

# Pancreas Islet Transplantation for Patients With Type 1 Diabetes Mellitus: OHTAC Recommendation

## HEALTH QUALITY ONTARIO

### ONTARIO HEALTH TECHNOLOGY ADVISORY COMMITTEE RECOMMENDATIONS

- OHTAC recommends that pancreas islet cell transplantation be publicly funded as a treatment option for eligible adults with type 1 diabetes mellitus who have frequent episodes of hypoglycemic unawareness and/or uncontrollable diabetes despite optimal medical therapy

### BACKGROUND

Diabetes mellitus is a chronic condition characterized by high blood glucose levels. Type 1 diabetes mellitus, which affects a small proportion of patients with diabetes, is a result of autoimmune destruction of the pancreatic beta ( $\beta$ ) cells causing severe insulin deficiency.

Patients with type 1 diabetes require lifelong insulin therapy to control their blood glucose levels. However, despite optimal insulin treatment, a very small proportion of patients (< 1%) still experience frequent large and unpredictable fluctuations in their blood glucose levels. Some of these patients also become unaware of hypoglycemia. For these patients, the unstable blood glucose levels lower quality of life, potentially lead to recurrent or prolonged hospitalization, and result in complications including premature death. (1)

Improvements in insulin delivery systems still fail to provide an effective treatment for some patients with type 1 diabetes. Efforts to preserve and restore pancreatic function through  $\beta$ -cell replacement therapy offer an alternative treatment option. Islet transplantation is one such treatment.

Health Quality Ontario initiated this review after receiving a request from the Ministry of Health and Long-Term Care.

### KEY QUESTIONS AND FINDINGS

Health Quality Ontario reviewed the clinical evidence to answer the questions below:

- What is the effectiveness of islet transplantation for patients with type 1 diabetes mellitus?
  - What is the effectiveness of islet transplantation alone for patients with non-uremic type 1 diabetes?
  - What is the effectiveness of islet-after-kidney transplantation or simultaneous islet-kidney transplantation for patients with uremic type 1 diabetes?

Health Quality Ontario also asked researchers at McMaster University to conduct a qualitative review to answer a question about the impact of uncontrolled diabetes on quality of life:

- How does the experience of uncontrolled diabetes impact the quality of life of people with type 1 diabetes?

There is high quality evidence that islet transplantation is more likely to result in patients not needing insulin compared to intensive insulin therapy, in patients with type 1 diabetes with difficult-to-control blood glucose levels. For all other outcomes including health-related quality of life, secondary complications of diabetes, glycemic control, and adverse events, the evidence is of very low or low quality. More details can be found in the clinical evidence review. (2)

The review of qualitative studies showed that long- and short-term negative consequences of uncontrolled type 1 diabetes affect all aspects of patients' lives: physical, emotional, practical, and social. Patients live in fear of complications from diabetes over the long term. In the shorter term, they are anxious about the personal, social, and professional consequences of hypoglycemic episodes (e.g., injury, humiliation), and may curtail normal activities such as driving or socializing because they are worried about having an episode. The quality of life for patients' family members is also negatively impacted by uncontrolled type 1 diabetes. More details can be found in the qualitative report. (3)

## OHTAC DELIBERATIONS

OHTAC agreed with the conclusions of both the clinical and qualitative evidence reviews.

OHTAC members acknowledged that there was uncertainty in the evidence that islet transplantation improved secondary complications of diabetes and quality of life. However, OHTAC also recognized that patients being treated with islet transplantation had a very complicated form of diabetes and that a substantial proportion of these patients achieved insulin independence for at least several years. For the patients who did not achieve insulin independence, or in later years lost insulin independence, other outcomes for glycemic control were generally improved. For example, many patients required less insulin than they did before transplantation, and had better blood glucose control. The clinical benefits of islet transplantation were considered, along with the adverse events that may occur as a result of the procedure and the lifelong immunosuppression regimens that are required.

OHTAC also noted that the number of patients eligible for this treatment would be small; hence, the total budget impact would be limited.

Health Quality Ontario has developed a decision-making framework to help guide deliberation and support the development of OHTAC recommendations regarding the uptake, diffusion, distribution, or removal of health interventions in Ontario. Table 1 provides a summary of the decision determinants for this recommendation.

## Decision Determinants

**Table 1: Decision Determinants for Pancreas Islet Transplantation for Type 1 Diabetes Mellitus**

Decision Criteria	Subcriteria	Decision Determinants	Considerations
<b>Overall clinical benefit</b> How likely is the health technology/intervention to result in high, moderate, or low overall benefit?	<b>Effectiveness</b> How effective is the health technology/intervention likely to be (taking into account any variability)?	Islet transplantation alone improves: <ul style="list-style-type: none"> <li>• Glycemic control (GRADE: low to high)</li> <li>• Secondary diabetic complications (GRADE: very low to low)</li> <li>• Health-related quality of life (GRADE: very low)</li> </ul>	Simultaneous islet-kidney/islet-after-kidney transplantation improves: <ul style="list-style-type: none"> <li>• Glycemic control (GRADE: low to high)</li> <li>• Secondary diabetic complications (GRADE: very low to low)</li> <li>• Health-related quality of life (GRADE: very low)</li> </ul>
	<b>Safety</b> How safe is the health technology/intervention likely to be?	Procedure- and immunosuppression-related adverse events may occur. Patients require lifelong immunosuppression, similar to other solid organ transplantations. IT is a less invasive procedure than pancreas transplantation and results in fewer procedure-related adverse events. Compared with insulin therapy, it has greater safety risks	
	<b>Burden of illness</b> What is the likely size of the burden of illness pertaining to this health technology/intervention?	Estimated diabetes prevalence in Ontario in 2014 is 1.46 million people; 66,266 people with T1DM (4) Brittle/labile diabetes affects about 3 in 1,000 people with T1DM (about 200 patients) (1)	
	<b>Need</b> How large is the need for this health technology/intervention?	Estimated 15–20 patients/year would benefit from IT (Marnie Weber, UHN, personal communication, June 2015)	
<b>Consistency with expected societal and ethical values<sup>a</sup></b> How likely is adoption of the health technology/intervention to be congruent with societal and ethical values?	<b>Societal values</b> How likely is the adoption of the health technology/intervention to be congruent with expected societal values?	Uncontrolled T1DM affects all domains of a person's quality of life	
	<b>Ethical values</b> How likely is the adoption of the health technology/intervention to be congruent with expected ethical values?	Relief from hypoglycemia, ketoacidosis, and unpredictability of blood glucose levels would significantly improve patient and family member experiences	
<b>Value for money</b> How efficient is the health technology likely to be?	<b>Economic evaluation</b> How efficient is the health technology/intervention likely to be?	Cost-effectiveness of IT compared with pancreas transplantation or intensive insulin therapy is undetermined based on the limited evidence	

Decision Criteria	Subcriteria	Decision Determinants Considerations
<b>Feasibility of adoption into health system</b> How feasible is it to adopt the health technology/intervention into the Ontario health care system?	<b>Economic feasibility</b> How economically feasible is the health technology/intervention?  <b>Organizational feasibility</b> How organizationally feasible is it to implement the health technology/intervention?	Budget impact estimated at less than \$5 million per year (Marnie Weber, UHN, personal communication, June 2015)  Currently not available in Ontario, but UHN has created an IT team and partnered with Trillium Gift of Life to provide IT in Ontario. UHN has also established a collaborative partnership with McGill University where islets would be processed and shipped back to UHN for transplantation; however, there is a plan in the near future to develop an isolation facility at UHN

Abbreviations: IAK, islet-after-kidney transplantation; IT, islet transplantation; T1DM, type 1 diabetes mellitus; UHN, University Health Network.

<sup>a</sup>The anticipated or assumed common ethical and societal values held in regard to the target condition, target population, and/or treatment options. Unless there is evidence from scientific sources to corroborate the true nature of the ethical and societal values, the expected values are considered.

## REFERENCES

- (1) Brittle diabetes (labile diabetes) [Internet]. United Kingdom: Diabetes.co.uk; 2015 [cited 2015 Feb 5]. Available from: <http://www.diabetes.co.uk/brittle-diabetes.html>
- (2) Health Quality Ontario. Pancreas islet transplantation for patients with type 1 diabetes mellitus: a clinical evidence review. Ont Health Technol Assess Ser [Internet]. 2015 Sep;15(16):1–84. Available from: <http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series/eba-pancreas-islet-transplantation>
- (3) Vanstone M, Rewegan A, Brundisini F, Dejean D, Giacomini M. Patient perspectives on quality of life with uncontrolled type 1 diabetes mellitus: a systematic review and qualitative meta-synthesis. Ont Health Technol Assess Ser [Internet]. 2015 Sep;15(17):1–29. Available from: <http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series/fev-pancreas-islet-transplantation>
- (4) Canadian Diabetes Association, Diabète Québec. Diabetes: Canada at the tipping point [Internet]. Toronto (ON): The Association; 2015 [cited 2015 Feb 6]. Available from: <http://www.diabetes.ca/CDA/media/documents/publications-and-newsletters/advocacy-reports/canada-at-the-tipping-point-english.pdf>

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