1921-2021:from insulin discovery to islet transplantation in type 1 diabetes.

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1921-2021 : de la découverte de l'insuline à la greffe d'îlots dans le diabète de type 1

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One century after the discovery of insulin, the French Health authorities authorized the health care reimbursement for islet transplantation with the execution order published on March 31st 2021 in 3 main indications:

- Islet transplantation alone in diabetes with non-detectable C-peptide, mainly *type 1 diabetes* (T1D)
- Islet transplantation after another transplantation, mainly kidney
- Auto-transplantation after pancreatic surgery, which does not require immunosuppression.

Islet transplantation is mainly performed in patients with T1D and hypoglycemia unawareness and/or a functioning kidney graft (1, 2). The general therapeutic strategy in these cases of severe diabetes has been detailed in different reviews and expert consensus (3-5), including closed-looped pumps (6-8). Recommendations concerning *continuous glucose monitoring* (CGM) targets in high-risk and non-high-risk patients suffering from diabetes have been already published, helping to compare the results of these different approaches (9).

Restoration of C-peptide secretion with islet transplantation

Compared with closed-loop pumps, the specificity of islet transplantation is the restoration of C-peptide secretion. As recently shown both after islet transplantation and in slow T1D, restoration or preservation of even minimum levels of C-peptide are associated with fewer low-glucose events and less glucose variability.

In a series of 14 islet-transplanted alone and 14 islet-after-kidney transplanted T1D patients studied in our Department in intention-to-treat over a decade, findings at 1, 5 and 10 years of transplantation showed a significant decrease in the mean CGM "time below range" (TBR) < 3.9 mmol/L, "time above range" (TAR) > 10 mmol/L, the number of severe hypoglycemia events and the mean values of glucose levels compared with pretransplantation levels, while the "time in range" (TIR) significantly increased (10) (**Figure 1**).

In addition, the CGM mean glucose, glucose standard deviation (SD), TAR > 10 mmol/L and TBR < 3.9 mmol/L were strongly related to the β-score, a previously validated index for islet transplantation success based on C-peptide, fasting blood glucose, glycated hemoglobin levels and antidiabetic treatment requirements. Interestingly, partial function (β-score > 3, meaning borderline detectable C-peptide) seems to be sufficient to abrogate hypoglycemia. Moreover, the suboptimal function with β-score > 5 is enough to significantly improve mean glucose and glucose SD in addition to TBR (11). Other teams have confirmed this relationship between restoration of C-peptide, hypoglycemia and glucose variability after islet transplantation. For instance, increasing β-cell function across predefined C-peptide groups was associated with reduced insulin dose, HbA1c, mean glucose levels, and mean glucose SD (12).

Preservation of islet transplantation in T1D

Highly significant continuous associations have also been confirmed between stimulated C-peptide and mean interstitial glucose, mean glucose SD, time outside glucose target range and measures of hyper- and hypoglycemia risk (13). In adults with T1D whose TBR was around 3% compared with 5% for the group with undetectable C-peptide, preserved C-peptide secretion was also associated with fewer low-glucose events and lower glucose variability on flash glucose monitoring (14). Similar lower risk of hypoglycemia was found in the DCCT (15) and in a clinical study in the United Kingdom (16).

Altogether, these results confirm that C-peptide restoration or preservation in T1D could significantly decrease the duration of time spent in hypoglycemia as well as the number of severe hypoglycemic events while improving overall glucose balance and variability. However, three questions still remain:

(1) Why not aim for tighter glycemic targets when C-peptide is still present in T1D, thus limiting hypoglycemic events?
(2) What would be the strategies for C-peptide preservation in T1D?
(3) Which would be the best strategy for patients with T1D between closed-loop systems and C-peptide restoration, especially with islet transplantation?

Considering point 1, the tighter glycemic targets, such as those recommended by CGM consensus on non-high risk T1D patients (time in range [TIR 3.9-10.0 mmol/L] higher than 70%, time below range [TBR < 3.9 mmol/L] lower than 4%, time above range [TAR > 10 mmol/L] lower than 25%) could be achieved in T1D patients with restored or preserved C-peptide (10) and further contribute to preserving C-peptide secretion in patients with residual C-peptide. Moreover, the preservation of C-peptide secretion has been shown to limit the microangiopathic diabetic complications, especially retinopathy and to reduce the hospital admission for ketoacidosis (17).

Considering point 2, the preservation of C-peptide can be achieved by a better glycemic control - thus avoiding beta cell glucose toxicity - or by immunomodulation therapies. Although early immunosuppressive approaches have been associated with side effects, more recent strategies such as interleukin-21 and glucagon receptor blockade offer better chances (18,19).

Finally, point 3 concerns the best strategy for T1D patients between closed loop systems and C-peptide restoration, especially with islet transplantation. No study is available comparing results of islet transplantation with closed-loop systems. However, a clinical trial comparing islet transplantation with optimal medical treatment (insulin pump therapy coupled with real time CGM) is ongoing (STABILOT study; *NCT02854696*). Most randomized studies have compared hybrid closed-loop systems in T1D patients with conventional insulin pump therapy (8, 21), sensor-assisted pump therapy (6, 22) and sensor-augmented pump therapy with predictive low glucose suspend (7). All these studies have shown an improvement of TIR (59-68% (6); 65-76% (21), 54-65% (22), 64-72% (7) and significantly less time spent in TBR < 3 mmol/L, and TBR < 3.9 mmol/L decreasing for instance from 3.1 to 2.1% (7). Overall, these studies were performed in young or adult patients without impaired hypoglycemia awareness and did not exceed 3 to 6-month period. They were able to demonstrate the efficacy of the system, although the success in the long-term and in reaching the non-high risk CGM targets remains unknown.

Conclusion

These data confirm the crucial importance of C-peptide preservation at the beginning of T1D history and the major role of C-peptide restoration after □-cell replacement therapy in order to improve overall glycemic balance. The presence of C-peptide allows to reassess CGM guidelines in high-risk T1D patients with the goal to avoid severe hypoglycemic events. Detectable C-peptide enables to maintain more rigorous CGM objectives for TBR and TIR (similar to “non-high risk” patients) while decreasing TBR < 3.9 mmol/L below or equal to 3%. These goals would help the high-risk group who probably deserves the best glucose balance, to avoid life-threatening hypoglycemia while preserving their overall glucose balance and limiting the risk of microangiopathic complications. In the clinical setting, the preservation of

C-peptide at the onset of T1D is currently approached with less aggressive therapies. Closed-loop systems and □-cell replacement therapies have each their own indications but are not competitive. Indeed, preservation of C-peptide at early stage of T1D, multi-injections, sensors, insulin pump, closed-loop systems at later stages, and islet transplantation when hypoglycemia awareness becomes impaired are complementary for a personalized care all along the different steps of T1D.

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FIGURE LEGENDS

Figure 1. CGM targets observed before and at 1, 5 and 10 years after islet transplantation (left panel) compared with CGM 2019 guidelines (9). In the CGM guidelines (right panel), non-high-risk T1D or T2D should reach a time in range (TIR) 3.9-10.0 mmol/L above 70%, a time below range (TBR) below 4%, a time above range (TAR) below 25%; older or high-risk patients have a goal that first aims at limiting life-threatening TBR below 1%, therefore decreasing the requirement of TIR above 50% with TAR below 50%. In islet-transplanted patients (n = 28) (left panel), one-way ANOVA for matched-measures for linear trend show that TIR significantly increased (p = 0.0003) while TAR and TBR decreased (p = 0.0037 and p = 0.0004, respectively) over the ten-year period following islet transplantation as compared to pre-transplantation levels (10).

Figure 1*. Cibles de CGM observées avant et 1, 5 et 10 ans après greffe d'îlots (panneau de gauche) par rapport aux recommandations générales des cibles CGM 2019 chez le patient diabétique (9). Selon les recommandations CGM (panneau de droite), le DT1 ou le DT2 non à haut-risque devrait atteindre un temps dans la cible (TIR) 3,9-10,0 mmol / L de plus de 70%, un temps en-dessous de la cible(TBR) (< 3.9mmol/L) inférieur à 4%, un temps au-dessus de la cible 10 mmol/L (TAR) inférieur à 25%; les patients plus âgés ou à haut risque ont un objectif qui vise d'abord à limiter le TBR, correspondant aux hypoglycémies potentiellement mortelles, à moins de 1%, diminuant ainsi l'exigence de TIR à au moins 50% avec TAR à moins de 50%. Chez les patients transplantés d'îlots (n = 28) (panneau de gauche), le TIR a augmenté de manière significative (p = 0,0003) tandis que le TAR et le TBR ont diminué (p = 0,0037 et p = 0,0004, respectivement) au cours des 10 ans suivant la greffe par rapport aux données pré-greffe (ANOVA unidirectionnelle pour les mesures appariées de la tendance linéaire) (10).*

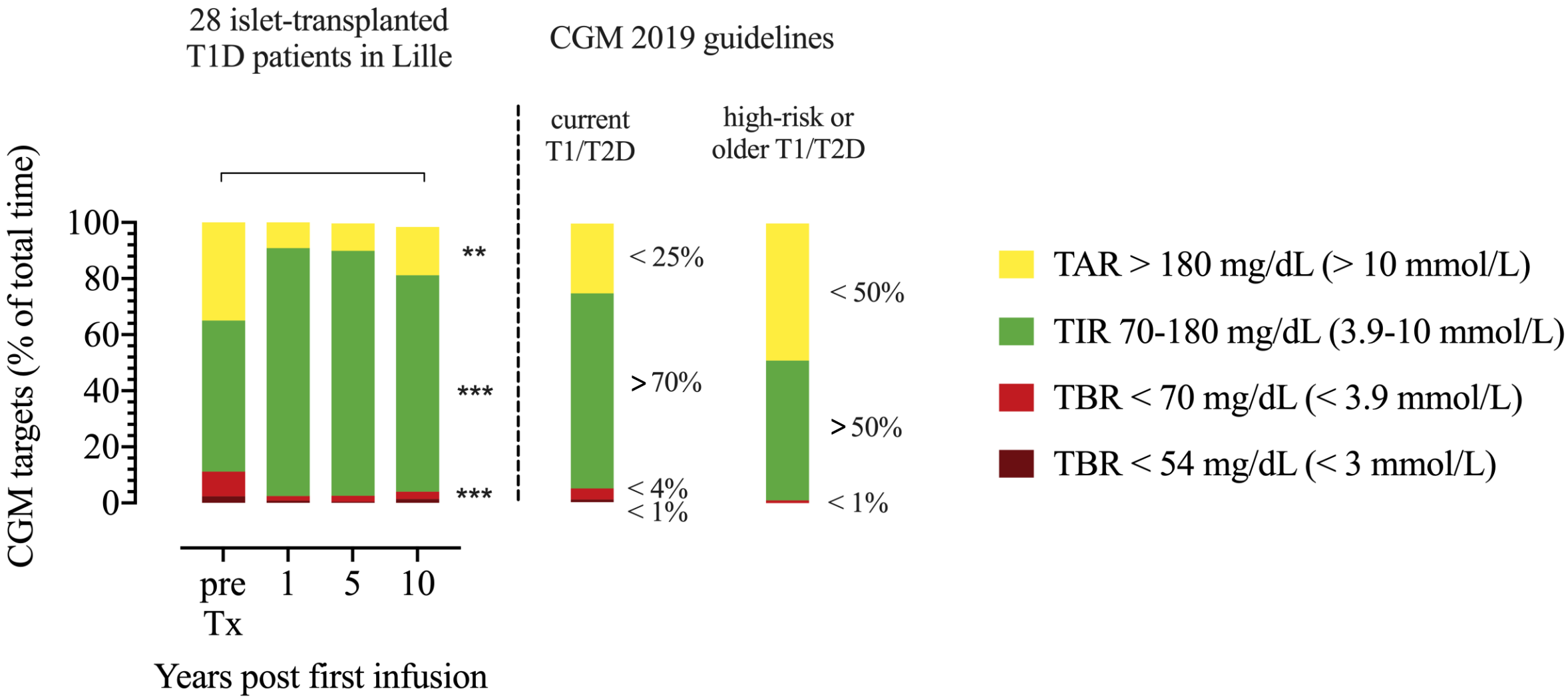
Table 1
CGM evaluations over a decade of 14 islet-transplanted alone and 14 islet-after-kidney transplanted T1D patients studied in intention-to-treat. Compared to pre-transplantation values at 1, 5 and 10-year values after transplantation, the mean values of TBR (Time below range) significantly decreased, that of TIR (Time in range) significantly increased and that of TAR (Time above range) significantly decreased. P values were obtained with one-way ANOVA for matched-measures linear trend, as indicated in Ref 10. SHE stands for severe hypoglycemic events. Values are presented as mean ± SD.

Table 1
Évaluations CGM sur une décennie de 28 patients atteints de DT1 ayant reçu une greffe d'îlots seuls (n=14) ou une greffe d'îlots après greffe de rein (n=14) étudiés en intention de traiter. Par rapport aux valeurs pré-transplantation, 1, 5 et 10 ans après la greffe, les valeurs moyennes du TBR (Time below range< 3.9 mmol/L) ont significativement diminué, celles du TIR (Time in range 3.9-10 mmol/L) significativement augmenté et celle du TAR (Time above range > 10 mmol/L) significativement diminué. Les valeurs de p ont été obtenues avec une ANOVA à un facteur pour la tendance linéaire des mesures appariées, comme indiqué dans la référence 10. SHE signifie « événement hypoglycémique grave ». Les valeurs sont présentées sous forme de moyenne ± écart-type.

Table 1

Mean± SD	Pre transplant	1 year post transplant	5 years post transplant	10 years post transplant	p
TBR < 70mg/dl (%)	11.3 ± 9.5	2.4 ± 4.3	2.8 ± 5.5	5.6 ± 6.7	0.0004
TIR 70-180 mg/dl (%)	53.9 ± 20.1	88.4 ± 18.8	87.3 ± 14.8	77.2 ± 23.9	0.0003
TAR > 180 mg/dl (%)	35.3 ± 27.0	9.2 ± 16.1	9.8 ± 12.6	17.2 ± 21.0	0.0037
SHE (n events/year)	3.2 ±3.5	0 ± 0	0.1 ± 0.4	0.1 ± 0.5	< 0.0001
Mean glucose (mmol/l)	9.0 ±2.4	6.6 ±1.5	7.0 ± 1.3	7.3 ±1.8	0.0051

Fig 1


28 islet-transplanted
T1D patients in Lille
CGM 2019 guidelines
current
T1/T2D
high-risk or
older T1/T2D
CGM targets (% of total time)
100
80
60
40
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0
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< 25%
> 70%
< 4%
< 1%
< 50%
> 50%
< 1%
pre
Tx
1
5
10
Years post first infusion
TAR > 180 mg/dL (> 10 mmol/L)
TIR 70-180 mg/dL (3.9-10 mmol/L)
TBR < 70 mg/dL (< 3.9 mmol/L)
TBR < 54 mg/dL (< 3 mmol/L)