Islet transplantation for the treatment of type 1 diabetes: an update
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CRD summary
This generally well-conducted review concluded that islet cell allotransplantation was an alternative treatment for patients with non-uremic type-1 diabetes with severe hypoglycaemia and uncontrolled diabetes; this conclusion is likely to be reliable for the restricted population stated, although it is based on a only small number of patients.

Authors' objectives
To evaluate the effectiveness and safety of islet cell transplantation for patients with non-uremic type 1 diabetes who have severe hypoglycaemia or hypoglycaemia unawareness.

Searching
PubMed, EMBASE, CINAHL, BIOSIS Previews, The Cochrane Library, Web of Science, HTA database, DARE, NHS EED, Biological Abstracts and HealthSTAR were searched for English-language studies; the search strategy was reported. Regulatory and licensing sites, trials registers and HTA websites were searched. Reference lists of relevant articles were scanned. As this was an update of a review published in 2003, searches were run between 2002 and 2008.

Study selection
Any study that compared pancreatic islet cell allotransplantation using the Edmonton protocol (or a modification of it) against whole organ pancreas transplantation or intensive insulin therapy in adults with type 1 diabetes for more than 5 years and a history of severe hypoglycaemia or hypoglycaemia unawareness without end stage renal disease was eligible for inclusion. Studies had to report one of the following outcomes: mortality; adverse events; insulin independence or requirement; hypoglycaemic episodes; HbA1c; health-related quality of life (HRQoL); or secondary complications of diabetes.

Studies that performed transplantations of islet cell auto-, xeno/xenogeneic, genetically altered or stem cell prepared islets, foetal pancreatic islet, liver-islet, kidney-islet, lung-islet, pancreas and liver as the primary intervention of interest were excluded. Included studies used up to three infusions. The mean age of participants ranged from 33 to 50 years. Where reported, duration of diabetes ranged from 23 to 29 years.

One reviewer selected studies for inclusion in the review.

Assessment of study quality
Study quality was assessed by two independent reviewers using an 18-point scale that included five mandatory items (multicentre design, consecutive recruitment, before and after measurements and reporting of duration of and loss to follow up. Further criteria related to study objectives, patient characteristics, intervention and co-intervention, outcome measures, analysis, results and conclusions, and competing interests. Each criterion was scored yes or no and a total score of the number of yes responses counted. Disagreements were resolved by discussion or referral to a third reviewer.

Data extraction
Authors were contacted to clarify data or provided missing data. Data were extracted by one reviewer and checked by a second.

Methods of synthesis
Studies were combined in a narrative synthesis. Differences between studies were discussed in the text and study details and results tabulated.

Results of the review
Fourteen studies met the inclusion criteria (n=321): 12 case series (n=213, range 5 to 67); one prospective cross-over
trial (n=65); and one retrospective analysis (n=43). Quality scores ranged from 10 to 16 for the 11 case series that reported effectiveness outcomes; eight scored 14 or more. The review concentrated on the results from the 11 case series that reported effectiveness outcomes, which they termed key studies (n=208).

In the 11 key studies, the rate of insulin independence ranged from 30% to 69% at one year (nine studies) to 14% to 33% at two years (three studies); it was 7.5% at five years (one study). All patients who achieved insulin independence were free from hypoglycaemic episodes. HbA1c levels were reduced in all studies following islet cell allotransplantation. Two studies reported inconsistent results regarding HRQoL, although both reported a reduction in the fear of hypoglycaemic attacks. Two studies reported stabilisation or improvement of retinal complications.

In the 11 key studies, intraperitoneal bleeding occurred in 0 to 23% of patients (seven studies), partial portal vein thrombosis in 6% to 17% (six studies), increased liver enzymes in 10% to 100% (eight studies), hepatic steatosis in 8% to 33% (four studies), a decline in renal function in 17% to 50% (seven studies) and 10% to 37% of patients had to change their immunosuppressive regimen due to adverse events (seven studies) following islet cell allotransplantation. No study reported any islet cell allotransplantation-related peri- or post-operative deaths. More minor complications were common (results were provided).

Compared to intensive insulin therapy, islet cell allotransplantation significantly lowered HbA1c levels, but there was no difference in terms of glomerular filtration rate (one study). Compared to pancreas transplantation, islet cell allotransplantation had less severe post-operative complications, however, pancreas transplantation was superior in terms of C-peptide and HbA1c levels, and insulin requirements; there was no difference in terms of mortality or graft survival (one study).

Authors’ conclusions
Islet cell allotransplantation is an alternative treatment for patients with non-uremic type-1 diabetes with severe hypoglycaemia and uncontrolled diabetes.

CRD commentary
The authors addressed a clear research question supported by appropriate inclusion criteria. An extensive search was undertaken for published and ongoing studies, although language bias could not be ruled out. Data extraction and quality assessment were conducted in duplicate; this was not the case during study selection, which could have led to selection bias and missed studies. Quality was assessed using appropriate criteria and the results for each criterion were reported. The decision to combine studies in a narrative synthesis was appropriate. Many of the included studies were very small (fewer than 10 participants). This was a generally well-conducted review. The cautious conclusions are likely to be reliable for the restricted population the review evaluated; the very small sample sizes must be kept in mind when considering the results of the review.

Implications of the review for practice and research
Practice: The authors stated that there was insufficient evidence to consider islet cell allotransplantation as standard care in patients with non-uremic type-1 diabetes with severe hypoglycaemia and uncontrolled diabetes.

Research: The authors stated a number of implications for research, including the development of more sensitive methods to predict and detect graft loss, and the need for studies that were larger, prospective and had longer follow-up periods. Studies of single donors with standardised immunosuppressive regimens and studies of patients with and without renal dysfunction were also recommended.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.