Unraveling the puzzle of islet delivery devices

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Only in the Netherlands, there are over 109,000 people diagnosed with type 1 diabetes (T1D), and this number will increase to around 3,400 people every year. T1D is an autoimmune disease where the insulin-producing cells residing in the pancreatic islets of Langerhans are destroyed by an autoimmune reaction leading to an insulin deficiency. Currently, there are no treatment options available to prevent the occurrence of T1D or to definitive cure a patient from T1D. To survive, lifelong insulin administration multiple times a day is required, either by using an insulin pen or an insulin pump. Despite the treatment, the average life expectancy of diagnosed patients is 11 to 13 years shorter, and for 7% of the patients, is diabetes the cause of death. Although T1D can occur at any age, most patients get diagnosed in childhood between 5 and 7 years. T1D has a major influence on the quality of life because of the intensive treatment to regulate the blood glucose levels to prevent long-term complications and premature mortality. For children, is diabetes management especially hard as it limits the child from performing daily activities, and parents and caretakers are responsible for regulating blood glucose levels. Although monitoring the blood glucose levels regularly, there always remains the fear of experiencing hypoglycemic events. In addition, the quality of life decreases when patients experience more hypoglycemic events, not only in physical terms but also in mental health and in social terms. It is estimated that 1 in 6 patients experience depressions or symptoms of depressions caused by diabetes. Besides the impact on the diagnosed patient, T1D also influences the quality of life of the other family members, mainly because family members are not aware of how they can support the diagnosed person the best. Indicating that T1D influences both the quality of life of the patient and the surrounding family members. Besides the personal impact, there are also economic burden costs of T1D. Including direct and indirect medical costs, such as insulin and hospital visits, and the costs caused by the loss of productivity. Moreover, the labor participation of T1D patients is 40%, lower than the participation rate of the general population with 63%. The total economic burden is double for people diagnosed with T1D compared to the control group, estimated to be over €870 million per year in the Netherlands, which is 1.3% of the total healthcare cost. The associated costs are also dependent on glycemic control based on hemoglobin A1c levels.
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(HbA1c). Young patients with better glycemic control make less direct medical costs in comparison to patients with high HbA1c levels.\textsuperscript{11}

The work performed in this thesis is part of a larger consortium known as Regenerative Medicine Crossing Borders (RegMed XB). The goal of RegMed XB is to find solutions to cure four chronic diseases, of which T1D is one. Within the consortium are not only scientists involved to perform the research but also health foundations to make sure that the research focuses on the patient’s needs. Industrial partners are involved in scaling up the developed product for commercialization.\textsuperscript{12} In this thesis, we would like to impact people’s life diagnosed with T1D in three different ways.

We developed a tailor made immunoprotective delivery device made of polyvinylidene fluoride (PVDF), which can serve as a beta cell delivery device alternative to current clinical islet transplantation (\textbf{chapter 2}). The delivery device protects the encapsulated islets from immune cells to prevent rejection of the transplanted islets, and reverse protects the recipient from not fully differentiated cells in the case of stem cell-derived beta cells. The device can be used without immunosuppressive therapy to eliminate any unwanted side effects associated with this treatment. Using a cell delivery device can potentially increase the efficiency of beta cell replacement therapy. When fewer islets are needed to transplant one patient, we can increase the number of patients treated with the same number of donor islets. Other researchers in the RegMed XB consortium try to overcome the donor shortage by differentiating human embryonic stem cells into beta cells. Once these differentiation protocols are optimized to generate a large pool of beta cells in a reproducible manner, the delivery devices developed in this thesis can be used to transplant these “new” beta cells. By using an immunoprotective delivery device, one can hopefully prevent more hypoglycemic events and long-term complications in a large number of patients, thereby lowering the economic burden and improving the quality of life of people affected by T1D.

Currently, there is no clear consensus on the ideal site for implanting beta cell delivery devices. By studying different implantation sites in different animal models, we were able to make a direct comparison between sites, providing insight into what could be considered
the most optimal transplant site based on extensive histological evaluation and surgical implementation. This knowledge can be used to extrapolate what an ideal site for humans should look like to improve clinical outcomes. Here, we found that the subcutaneous implantation site, often used in (pre)clinical studies, is less convenient because of the severe immune response leading to a fibrotic capsule around devices. This fibrotic capsule prevents the diffusion of oxygen and nutrients toward the cells inside the delivery device. Therefore, the device's function decreases because of the reduced beta cell survival and endocrine function. In chapter 6, we suggested an alternative implantation site similar to subcutaneous implantation based on studies done in a large human-sized model. The pre-peritoneal site can be approached relatively minimally invasive, and the immune response toward delivery devices was found to be significantly lower. These findings hopefully lead to better clinical outcomes when combining islet transplantation with delivery devices.

Finally, we created an impact on the T1D population by evaluating the preferences of potential future device users through a survey as discussed in chapter 7. It is important to evaluate the preferences and wishes of the T1D population as there are more than 100,000 people diagnosed with T1D in the Netherlands.10 We evaluated, among other things, the accepted device sizes and whether the respondent accepts multiple delivery devices simultaneously to transplant the required beta cell mass. In addition, we evaluated the preferred location to receive the delivery device and the minimal improvement they would like to notice after transplantation. The gained knowledge is valuable to all researchers working on islet delivery devices. Because the quality of life will only increase when the developed devices are accepted within the patient population. A physician can use this knowledge in the future to align the expectations of the patients with the expected clinical outcome, to prevent the mismatch in the patient perspective.

Overall, we hope that with the research performed in this thesis, we are a step closer to making T1D patients insulin-independent. Then, patients get back control in their daily life without the constant need to monitor their blood glucose levels and experience a better quality of life, and eventually lower the rising healthcare costs.
References