Progress in islet transplantation is more important than ever

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It is increasingly clear that pancreatic islet replacement is needed to provide a comprehensive treatment for the growing numbers of patients with type 1 diabetes mellitus. Advances from the past year suggest that this goal might now be within reach.

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We are currently celebrating 100 years of insulin therapy for patients with diabetes mellitus, but morbidity, mortality and quality of life remain a challenge for our patients. In 2021, the International Diabetes Federation's Diabetes Atlas estimated that around 537 million adults worldwide are living with diabetes mellitus. Of these, 5–10% have type 1 diabetes mellitus (T1DM). In the past two decades, technological advances in monitoring blood levels of glucose and therapeutics have considerably improved care and management of people with diabetes mellitus. However, due to delays in glucose sensing and insulin absorption with these approaches, a physiological and pulsatile glycaemic control, as provided by native islets, is still not provided. Cellular regenerative therapy for T1DM has the potential to provide a more curative therapy.

Why is insulin therapy not enough?

T1DM is characterized by an autoimmune reaction that leads to destruction of the pancreatic β-cells, which causes insulin deficiency. Yet, for pancreatic islets to operate properly, it is not just a question of whether there is functional insulin secretion. First, adequate function of a β-cell requires continuous and pulsatile secretion of insulin and other growth factors[1]. Second, it is now clear that islets are mini-organs that require complex intercellular interplay[1]. Studies from the past 4 years have shown that β-cells are in critical crosstalk with α-cells and that the core secretion and regulation of α-cells and β-cells is crucial for precise metabolic control[1]. Finally, β-cells and other endocrine cells are embedded in an intricate network of vascular cells that allow fine regulation of glucose metabolism[1].

Intensive insulin treatment of T1DM might lead to severe hypoglycaemia, which is associated with altered mental state, seizures, cardiac arrhythmias and even death. At least 25% of patients with T1DM have an impaired awareness of hypoglycaemia, also known as hypoglycaemia unawareness; this prevalence has been stable over the past two decades[2]. As patients with hypoglycaemia unawareness do not recognize hypoglycaemic events, they might miss the opportunity to treat their hypoglycaemia in time to avoid hypoglycaemic coma, which can be fatal. In people without T1DM, strong counter-regulatory mechanisms exist to quickly increase glucose levels and protect the body from the negative consequences of hypoglycaemia. This counter-regulatory response includes inhibition of endogenous insulin secretion and stimulation of secretion of glucagon, catecholamines, cortisol and growth hormone to increase the plasma levels of glucose by stimulating hepatic glucose production and decreasing the utilization of glucose in peripheral tissues. For patients with hypoglycaemia unawareness and impaired adrenomedullary responses, these counter-regulatory responses do not function correctly, and patients have a high risk of severe hypoglycaemia and associated morbidities[2]. Therefore, optimal glycaemic control without episodes of hypoglycaemia is of immense importance. Hypoglycaemia unawareness is often a devastating condition in itself that cannot be addressed solely with insulin administration.

Although modern continuous insulin administration via new generation insulin pumps in combination with continuous glucose monitoring has provided considerable progress, external administration of insulin cannot address the root of the problem. Only replacement of the endocrine pancreas with a correctly functioning mini-organ can restore this ability to regulate glucose levels. Data published in 2021 have confirmed that islet transplantation is superior to intensified insulin therapies regarding survival and is especially superior in relation to quality of life[1].

Why is islet restoration important now?

Because of our success in treating metabolic and cardiovascular complications of diabetes mellitus, we are increasingly seeing more patients with T1DM reaching older ages than previously; thus, the prevalence of a highly multimorbid group of patients is also increasing[3]. In around 10% of patients with T1DM, the disease is hard to control, meaning that worldwide up to five million patients are in need of islet transplantation[3].

Adding to the need for regenerative therapies, the incidence of T1DM is also rapidly increasing worldwide,

reflecting the increasing role of environmental factors over genetic factors[4]. Particularly, with the coronavirus pandemic and in its aftermath, there might be a further increase in diabetes mellitus, including T1DM. We and others have shown that the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infects cells of both the endocrine and exocrine pancreas, which might lead to necroptotic cell death[5], as previously observed for enteroviruses[4]. The Centers for Disease Control and Prevention (CDC) have reported an increased risk of new-onset diabetes mellitus in children and adolescents after having COVID-19. Other studies have indicated that an infection with SARS-CoV-2 might lead to T1DM in rare cases[5]. Whether this condition is permanent or temporary is currently under investigation in an international registry, CoviDIAB.

The increase in numbers of patients with insulin-dependent diabetes mellitus is not the only problem exacerbating the need for islet restoration. The autoimmune inflammatory process that leads to destruction of islet function in early life also predisposes these patients to many other complications of diabetes mellitus, such as hypoglycaemia unawareness and peripheral neuropathy, as well as cardiac, renal and retinal disease[3].

Toward treating large patient numbers

Widespread use of pancreatic islet allotransplantation has been prevented by a lack of cadaveric donors. Transplantations have been limited to a small number of patients in specialized centres, mostly in the USA and Europe. Stem-cell derived islets provide a promising direction for personalized regenerative therapies as this approach is potentially curative and solves the issues with tissue supply shortages[1,3].

Published at the end of 2021, three major developments constitute a potential game changer for the entire field. For the first time, a multicentre clinical trial assessed pluripotent stem cell-derived pancreatic endoderm cells (PECs) for treatment of T1DM. Two participating centres established that these cells are able to survive and secrete insulin, though so far without relevant clinical effect. In these two centres, 15 and 17 patients received subcutaneous implants with PECs in non-immunoprotective macroencapsulation devices, enabling direct vascularization of the cells[6,7]. In another study, a single patient was infused in the portal vein with pluripotent stem cell-derived pancreatic cells. This procedure showed a relevant clinical effect with detectable C-peptide levels, showing that stem-cell based therapies are indeed possible[8]. Even if these stem cell-derived pancreatic cells do not produce enough insulin to allow the patient to be insulin-free, they produce enough baseline insulin to provide restoration of counter-regulatory responses to avoid hypoglycaemia unawareness. Islets are highly vascularized and many clinically relevant transplantation sites, such as the intraperitoneal cavity or the liver (intrahepatic), exhibit insufficient islet revascularization[1,3]. Using direct infusion in the portal vein, oxygen and nutrient supply is easily available. However, an instant blood-mediated inflammatory reaction might lead to massive islet loss from the transplant. Therefore, this patient received immunotherapy[8]. To protect the cells from destruction, but also to protect the patient from potential tumour formation, the transplantation procedure needs optimization. One approach is to use macroencapsulation, which we have previously tested in the first clinical trial using xenotransplantation[9]. Here, porcine islets were isolated from Goettingen minipigs, encapsulated in a bioartifical device and successfully transplanted into Rhesus macaques without immunosuppression[9].

A third breakthrough is xenotransplantation using organs from humanized animals. By using islets from humanized pigs, as demonstrated in January 2022 with hearts from humanized pigs, immunosuppression can be avoided[10]. These advances in islet transplantation mean that we are well on our way to developing a more curative and regenerative therapy for T1DM. There is light at the end of the tunnel, and we are closer than ever to therapies that are desperately needed.

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Competing interests
The authors declare no competing interests.

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