and 6.8% ± 1.2% in group 2B, respectively. Group 2A + 2B also showed fasting and postprandial blood C-peptide levels of 1 and >2 ng/mL, respectively, compared with undetectable levels in the control group (group 1). Fasting and postprandial mean blood glucose levels were higher in the T1D control group, respectively: 210 ± 120 and 200 ± 90 mg/dL compared with the transplanted group (group 2A + 2B), 140 ± 50 and 160 ± 70 mg/dL, respectively. The median levels of blood triglyceride, high-density lipoprotein, and low-density lipoprotein cholesterol were grossly similar across the different groups. The median time spent in hyperglycemia on CGMS was higher in the T1D control group (56.5% [34.5%–71%] versus 1% [0%–20%]) in the transplanted patients (group 2A + 2B). The median time spent in hypoglycemia was overtly higher in the T1D control group (6.5% [2%–20%] versus 0% [0%–3%]) in the transplanted patients (group 2A + 2B) in regard to a lower average median glucose in this last group (120 [110–150] mg/dL) than in the control group (180 [160–200] mg/dL). Most patients were nonsmokers at the time of cognitive evaluation.

MMSE and Cognitive Function Assessment

The results of the cognitive function assessment are summarized in Table 3. A grossly similar proportion of patients (45%–66%) reported a cognitive complaint at systematic screening before the cognitive assessment across the 3 groups. Regarding the primary endpoint, the minimal and maximal values of the MMSE score varied between 19 and 30 when all groups were combined and when the T1D control group only was considered. The MMSE score varied between 20 and 30 in the T1D islet-transplanted group. Overall, the median MMSE score (between 27 and 29) did not differ significantly across the 3 groups ($P = 0.70$). There was also no difference across the 3 groups in the frequency of impairment of higher cognitive functions: episodic memory ($P = 0.54$; even if it was more often impaired in the control group—>50% versus about one-third—than in the transplanted patients), executive functions ($P = 0.92$; which was grossly impaired in half of the patients in a homogeneous way across the 3 groups), attention ($P = 0.60$; impaired around an average 60% of cases across the 3 groups), visual-constructive skills ($P = 0.63$; altered in an average 20% of cases), and working memory ($P = 0.85$; impaired in about 50% of cases). There was no statistically feasible comparison for gnosis, language, and orientation because the prevalence of impairment for each of these functions was <8 patients in each group.

Correlation Between MMSE and Clinical and Metabolic Parameters

In the whole cohort, the MMSE score was positively correlated with education level ($r = 0.37$, $P = 0.01$) and negatively correlated with HbA1c ($r = –0.30$, $P = 0.048$) and time spent in hypoglycemia on the CGMS ($r = –0.32$, $P = 0.041$; Figure 2A and B). There was no correlation with age at cognitive assessment, duration of diabetes, average blood glucose, the time spent in hyperglycemia, duration of immunosuppression, fasting C-peptide, or beta-score.

Details of Spearman coefficients are specified in Table 4. Details of the cognitive tests performed are available in the appendix in **Table S1** (**SDC**, http://links.lww.com/TXD/A531). Details about the evolution of metabolic parameters before

TABLE 2.

Biological metabolic parameters and smoking habits at time of cognitive assessment

	All patients	Controls T1D	T1D islet-transplanted	T1D islet-transplanted treated by MMF	T1D islet-transplanted treated by sirolimus
	(N = 43)	Group 1 (n = 9)	Group 2A+2B (n = 34)	Group 2A (n = 14)	Group 2B (n = 20)
HbA1c, %	7.1 ± 1.4	8.5 ± 1.6	6.7 ± 1.1	6.5 ± 1	6.8 ± 1.2
C-peptide					
Fasting, ng/mL	0.8 ± 0.7	0.1 ± 0.1	1 ± 0.7	1.1 ± 0.7	1 ± 0.8
Postprandial, ng/mL	1.9 ± 2	0.1 ± 0.1	2.3 ± 2	2.6 ± 2.1	2.2 ± 1.9
Blood glucose					
Fasting, mg/dL	150 ± 70	210 ± 120	140 ± 50	120 ± 40	140 ± 50
Postprandial, mg/dL	160 ± 80	200 ± 90	160 ± 70	170 ± 90	150 ± 60
Lipid parameter					
Triglycerides, mg/dL	100 ± 60	110 ± 80	90 ± 50	90 ± 30	100 ± 60
HDL cholesterol, mg/dL	60 ± 20	50 ± 20	60 ± 20	60 ± 20	60 ± 20
LDL cholesterol, mg/dL	100 ± 30	100 ± 30	100 ± 30	100 ± 40	100 ± 30
CGMS					
Average blood glucose, mg/dL	130 (110–170)	180 (160–200)	120 (110–150)	130 (110–150)	120 (110–160)
Time spent <70 mg/dL, %	0 (0–7)	6.5 (2–20)	0 (0–3)	0 (0–5)	0 (0–3)
Time spent >180 mg/dL, %	6 (0–40)	56.5 (34.5–71)	1 (0–20)	0 (0–6)	2 (0–22)
Smoking					
Never	25 (58.1)	5 (55.6)	20 (58.8)	10 (71.4)	10 (50)
Current	2 (4.7)	0 (0)	2 (5.9)	0 (0)	2 (10)
Former	16 (37.2)	4 (44.4)	12 (35.3)	4 (28.6)	8 (40)

Values are expressed as number (%), mean ± standard deviation, or median (interquartile range).

CGMS, continuous glucose monitoring system; HbA1c, glycated hemoglobin; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; MMF, mycophenolate mofetil; T1D, type 1 diabetes.

TABLE 3.

MMSE and characterization of impaired cognitive functions between the 3 groups

	T1D controls	T1D islet-transplanted	*P* value control vs transplanted[a]	T1D islet-transplanted treated with MMF	T1D islet-transplanted treated with sirolimus	*P*[b] across the 3 groups
	Group 1 (N = 9)	Group 2 (= 2A + 2B) (n = 34)		Group 2A (n = 14)	Group 2B (n = 20)	
MMSE score (patients)	27 (25–30)	28 (27–30)	0.44	29 (27–30)	28 (27–30)	0.70
Impaired episodic memory	5 (55.6)	12 (35.3)	0.44	5 (35.7)	7 (35)	0.54
Impaired language	1 (11.1)	4 (11.8)	–	4 (28.6)	0 (0)	–
Impaired orientation	0 (0)	1 (2.9)	–	1 (7.1)	0 (0)	–
Impaired executive functions	5 (55.6)	16 (47.1)	0.72	7 (50)	9 (45)	0.92
Impaired attention	6 (66.7)	21 (61.8)	1	10 (71.4)	11 (55)	0.60
Impaired visual-constructive skills	2 (22.2)	7 (20.6)	1	4 (28.6)	3 (15)	0.63
Impaired gnosis	2 (22.2)	4 (11.8)	–	1 (7.1)	3/20 (15)	–
Impaired working memory	4 (44.4)	15 (44.1)	1	7 (50)	8 (40)	0.85

Values are expressed as the number (%) or median (interquartile range).
[a]*P* values for the comparisons of group 1 vs all transplanted patients.
[b]*P* values for the comparisons of the 3 groups (group 1 vs group 2A vs group 2B).
–, not feasible because of small numbers of patients (N < 8); MMSE, Mini-Mental State Examination/30 points; T1D, type 1 diabetes.

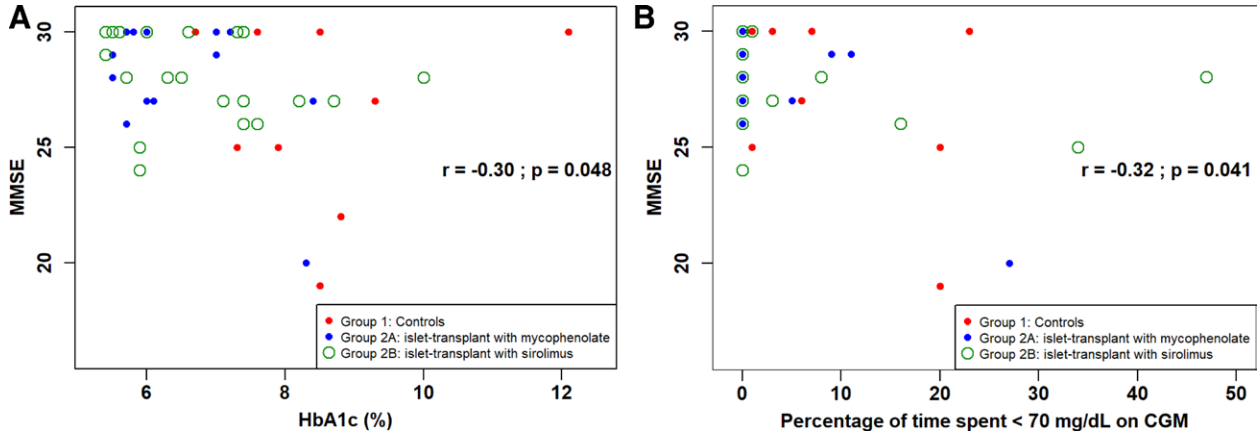


FIGURE 2. Correlation between MMSE score and HbA1c level (A) or percentage of time spent in hypoglycemia on CGM (B). CGM, continuous glucose monitoring; HbA1c, glycated hemoglobin; MMSE, Mini-Mental State Examination.

TABLE 4.

Correlation between MMSE score, HbA1c, CGMS parameters, and clinical parameters in the whole population

Global population	Spearman correlation	*P*
Age at cognitive assessment	0.02	0.9
Duration of diabetes	0.28	0.067
Educational level	0.37	**0.01**
HbA1c	–0.30	**0.048**
Average blood glucose	–0.17	0.30
Time spent <70 mg/dL	–0.32	**0.041**
Time spent >180 mg/dL	–0.26	0.10
Time under immunosuppression (since islet transplantation)	–0.28	0.10
Time under immunosuppression (since islet or kidney transplant)	–0.21	0.24
Fasting C-peptide	0.24	0.12
Beta-score	0.27	0.15

CGMS, continuous glucose monitoring system; HbA1c, glycated hemoglobin; MMSE, Mini-Mental State Examination.

and after islet transplantation are available in the appendix in **Table S2** (SDC, http://links.lww.com/TXD/A531).

DISCUSSION

Overall, this first study on cognitive function in islet- or non–islet-transplanted T1D patients did not show any difference in cognitive scores—assessed with the MMSE and with higher cognitive function tests—between not yet islet-transplanted patients and islet-transplanted patients, whatever the type of immunosuppression. In contrast, a weak but significant correlation was found between MMSE score and glucose balance reflected by HbA1c and time spent in hypoglycemia on CGMS. These results argue for a lack of impact of the presence, duration, and type of immunosuppressive regimen (mycophenolate mofetil versus sirolimus) on cognition and emphasize the major impact of glucose balance.

Of course, these results should be taken with caution because of different limitations, among which is the ancillary and cross-sectional character of the study performed in a monocentric small series with different periods between the 3 groups concerning the time under immunosuppression and the duration of diabetes. These limitations are related to the still rare and recent technique of islet transplantation and to the refusal of some transplanted patients to participate. This may have created a potential selection bias because the refusal to participate

could potentially be related to incipient cognitive impairment or the fear of evidence of cognitive impairment. T1D patients who were listed for transplantation were defined as the control group, but no control groups of (1) T1D patients, finally not eligible for islet transplantation; (2) age-matched well-balanced T1D patients (therefore not eligible for islet transplantation); and (3) healthy age-matched control group were included. All these groups could also have been interesting study groups. Because of these limitations, this study is probably underpowered to detect small differences. Entanglement between cognition and glucose balance is also possible, poor cognition being susceptible to impairing insulin adjustment from the patient and overall glucose balance. Nevertheless, the median MMSE score was globally normal between 27 and 29 across the 3 groups of patients. Finally, the choice of the MMSE, rather than the Montreal Cognitive Assessment, could be questioned. Both are the most commonly used tools for cognitive impairment screening.[27-31] The results of studies evaluating the superiority of the MMSE or Montreal Cognitive Assessment in the detection of cognitive impairment are controversial.[32-35] MMSE has been previously recommended in the GRECO (Groupe de Réflexion sur les Evaluations Cognitives), a French group working on cognitive assessment.[36]

In contrast with these limitations, the present exploratory study is the first study to evaluate cognitive function in islet-transplanted T1D patients with assessment of the type of impairment of the higher cognitive functions by comparison with a control group of potentially eligible poorly controlled age-matched T1D patients. Moreover, an assessment of the type and duration of immunosuppression on cognitive function was also performed.

The first finding of the study is the absence of differences of MMSE and other higher cognitive function scores between the 3 groups of patients, suggesting the lack of effect of immunosuppressive drugs or transplantation itself on cognitive functions. The consequences of immunosuppressive drugs on cognition are debated in the literature. Some studies indicate a negative impact after major organ transplantation, such as heart or lung,[17-19] but in these patients, cognitive impairment was observed 20 y after transplantation.[17] This is not the case in the present study, in which the time under immunosuppression was between 3 and 6 y. In contrast, a positive impact of kidney transplantation was observed on certain cognitive functions compared with the cognitive status before transplantation.[23] Results of the present study comparing cognitive functions before and after islet transplantation are intermediate between the previously published studies in solid organ transplantation showing no impact, either positive or negative, of the presence or the duration of immunosuppression or transplantation on cognitive function in our population. Note that the patients included after "islet-after kidney" transplantation were assessed uniquely after both kidney and islet transplantation. The number of patients included was nevertheless too low to adjust the comparison. The lack of positive cognitive impact of islet transplantation may result from the small size of the control group or from the macro- and microangiopathic complications of these patients, who had high blood pressure and disturbed lipid balance, despite both disorders were treated.[37]

In addition, no difference in cognitive function was found concerning the type of immunosuppression between the 2 islet-transplanted groups receiving either mycophenolate or sirolimus or between each group and the control group. Therefore, the results of the present study are reassuring regarding the long-term neurological safety of immunosuppressive drugs, especially sirolimus, an mTOR inhibitor. This is in accordance with the absence of cognitive impairment in heart transplant patients receiving everolimus-based, another mTOR inhibitor, or calcineurin inhibitor–based immunosuppressive therapy.[17] Moreover, a significant cognitive and affective improvement was observed with everolimus in another study.[37] Interestingly, induction type (antilymphocyte antibodies associated with anti–interleukin 2 receptor antibodies and etanercept for the mycophenolate-associated protocol (group 2A), and anti–interleukin 2 receptor antibodies for the sirolimus-associated protocol (group 2B) do not seem to impact cognition. Indeed, the cognitive consequences of induction protocols have never been studied to our knowledge.

Aging and a lower education level are known factors negatively influencing cognition. In the present study, the islet-transplanted patients were aged about 57 y old, with a higher proportion of people with lower education level in the control group. Nevertheless, there was no difference in the cognitive functions across the 3 groups.

The second important result is the significant correlation found between MMSE score and the glucose balance at the time of cognitive assessment, reflected by HbA1c level on the one hand and time spent in hypoglycemia on CGMS on the other hand. Previous studies have shown a correlation between the coefficient of variation of HbA1c and the results of different cognitive tests, even if it was in type 2 diabetes.[38-40] In T1D, and in perfect concordance with our results, a recent study of the DCCT/EDIC has demonstrated that, besides elevated systolic blood pressure, exposure to higher HbA_{1c} levels and more episodes of severe hypoglycemia were associated with greater decrements in psychomotor and mental efficiency that was increased by the duration of diabetes contributing to premature aging of about 9 y.[41] These results suggest that islet transplantation by correcting glucose balance and suppressing hypoglycemia[42] could participate in the protection of cognitive function. The fact that the correlations were found between MMSE score and the glucose balance at the time of cognitive assessment (and not the lifetime glucose balance we did not know) may further suggest that cognitive impairment is not definitive and could be improved by a period of satisfying glucose balance. To confirm these results, it would be interesting to continue the exploration of cognitive disorders in islet transplant patients by performing a prospective matched study in pre- and posttransplant patients.

CONCLUSION

The importance of glucose balance on cognitive function is highlighted by the double negative correlation between the MMSE score and HbA1c level and time spent in hypoglycemia on CGMS. Therefore, all efforts should converge toward an improvement of long-term glucose balance, especially avoiding hypoglycemia events in T1D. No difference in the MMSE score or higher cognitive functions evaluation was found between islet-transplanted recipients and T1D controls, suggesting the lack of major deleterious effects of immunosuppressive drugs, especially sirolimus, which had never been used for such a long time before this study. Islet transplantation may constitute one of the tools available to protect

cognitive function in T1D with glucose lability or impaired hypoglycemia awareness.

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REFERENCES

1. Michels AW, Redondo MJ, Atkinson MA. The pathogenesis, natural history, and treatment of type 1 diabetes: time (thankfully) does not stand still. *Lancet Diabetes Endocrinol.* 2022;10:90–92.
2. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the american diabetes association workgroup on hypoglycemia. *Diabetes Care.* 2005;28:1245–1249.
3. Zoungas S, Patel A, Chalmers J, et al; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med.* 2010;363:1410–1418.
4. Jaser SS, Jordan LC. Brain health in children with type 1 diabetes: risk and protective factors. *Curr Diab Rep.* 2021;21:12.
5. McCrimmon RJ. Consequences of recurrent hypoglycaemia on brain function in diabetes. *Diabetologia.* 2021;64:971–977.
6. Shalimova A, Graff B, Gąsecki D, et al. Cognitive dysfunction in type 1 diabetes mellitus. *J Clin Endocrinol Metab.* 2019;104:2239–2249.
7. Lin CH, Sheu WHH. Hypoglycaemic episodes and risk of dementia in diabetes mellitus: 7-year follow-up study. *J Intern Med.* 2013;273:102–110.
8. Nevo-Shenker M, Shalitin S. The impact of hypo- and hyperglycemia on cognition and brain development in young children with type 1 diabetes. *Horm Res Paediatr*. 2021;94:115–123.
9. Stantonyonge N, Martinez-Horta S, Sampedro F, et al. Defective involuntary attention to novelty in type 1 diabetes and impaired awareness of hypoglycaemia. *Diabetes Res Clin Pract.* 2021;177:108898.
10. Frier BM. Cognitive decline in longstanding type 1 diabetes: a role for severe hypoglycaemia. *Lancet Diabetes Endocrinol.* 2021;9:411–412.
11. Chandran SR, Jacob P, Choudhary P. A systematic review of the effect of prior hypoglycaemia on cognitive function in type 1 diabetes. *Ther Adv Endocrinol Metab.* 2020;11:2042018820906017.
12. Brands AMA, Biessels GJ, de Haan EHF, et al. The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care.* 2005;28:726–735.
13. Gao R, Ren L, Zhou Y, et al. Recurrent non-severe hypoglycemia aggravates cognitive decline in diabetes and induces mitochondrial dysfunction in cultured astrocytes. *Mol Cell Endocrinol.* 2021;526:111192.
14. Vantyghem MC, Chetboun M, Gmyr V, et al; Members of the Spanish Back Pain Research Network Task Force for the Improvement of Inter-Disciplinary Management of Spinal Metastasis. Ten-year outcome of islet alone or islet after kidney transplantation in type 1 diabetes: a prospective parallel-arm cohort study. *Diabetes Care.* 2019;42:2042–2049.
15. Lablanche S, Vantyghem MC, Kessler L, et al; TRIMECO trial investigators. Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poorly controlled glycaemia after kidney transplantation (TRIMECO): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol.* 2018;6:527–537.
16. Vantyghem MC, de Koning EJP, Pattou F, et al. Advances in β-cell replacement therapy for the treatment of type 1 diabetes. *Lancet Lond Engl*. 2019;394:1274–1285.
17. Bürker BS, Gude E, Gullestad L, et al. Cognitive function among long-term survivors of heart transplantation. *Clin Transplant.* 2017;31:e13143.
18. Smith PJ, Blumenthal JA, Hoffman BM, et al. Postoperative cognitive dysfunction and mortality following lung transplantation. *Am J Transplant.* 2018;18:696–703.
19. Hoffman BM, Blumenthal JA, Carney RC, et al. Changes in neurocognitive functioning following lung transplantation. *Am J Transplant.* 2012;12:2519–2525.
20. Griva K, Hansraj S, Thompson D, et al. Neuropsychological performance after kidney transplantation: a comparison between transplant types and in relation to dialysis and normative data. *Nephrol Dial Transplant.* 2004;19:1866–1874.
21. Harciarek M, Biedunkiewicz B, Lichodziejewska-Niemierko M, et al. Cognitive performance before and after kidney transplantation: a prospective controlled study of adequately dialyzed patients with end-stage renal disease. *J Int Neuropsychol Soc.* 2009;15:684–694.
22. Radić J, Ljutić D, Radić M, et al. Kidney transplantation improves cognitive and psychomotor functions in adult hemodialysis patients. *Am J Nephrol.* 2011;34:399–406.
23. Joshee P, Wood AG, Wood ER, et al. Meta-analysis of cognitive functioning in patients following kidney transplantation. *Nephrol Dial Transplant.* 2018;33:1268–1277.
24. Klawitter J, Gottschalk S, Hainz C, et al. Immunosuppressant neurotoxicity in rat brain models: oxidative stress and cellular metabolism. *Chem Res Toxicol.* 2010;23:608–619.
25. Dirks M, Pflugrad H, Tryc AB, et al. Impact of immunosuppressive therapy on brain derived cytokines after liver transplantation. *Transpl Immunol.* 2020;58:101248.
26. Palacín M, Coto E, Llobet L, et al. FK506 affects mitochondrial protein synthesis and oxygen consumption in human cells. *Cell Biol Toxicol.* 2013;29:407–414.
27. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189–198.
28. Rickels MR, Stock PG, de Koning EJP, et al. Defining outcomes for β-cell replacement therapy in the treatment of diabetes: a consensus report on the Igls criteria from the IPITA/EPITA opinion leaders workshop. *Transplantation.* 2018;102:1479–1486.
29. Hawkins MAW, Gathright EC, Gunstad J, et al. The MoCA and MMSE as screeners for cognitive impairment in a heart failure population: a study with comprehensive neuropsychological testing. *Heart Lung J Crit Care*. 2014;43:462–468.
30. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53:695–699.
31. Lim MYL, Loo JHY. Screening an elderly hearing impaired population for mild cognitive impairment using Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). *Int J Geriatr Psychiatry.* 2018;33:972–979.
32. Pellicer-Espinosa I, Díaz-Orueta U. Cognitive screening instruments for older adults with low educational and literacy levels: a systematic review. *J Appl Gerontol.* 2022;41:1222–1231.
33. Jia X, Wang Z, Huang F, et al. A comparison of the Mini-Mental State Examination (MMSE) with the Montreal Cognitive Assessment (MoCA) for mild cognitive impairment screening in Chinese middle-aged and older population: a cross-sectional study. *BMC Psychiatry.* 2021;21:485.
34. Arevalo-Rodriguez I, Smailagic N, Roqué-Figuls M, et al. Mini-Mental State Examination (MMSE) for the early detection of dementia in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev.* 2021;7:CD010783.
35. Zhang S, Qiu Q, Qian S, et al. Determining appropriate screening tools and cutoffs for cognitive impairment in the Chinese elderly. *Front Psychiatry.* 2021;12:773281.

36. Derouesne C, Poitreneau J, Hugonot L, et al. [Mini-Mental State Examination: a useful method for the evaluation of the cognitive status of patients by the clinician. Consensual French version]. *Presse Medicale Paris Fr 1983*. 1999;28:1141–1148.
37. Johnston SD, Morris JK, Cramb R, et al. Cardiovascular morbidity and mortality after orthotopic liver transplantation. *Transplantation.* 2002;73:901–906.
38. Minami T, Ito Y, Yamada M, et al. The effect of long-term past glycemic control on executive function among patients with type 2 diabetes mellitus. *Diabetol Int.* 2020;11:114–120.
39. Kim C, Sohn JH, Jang MU, et al. Association between visit-to-visit glucose variability and cognitive function in aged type 2 diabetic patients: a cross-sectional study. *PLoS One.* 2015;10:e0132118.
40. Gorst C, Kwok CS, Aslam S, et al. Long-term glycemic variability and risk of adverse outcomes: a systematic review and meta-analysis. *Diabetes Care.* 2015;38:2354–2369.
41. Jacobson AM, Ryan CM, Braffett BH, et al; DCCT/EDIC Research Group. Cognitive performance declines in older adults with type 1 diabetes: results from 32 years of follow-up in the DCCT and EDIC Study. *Lancet Diabetes Endocrinol.* 2021;9:436–445.