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The role of genetic risk factors, diet, and gut microbiota in type 1 diabetes mellitus, pancreas and pancreatic islet transplantation

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Abstract

Despite advances in insulin delivery and glucose monitoring technology, prevention of the progression of secondary complications in patients with type 1 diabetes (T1DM) remains a challenge. Beta cell replacement therapy in the form of islet or pancreas transplantation can restore long-term normoglycaemia with sustained periods of insulin independence among T1DM patients. However, the same genetic, behavioural, or gut microbiota-related factors that promoted autoimmunity and primary islet destruction may also affect the function of transplanted islets and the ultimate results of transplant procedures. In such cases, identifying genetic risk factors and modifying behavioural factors and those related to gut microbiota may be beneficial for the outcomes of transplant procedures. Herein, we review related literature to the identified current gap in knowledge to be addressed in future clinical trials. **(Endokrynol Pol 2024; 75 (2): 140–147)**

Key words: *pancreatic islets transplantation; genes; gut microbiota; diet; type 1 diabetes*

Introduction

Type 1 diabetes mellitus as an autoimmune disease

Type 1 diabetes mellitus (T1DM) is an autoimmune disease in which pancreatic beta cells are selectively destroyed, leading to a deficiency in insulin production in the body and subsequent hyperglycaemia. Despite technological advancement in exogenous insulin supplementation and blood glucose monitoring, the disease still presents a significant clinical challenge, suboptimal blood glucose control, and the development of secondary diabetic complications. Epidemiological data indicate that microangiopathic complications affect approximately 30% of patients with diabetes, and macroangiopathy is still a primary cause of mortality, significantly higher than in the general population. Patients with T1DM have reduced life expectancy and live with significant disabilities and poor quality of life. Increasingly, researchers are looking for alternative ways to treat diabetes in the form of beta cell replacement therapy with islet cell or pancreas transplantation. However, the need for toxic lifelong immunosuppressive medication remains a considerable hurdle precluding the extensive application of this therapy. The review aims to establish the current knowledge about genetic and behavioural determinants, abnormalities in the gut microbiota concerning the severity of diabetic complications, and the outcomes after pancreas and pancreatic islet transplantation.

Genetic factors and progression of secondary complications in patients with T1DM

There seem to be other factors affecting the progression of secondary diabetic complications besides poor blood glucose control. There are patients with similar duration of diabetes and degree of glycaemic control but with very different severity of microangiopathy (particularly diabetic retinopathy and nephropathy) [1, 2]. Hence, it is essential to look for predictors of severe course and progression of complications. The Family Investigation of Nephropathy and Diabetes (FIND-Eye

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research) found a significant heritability of diabetic retinopathy at 27%, and a study of a group of 8114 DM1 patients among 6707 American families confirmed a serious familial risk of diabetic retinopathy, regardless of disease duration [3, 4]. The literature describes numerous genes potentially related to the progression of diabetic complications, but there is a lack of consistent findings and use of this knowledge in clinical practice [5, 6]. Thus, it is crucial to conduct further molecular genetic studies to define the genetic factors associated with retinopathy and other complications and the severe course of diabetes in these patients. Advanced genetic techniques may help identify patients more prone to develop microangiopathic complications, in whom the use of beta cell replacement therapy may provide more clinical benefit. Based on previous scientific studies, especially genome-wide association studies (GWAS), numerous candidate genes have been identified that may be involved in determining the course of DM1. They are summarised in Table 1.

Table 1. *Candidate gene studies in diabetic retinopathy, nephropathy, and neuropathy*

Candidate gene	Gene location	OMIM entry	Polymorphism	Effect on T1DM	Reference
Folliculin (*FLCN*)	17p11.2	607273	rs11867934	Susceptibility to diabetic retinopathy	Skol et al. 2020 [7]
Aldose reductase (*AKR1B1*)	7q33	103880 rs9640883	rs759853	Protection from diabetic retinopathy	Cao et al. 2018 [8]
			Duration of diabetes	Abhary et al. 2010 [6]	
Receptor for advanced glycation end product (*AGER*)	6p21.32	600214		Risk of diabetic retinopathy	Balasubbu et al. 2010 [9]
Vascular endothelial growth factor (*VEGFA*)	6p21.1	192240 rs3025039 rs25648	rs3025039 rs3025021 rs13207351 rs2146323 rs2010963 rs25648 rs833061 rs2010963	Risk of diabetic retinopathy	Yang et al. 2020 [10]
			Susceptibility to diabetic neuropathy.	Politi et al. 2016 [11]	
Endothelial nitric oxide synthase (*NOS3*)	7q36.1	163729 rs270744	rs869109213 rs2070744	Risk of diabetic retinopathy	Midani et al. 2019 [12]
			Susceptibility to diabetic neuropathy		
Angiotensin I converting enzyme (*ACE*)	17q23.3	106180 rs1799752	rs1799752 rs4343	Risk of diabetic retinopathy	Luo et al. 2016 [13]; Liang et al. 2013 [14]
			Risk of diabetic retinal and renal complications	Marre et al., 1994 [15]	
Erythropoietin (*EPO*)	7q22.1	133170	rs551238 rs1617640 rs507392	Risk of diabetic retinopathy	Fan et al. 2016 [16]; Abhary et al. 2010 [6]; Manko˘c Ramuš et al. 2021 [17]
Calcium channel voltage dependent beta-2 sub unit (*CACNB2*)	10p12.33-p12.31	600003	rs202152674 rs137886839	Increased risk of proliferative diabetic retinopathy	Vuori et al. 2019 [18]
Intergenic locus in between *AKT3* and *ZNF238*	1:24401312	-	rs476141	Increased risk of diabetic retinopathy	Grassi et al. 2011 [19]
Calcium/calmodulin-dependent protein kinase IV (*CAMK4*)	5q22.1	114080	rs2300782	Increased risk of diabetic retinopathy	Fu et al. 2009 [20]
Formin 1 (*FMN1*)	15q13.3	136535	rs2300782	Increased risk of diabetic retinopathy	Fu et al. 2009 [20]
Growth factor receptor bound 2 (*GRB2*)	17q25.1	108355	rs9896052	Sight threatening diabetic retinopathy	Burdon et al. 2015 [21]
Valosin-containing protein-like (*NVL*)	1q42.11	602426	rs142293996	Increased risk of diabetic retinopathy	Pollack et al. 2019 [22]

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Table 1. *Candidate gene studies in diabetic retinopathy, nephropathy, and neuropathy*

Candidate gene	Gene location	OMIM entry	Polymorphism	Effect on T1DM	Reference
STT3 Oligosaccharyltransferase complex catalytic subunit B (*STT3B*)	3p23	608605	rs12630354	Increased risk of diabetic retinopathy	Imamura et al. 2021 [23]
Paralemmin 2 (*PALM2AKAP2*)	9q31.3	604582	rs140508424	Increased risk of diabetic retinopathy	Mathebula et al. 2015 [24]
Methylenetetrahydrofolate reductase (*MTHFR*)	1p36.22	607093	rs1801133	Susceptibility to diabetic neuropathy	Politi et al. 2016 [11]
Glyoxalase I (*GLO1*)	6p21.2	138750	rs2736654		
Apolipoprotein E (*APOE*)	19q13.32	107741	rs429358		
Interleukin 4 (*IL4*)	5q31.1	147780	VNTR (P1/P2 allele)		
Glutathione peroxidase 1 (*GPX1*)	3p21.31	138320	rs1050450		
Adrenoceptor alpha 2B (*ADRA2B*)	2q11.2	104260	rs879255577		
MicroRNA 146A (*MIR146A*)	5q33.3	610566	rs2910164	Decreased risk of neuropathy	
MicroRNA 128A (*MIR128A*)	2q21.3	611774	rs11888095	Susceptibility to diabetic neuropathy	
GDNF family receptor alpha 2 (*GFRA2*)	8p21.3	601956	rs7428041	Decreased risk of neuropathy	
Glutathione S-transferase theta 1 (*GSTT1)*	22q11.2	600436	wild/nul	Susceptibility to diabetic neuropathy	
Transcription factor 7 like 2 (*TCF7L2*)	10q25.2-q25.3	602228	rs7903146		

OMIM — Online Mendelian Inheritance in Man;T1DM — type 1 diabetes mellitus

Beta cell replacement therapies: pancreas and pancreatic islet transplantation in T1DM

Pancreatic transplantation

Pancreas transplantation has been offered to patients with T1DM since 1966 [25]. Metabolic outcomes of the procedure are excellent; the transplant restores proper interaction between beta and alpha cells, resulting in appropriate regulation of insulin and glucagon secretion, optimal blood glucose control, and long-term insulin independence. It also improves lipid profile and normalises glucose production in the liver. Clinically, pancreas transplantation prevents the progression of neuropathy, retinopathy, and nephropathy and even, to some extent, reverses some pathological changes [26]. Unfortunately, despite improved surgical outcomes, the procedure still carries a substantial risk of morbidity, especially in patients with advanced cardiovascular disease. Also, the need for lifelong immunosuppression with related side effects (opportunistic infection, nephrotoxicity, neurotoxicity, hypertension, increased risk of skin cancer, and lymphoproliferative disease) limits pancreas transplantation utility to small patient populations [7]. Most commonly pancreas transplant is offered to patients with end-stage kidney disease who need surgery and immunosuppression for kidney transplantation. A pancreas can be offered at the time of kidney transplant as simultaneous kidney and pancreas transplantation (SPK), or subsequently after kidney transplant as pancreas after kidney transplantation (PAK). Pancreas transplant alone (PTA) is offered only to desperate patients with problematic hypoglycaemia despite optimal insulin treatment (Fig. 1) [27].

Microbiota is a factor that significantly influences the human immune system and may also affect the acceptance of the transplant [28, 29]. Pancreas transplantation can also affect patient microbiota by transmitting donor microbiota from donor duodenum transplanted together with the pancreas and by the effect of antibiotics and immunosuppression medication used after the transplant. In addition, the gut microbiota composition of T1DM patients differs from healthy adults [30], which may have an additional effect on

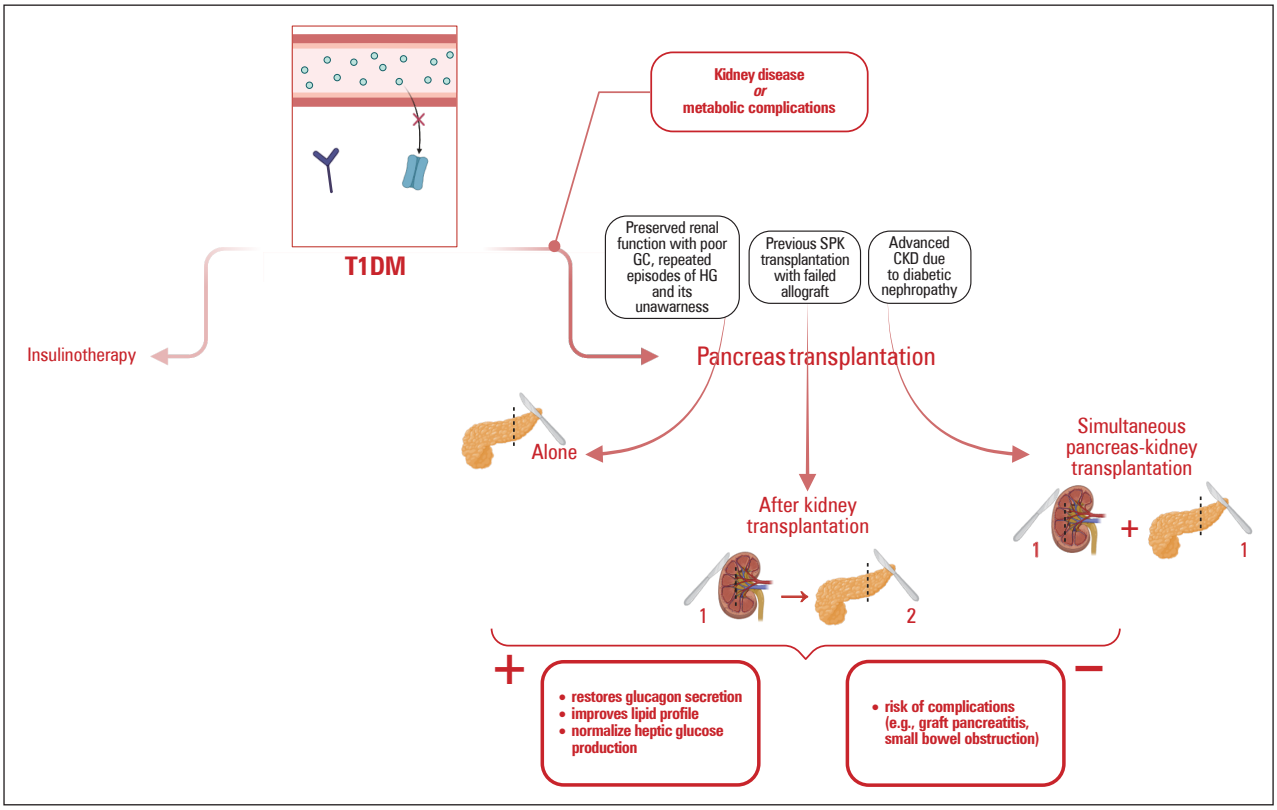

Figure 1. *Pancreas transplant in a patient with type 1 diabetes (T1DM). GC — glycemic control; HG — hypoglycemia; SPK — simultaneous kidney and pancreas transplantation; CKD — chronic kidney disease*

the graft. However, it is unknown whether and how gut microbiota affects the post-transplantation clinical course and complications [29]. Despite progression in surgical technique, the 10% risk of early pancreas graft thrombosis and even higher risk of postoperative infection remains a clinical challenge, and microbiota may play a dominant role in these complications.

Because genetic factors may affect the progression of microangiopathy in T1DM before transplant, they may also affect the progression or recovery from those complications after the transplant. However, we have not found any studies shedding any light on this relationship.

Pancreatic islet transplantation

Pancreatic islet transplantation is a minimally invasive alternative to whole pancreas transplantation. Islets are isolated from a deceased donor pancreas, suspended in a special media, and then infused into the patient portal vein via a small catheter placed through the skin under local anaesthesia by an interventional radiologist. Because no surgery is required, the risk of complication is minimal compared to whole pancreas transplantation. The risk of bleeding from the liver requiring blood transfusion is low and below 10%, while the need for surgical intervention to stop bleeding is very rare — below 1%. Unfortunately, since islets are allogeneic, patients still require the same lifelong immunosuppression as any other transplant recipients, which limits its utility again to a small population of patients with T1DM. Similarly to whole pancreas transplants, islets are offered to desperate patients with problematic hypoglycaemia (islet transplant alone — ITA) or kidney transplant recipients (islet after kidney — IAK). The lack of reimbursement for the procedure in the US due to outdated FDA regulations further limits islet transplantation availability [31].

Metabolically, islet transplantation restores endogenous insulin secretion and physiologic blood glucose regulation as whole pancreas transplantation. Five-year insulin independence might be as high as 50–60% in the most experienced centres, with most of the remaining patients maintaining partial islet function, which protects them from severe hypoglycaemic episodes much more effectively than optimal insulin therapy [32, 33]. By providing improved blood glucose control, islet transplantation also prevents the progression of microangiopathy, retinopathy, nephropathy, and macroangiopathy in the carotid artery despite immunosuppression toxicity [34–36].

Moreover, because nutrition is essential in the behavioural management of T1DM, its significance also

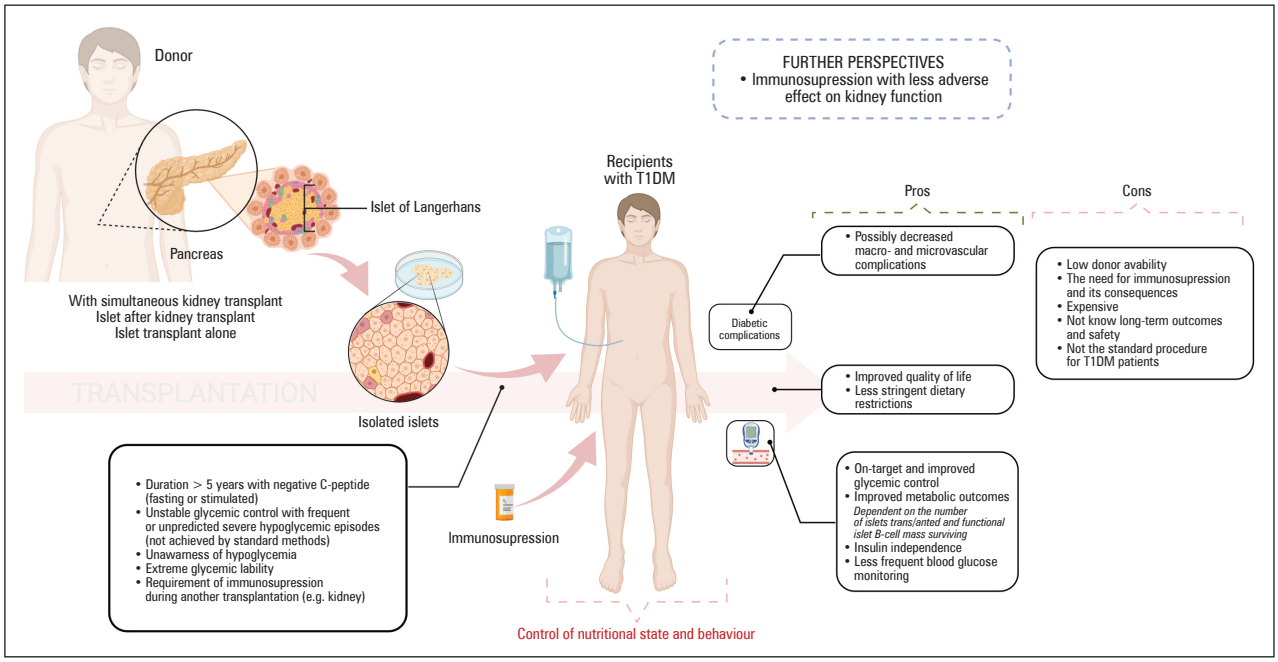

Figure 2. *The complex relationship between pancreatic islet transplantation and standard treatment of type 1 diabetes (T1DM)*

REVIEW

seems important after islet transplantation. The study of Poggioli *et al.* showed that anthropometric measures — body weight, waist circumference, and fat mass — significantly decreased after the procedure. Moreover, the intake of carbohydrates, protein, vitamin B12, B6, zinc, and phosphorus was also lower than before transplantation [37]. Interestingly, zinc can be beneficial posttransplant by improving glucose control and suppressing early graft failure in animal studies, and further studies on humans are warranted to confirm the effect. [38]. Therefore, perioperative management should consider counselling by a qualified dietitian and appropriate nutritional support.

Diet and lifestyle in patients with T1DM

Nutritional therapy and counselling are essential parts of T1DM treatment, and they aim to improve and maintain glycaemic control and prevent chronic complications (or to adjust diet if they occur) [39]. However, several data show that adherence to dietary guidelines may vary considerably among T1DM patients. Results from the non-systematic review of Patton showed that adherence to nutritional recommendations among youths with T1DM varied between 21 and 95%; however, many participants did not adhere to recommended intakes of fruits, vegetables, and whole grains [40]. In the study of Mohammed et al., 55.7% of patients (only 28.7% of participants had T1DM) did not adhere to the recommended dietary approach, and family/friends meetings and eating out were the main reasons [41]. However, attending to nutritional education and diabetes duration significantly increased nutritive adherence. Nutritional education and dietary counselling are essential because other studies have shown that they can also be associated with lower glycosylated haemoglobin (HbA_{1c}) values [42, 43]. However, studies are missing discussing whether adherence to dietary guidelines will delay the development of hypoglycaemia unawareness and the need for transplantation.

Due to limited engraftment and limited islet mass retrieved and transplanted from a deceased donor pancreas, islet transplantation usually provides lower than naturally present pancreas islet mass to the patients. As a result, islet mass, even in insulin-independent patients, is typically only borderline, and islet function can be affected by excessive carbohydrate intake, leading to chronic islet overstimulation, exhaustion, and graft failure. The gradual decline of islet graft function without signs of rejection has been described. Amyloid deposition found in failing islets may indicate misfolding mechanism and faulty protein production instead of insulin resulting from beta cell metabolic stress [44]. Therefore, dietary carbohydrate restrictions and physical activity promote stability of the islet graft and insulin independence and are highly recommended. However, reports with data supporting such recommendations are still lacking.

Because the aetiopathogenesis of T1DM is still not completely understood, it seems thqt environmental and genetic factors play a significant role. The same factors may lead to the reactivation of autoimmunity and ultimately affect the function of transplanted islets.

Therefore, an approach that will include proper nutrition and genetic factors is necessary [45, 47]. However, although food compounds potentially modify the expression of genes involved in the immune response — which is vital for T1DM patients — more studies investigating gene-nutrient interactions are needed beause current evidence regarding nutrigenetics and nutrigenomics are scarce [48, 49].

More studies are needed to evaluate the influence of nutritional factors during peri- and postoperative states on islet transplantation.

Gut microbiota composition in type 1 diabetes after pancreatic and pancreatic islet transplantation

The incidence rate of T1DM is increasing dramatically, but only 10% of genetically susceptible individuals will develop the disease. Therefore, there is no doubt that other factors, such as viral and bacterial infections and environmental factors, also play a role in developing T1D [50]. The microbiome may impact the development and course of this disease due to its proven influence on inflammation and the immune system [51]. Gut microbiota may influence signalling through TLR family receptors that are directly involved in autoimmunity in T1DM [52, 53]. The gut microbiota may also affect the development of type 1 diabetes through short chain fatty acids (SCFAs). An increased abundance of butyrate producing species was associated with an increased risk of T1DM [54, 55]. Other studies show that SCFAs protect genetically susceptible mice from developing diabetes. The epigenetic action of butyrate via histone acetylation at the Foxp3 locus promoter is responsible for differentiating regulatory T cells or inhibiting histone deacetylases in macrophages [56]. However, data on the impact of microbiota are still ambiguous [57]. Modulation of the microbiome leading to improved composition and diversity of the gut microbiota may include early exposure to beneficial bacteria, FMT transplants, dietary modifications, and probiotic and prebiotic supplementation [30]. Probiotic administration in early infancy positively correlated with decreased pancreatic islet specific autoantibodies [58]. Probiotic supplementation immunomodulates pancreatic islet function, which may improve glycaemic control and microflora changes to protect against systemic manifestations of pancreatic islet autoimmunity [59, 60].

The microbiota may also affect glycaemic control and, thus, the development of chronic complications, particularly in patients with already developed chronic kidney disease. In these patients, uraemia exacerbates dysbiosis, and regular use of probiotics improves metabolic control by reducing inflammation and oxidative stress, which improves renal flow.

Based on the current knowledge in the field of gut microbiota research in diabetes, it can be postulated that the understanding of the abnormal composition of the microorganisms inhabiting the gut may contribute to the greater effectiveness of pancreatic islet transplantation. It has been shown that the composition of microbiota in individuals with T1DM is significantly different than in healthy subjects, which may be an important modifiable risk factor for T1DM complications. The number of some bacterial groups (*Actinobacteria* and *Firmicutes*) and the ratio of *Firmicutes* to *Bacteroidetes* is lower in children with T1DM. However, these individuals have increased amounts of *Clostridium*, *Bacteroides*, and *Veillonella* [61]. In addition to quantitative changes, the microbiome of children with diabetes is also less diverse and relatively less stable [62]. Differences in the gut microbiota may also be observed after pancreatic islet transplantation in people with type 1 diabetes due to the interaction between the gut microbiota and the immune system. Studies in animals and humans have shown differences in gut microbial diversity before and after allogeneic organ transplants (liver, kidney, and haematopoietic stem cell transplantation) (29)but also closely related to the occurrence and development of various diseases. With the development of transplantation technologies, allogeneic transplantation has become an effective therapy for a variety of end-stage diseases. However, complications after transplantation still restrict its further development. Post-transplantation complications are closely associated with a host's immune system. There is also an interaction between a person's gut microbiota and immune system. Recently, animal and human studies have shown that gut microbial populations and diversity are altered after allogeneic transplantations, such as liver transplantation (LT. Dysbiosis was also observed to be exacerbated during the occurrence of graft versus host (GVHD) [29]. Moreover, numerous studies confirm that probiotic and prebiotic intake can effectively regulate the intestinal microflora and influence the incidence of posttransplant complications [63, 64]. Fewer complications after organ transplantation were also observed in rats with prior stool transplantation [65]. Precise identification by genetic methods of individuals predisposed to developing chronic complications may guide their further treatment in considering pancreatic islet transplantation. Assessment of differences in the gut microbiome composition in individuals before and after pancreas and pancreatic islet cell transplantation may give us the perspective to introduce new standards in the form of probiotic supplementation or stool transplantation in

individuals preparing for or after pancreas or beta-cell transplantation.

Summary

A patient with T1DM has a complex health problem developing early in life. A unique interest in the genetic determinants of the occurrence of chronic complications in diabetes can guide more personalised treatment. Diet and microbiota also have an indispensable influence on this process. Promoting better outcomes after islet and pancreas transplantation will benefit the patient's subsequent prognosis and survival. Investigating the interplay between these factors requires a great deal of research; nonetheless, it can significantly expand the medical knowledge of doctors and patients with type 1 diabetes, improve clinical outcomes, and ultimately improve quality of life.

Author contributions

Conceptualisation: A.Z. and I.K.-K.; writing — original draft preparation: A.Z., M.S.-Z., S.G., P.W., A.M.R., A.E.R.-P., M.K.; critical revision of the manuscript: A.D. and I.K.-K.; supervision: I.K.-K.; acceptance of the final version: all authors. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

Authors declare no conflict of interests.

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