Emerging Approaches to the Diagnosis, Prevention, and Personalised Management of Type 1 Diabetes in the Era of Personalised Medicine

By

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Declaration

It is hereby declared that:

- The thesis submitted is my own original work while completing degree at BRAC University.
- The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
- The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
- I have acknowledged all main sources of help.

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Approval

The thesis/project titled “Emerging Approaches to the Diagnosis, Prevention, and Personalised Management of Type 1 Diabetes in the Era of Personalised Medicine” submitted by MD. Sidratul Islam (19346056) of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on {11.05.2026}.

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Ethics Statement

The study does not involve any animal or human clinical trials.

Abstract

Type 1 diabetes (T1D) is an autoimmune condition characterised by selective destruction of pancreatic beta cells, resulting in complete insulin insufficiency and a lifelong need for insulin. Current diagnostic and therapeutic approaches focus on symptom management rather than retaining residual beta-cell function and/or preventing autoimmune attack. This thesis addresses new strategies for diagnosis, prevention and treatment of T1D, looking at combined genetic, immunologic, molecular and metabolic markers for risk prediction and early intervention. Immunomodulatory therapy (anti-CD3 antibodies, vaccines and regulatory T cells) is considered alongside regenerative therapies, such as stem cell-derived and gene-edited beta cells, encapsulation and combined immunotherapy-cell replacement therapy. Personalised approaches to glucose regulation, including continuous glucose monitoring, closed-loop insulin delivery, wearables, and pharmacogenomic approaches to therapy are discussed to optimise care. Ethical, regulatory and economic considerations are discussed, including the importance for fair access and implementation. Combining multi-omic technologies with machine learning allows disease and therapeutic response prediction, for predictive, precision medicine. These innovations will enable preventative, curative and personalised therapies, offering to transform treatment of T1D, prevent complications and enhance the quality of life.

Keywords: Type 1 Diabetes; Personalised Medicine; Immunotherapy; Beta-cell Regeneration; Continuous Glucose Monitoring; Pharmacogenomics

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List of Acronyms

T1D	Type 1 Diabetes
HLA	Human Leukocyte Antigen
GAD65	Glutamic Acid Decarboxylase 65
IA-2	Insulinoma Antigen 2
ZnT8	Zinc Transporter 8
CGM	Continuous Glucose Monitoring
ESC	Embryonic Stem Cell
iPSC	Induced Pluripotent Stem Cell
PRS	Polygenic Risk Score
SGLT	Sodium-Glucose Cotransporter
GLP-1 RA	Glucagon-like Peptide-1 Receptor Agonist
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CRS	Cytokine Release Syndrome
TNF-α	Tumour Necrosis Factor-Alpha
IL	Interleukin

Glossary

Autoimmunity:	A condition in which the immune system mistakenly attacks the body's own tissues.
Beta cells:	Insulin-secreting cells located in the islets of Langerhans in the pancreas.
Biomarker:	A measurable indicator of a biological state or condition used in diagnosis or monitoring.
C-Peptide:	A byproduct of insulin synthesis used as a marker of residual beta-cell function.
Immunomodulation:	Modification or regulation of the immune response to achieve a therapeutic goal.
Personalised medicine:	A medical model using an individual's genetic, molecular and lifestyle profile to guide treatment decisions.
Polygenic Risk Score:	A score that aggregates the effects of multiple genetic variants to estimate an individual's disease risk.

Chapter 1

Introduction

1.1 Overview of Type 1 Diabetes Mellitus (T1D)

Type 1 diabetes (T1D) is an autoimmune disorder that results in the selective destruction of pancreatic beta cells and consequently, absolute insulin deficiency (Atkinson et al., 2014). T1D incidence is increasing globally, with a projected increase in the number of children and adolescents with T1D, particularly in the developed world (DiMeglio et al., 2018). T1D often presents acutely, and people with T1D need lifelong insulin therapy to control their glucose and prevent acute complications, including diabetic ketoacidosis. Besides the acute metabolic complications, T1D is also a high-risk factor for chronic complications, including nephropathy, retinopathy, neuropathy and cardiovascular disease, resulting in morbidity and reduced health-related quality of life (Giwa et al., 2020). The psychological burden of insulin administration, dietary restrictions and ongoing blood glucose monitoring further complicates the management of T1D, revealing a need for more efficient and personalised therapies.

1.2 Pathophysiology and Autoimmune Mechanisms

T1D is an autoimmune condition, where the innate and adaptive immune responses are misdirected at insulin-secreting beta cells (Pociot & Lernmark, 2016). Islet-specific autoantibodies against glutamic acid decarboxylase (GAD65), insulinoma antigen 2 (IA-2) and zinc transporter 8 (ZnT8) are found months to years prior to onset and are a predictive

factor for T1D (Sugandh et al., 2023). Genetics play a key role, with human leukocyte antigen (HLA) haplotypes (HLA-DR3 and HLA-DR4) as significant risk factors (Atkinson et al., 2014). Other genetic markers, such as INS, PTPN22 and CTLA4, are involved in immune tolerance, and contribute to the breakdown of tolerance to beta cells (Giwa et al., 2020). Environmental factors, such as viruses, early nutrition and changes to the gut microbiome, may contribute to the development of autoimmune responses in genetically predisposed individuals (Sugandh et al., 2023). These interrelate genetic and environmental factors in the regulation of beta-cell loss.

1.3 Limitations of Conventional Diagnostic and Therapeutic Approaches

Traditional diagnostic and therapeutic strategies for T1D have relied on identification of hyperglycemia and implementation of standardised insulin therapies (DiMeglio et al., 2018). While these approaches are life preserving, they do not take into account the variable disease trajectory, do not preserve beta-cells and do not impact the autoimmune response. Furthermore, conventional management of disease does not consider individual patient characteristics, which may lead to suboptimal glucose control, variable risk of hypoglycemia and variable prevention of complications (Sugandh et al., 2023). There are few predictive models for the onset and progression of disease which would increase the likelihood of early interventions, which may preserve residual beta-cell function and improve outcomes (Shlyakhto, 2022). This would indicate a need for more targeted tools that can be used to take into account genetic, immunologic and metabolic information to guide personalised treatment.

1.4 Personalised Medicine in Autoimmune Diseases

Personalised medicine has emerged in the care of T1D to allow for the need to move beyond a “one size fits all” approach to individualise treatment based on genetic, molecular and lifestyle data (Shlyakhto, 2022). Personalised medicine accounts for risk prediction with HLA and non-HLA genes, autoantibodies and markers of beta-cell function to support screening and prevention of risk (Sugandh et al., 2023). Pharmacogenomics ensures the optimal selection of insulin and other treatments based on individual responses, and prediction models inform monitoring approaches to prevent complications. In addition, Personalised medicine also considers social and environmental factors, enabling patients to participate in self-care and implement lifestyle modifications in accordance with their own metabolic demands (DiMeglio et al., 2018).

1.5 Rationale and Objectives of the Review

The recognition of the complex and heterogenous nature of T1D suggests that there is a need for a review that reviews the current advances in diagnostic strategies, risk prediction and personalised treatment approaches. This review will explore new approaches for early diagnosis, immune modification, preserving beta cell function, and personalising the management of glycaemia in T1D. The review will provide an overview of how to implement a Personalised medicine approach using genetic and biomarker technologies and digital health solutions. It will aim to highlight existing approaches that are backed by evidence, and will improve patient outcomes, reduce the burden of disease, and inform future translational research for the management of autoimmune diabetes.

Chapter 2

Advances in the Diagnosis of Type 1 Diabetes

2.1 Evolution of Diagnostic Criteria and Staging of T1D

The diagnosis of Type 1 Diabetes (T1D) has evolved over time. Historically, the diagnosis of T1D was based on clinical presentation of hyperglycemia, polyuria, polydipsia and weight loss. But diagnosis using clinical symptoms often occurs following a substantial reduction in beta-cell mass (Atkinson et al., 2014). Current diagnostic criteria now recognise staging models that classify individuals from the pre-symptomatic stage (presence of autoantibodies), to clinical onset and overt disease (DiMeglio et al., 2018). This enables early identification of those at risk and helps tailor strategies for disease intervention (Giwa et al., 2020). Now, the American Diabetes Association and International Society for Pediatric and Adolescent Diabetes recognise multiple stages, and the need to use immunologic and metabolic markers for risk prediction (Sugandh et al., 2023).

2.2 Autoantibody Profiling and Predictive Value

Beta-cell autoantibodies are significant T1D risk factors. Those most commonly found are against glutamic acid decarboxylase 65 (GAD65), insulinoma antigen 2 (IA-2) and zinc transporter 8 (ZnT8) (Bonifacio et al., 2021). Multipositionality increases the risk of disease progression, which varies with age and genetic background (Steck et al., 2016). Longitudinal evidence shows seroconversion to multiple autoantibodies in early childhood is associated with rapid disease progression, while the presence of only a single

autoantibody may reflect slow disease progression (Bonifacio et al., 2021). This has informed the design of prevention trials and suggests frequent autoantibody testing may reveal potential targets for immunomodulation prior to irreparable beta cell destruction (Giwa et al., 2020).

2.3 Genetic Susceptibility and Polygenic Risk Scores

T1D is highly heritable and HLA and non-HLA genes are involved in susceptibility (Pociot & Lernmark, 2016). Polygenic risk scores, which aggregate the effects of multiple genetic variants, are now being used to assess risk (Atkinson et al., 2014). Variants in non-HLA genes such as INS, PTPN22 and CTLA4 play a role in immune regulation and impact the risk of autoimmune beta-cell destruction (Giwa et al., 2020). Polygenic models can be used to predict risk in children at risk of T1D and stratify risk for prevention studies (Sugandh et al., 2023).

2.4 Role of HLA Haplotypes in Disease Prediction

HLA class II genes HLA-DR3 and HLA-DR4 are the strongest genetic risk factors for T1D (DiMeglio et al., 2018). These are involved in presenting antigens to T-cells, rendering them susceptible to autoimmune attack of beta-cell (Giwa et al., 2020). HLA analysis, along with autoantibody analysis, enhances prediction models and allows early prediction of risk before the onset of the disease. There is emerging evidence that incorporating HLA haplotypes, in addition to polygenic risk scores and environmental risk factors, can improve prediction (Sugandh et al., 2023).

2.5 C-Peptide Measurement and Beta-Cell Function Assessment

C-peptide, a byproduct of insulin production, is a good indicator of beta-cell function. Low or declining C-peptide levels indicate progressive beta-cell destruction, assisting in diagnosis and disease management (Washburn et al., 2021). C-peptide is used to monitor the early stages of T1D, titrate insulin dose and for beta-cell preservation (Maddaloni et al., 2022). Emerging research also explores the beneficial effects of C-peptide supplementation on microvascular preservation and complications (Washburn et al., 2021).

2.6 Immunophenotyping and T-Cell Subset Characterization

High-resolution immunophenotyping enables profiling of disease-specific T-cells that kill beta-cells in T1D (CD4+ and CD8+ T-cells) (Grönholm & Lenardo, 2015). Technologies such as flow cytometry and single-cell RNA sequencing can accurately profile T-cell clonality, activation and inflammatory profiles. This not only gives clues to the underlying disease mechanisms, but also identifies individuals who will respond to immune-modulatory therapies. Immunophenotyping, autoantibody profiling and genetic risk scores better stratify patients, and enable targeted treatment strategies that enhance therapeutic response, while minimising the potential for immunosuppression (Sugandh et al., 2023).

2.7 Metabolomic and Proteomic Biomarkers

Metabolomic and proteomic profiling further provides additional evidence of the early stages of the T1D disease process, which reflect the metabolic and immunologic dysfunction in beta cells (Moulder et al., 2017). Blood metabolites, cytokines and proteins can be used as early markers of beta-cell dysfunction, immune response and disease progression. In children, proteomics has revealed a potential to predict autoantibody seroconversion, offering diagnostic and prognostic insights. Incorporating such signatures

in disease monitoring strategies will allow the detection of subclinical disease, enhanced risk stratification and prediction, and direction of prevention or therapeutic strategies based on individual metabolic and immune signatures (Grönholm & Lenardo, 2015).

2.8 Microbiome Signatures and Immune-Metabolic Interactions

Microbiome plays a pivotal role in T1D and immune tolerance. Prospective studies have demonstrated early life dysbiosis is associated with islet autoantibodies and T1D (Kostic et al., 2015). Metabolites produced by microbiome regulate the immune system, regulating T cell differentiation, regulatory T cells and inflammation. This suggests interventions which may affect the microbiome (such as probiotics, prebiotics and diet) may prevent disease in at-risk populations. Integration of microbiome, genetic and immunology research constitutes a comprehensive, personalised approach to prevent T1D (Sugandh et al., 2023).

2.9 Imaging Techniques for Beta-Cell Function and Inflammation

Emerging imaging approaches such as positron emission tomography (PET) and magnetic resonance imaging (MRI) can provide non-invasive assessment of beta-cell mass, function and inflammation in the pancreas (Wherrett et al., 2011). They can be used to track disease progression, detect insulitis and gauge functional beta-cell mass. The techniques provide functional and spatial information complemented by biochemical and immunologic measures. They can be applied to assess immune intervention, evaluate regeneration and calculate risk in pre-symptomatic individuals. This combination of imaging in conjunction with immunologic and metabolic factors guides personalised management and evidence-based early intervention strategies in T1D.

2.10 Machine Learning and Multi-Omic Integration in Risk Prediction

Machine learning approaches, incorporating multi-omic factors (genetic, immunologic, metabolomic, microbiome) enhance prediction of T1D (Shlyakhto, 2022). Machine learning approaches classify children based on risk of developing T1D, predict development of T1D in at-risk (autoantibody positive) children, and predict the response to preventative therapies. Harnessing multiple data sources can lead to the identification of novel biomarker combinations, improving prediction. This approach facilitates personalised monitoring programmes, immunotherapies and interventions for high-risk individuals. Multimodal machine learning is an emerging approach to transform multi-omic data into personalised therapies (Sugandh et al., 2023).

2.11 Current Challenges in Translating Biomarkers to Clinical Practice

Although there have been tremendous advances, there is a need for biomarker-based strategies in the clinic in T1D (Ehlers, 2016). Lack of laboratory and standardised assay protocols prevent quality control and implementation. Screening and treatment is held back by ethical considerations, particularly in children. Computational power, bioinformaticians and clinician education are needed for using multi-omic data. Privacy and security, regulatory approvals and verification of predictive models are further issues. Addressing these challenges is critical for the accurate, equitable and practical use of biomarker panels for early detection, disease prediction and treatment of T1D (Zala & Thomas, 2023).

Chapter 3

Emerging Strategies for Disease Prevention

3.1 Primary Prevention: Targeting At-Risk Individuals Before Autoimmunity

The aim of primary prevention for Type 1 Diabetes (T1D) is to prevent the autoimmune reaction from occurring in individuals genetically at risk of developing the disease. Common genetic risk factors for islet autoimmunity in children include high-risk HLA haplotypes, HLA-DR3 and HLA-DR4 (Pociot & Lernmark, 2016). Lifestyle and environmental factors, including early dietary exposures, viral infections and other environmental triggers, are believed to influence immune responses and may trigger beta cell destruction in genetically predisposed children (Giwa et al., 2020). For example, clinical investigations of early dietary interventions, such as delayed introduction of complex cow's milk proteins, suggest that immune priming in early life can impact the onset and frequency of autoantibody development (Sugandh et al., 2023). To achieve successful primary prevention, a combination of genetic screening, autoantibody testing, and polygenic risk scoring are needed to identify at-risk children and implement individualised surveillance and intervention strategies.

3.2 Secondary Prevention: Delaying Disease Onset in Autoantibody-Positive Individuals

Secondary prevention is aimed at people with one or more islet autoantibodies but without hyperglycemia. Presence of multiple autoantibodies is a strong predictor of symptomatic T1D and can be used to identify and treat early (Bonifacio et al., 2021). Prospective studies show the importance of screening and participating in immunomodulatory studies for children with multiple autoantibodies (Steck et al., 2016). The goal of treatment in these children is preserving beta-cells, C-peptide and delaying the progression to overt diabetes. This prevention period enables therapeutic strategies to be employed before the occurrence of diabetes, and may reduce metabolic complications and preserve insulin secretion.

3.3 Teplizumab and Anti-CD3 Monoclonal Antibodies

A very exciting development in secondary prevention is an anti-CD3 monoclonal antibody called teplizumab. In clinical trials, administration of teplizumab to high-risk, autoantibody-positive participants delayed the onset of clinical T1D by about 2 years compared to placebo (DiMeglio et al., 2018). Teplizumab targets T-cells, and induces a partial state of tolerance, while reducing the activity of the autoantigen-specific T-cells that are responsible for the beta-cell destruction (Sugandh et al., 2023). Teplizumab is safe to use in children, with side effects of transient lymphopenia and cytokine release syndrome (CRS). The drug's approval is a significant step in the transition from immunology to successful prevention of T1D.

3.4 Antigen-Specific Immunotherapies (Insulin, GAD65, Peptide Vaccines)

Antigen-specific immunotherapies induce tolerance to specific beta-cell antigens to prevent or delay autoimmune destruction. Administration of oral or nasal insulin, glutamic acid decarboxylase (GAD65) vaccines or peptides in clinical trials have shown modest efficacy in reducing autoantibodies and maintaining C-peptide (Zala & Thomas, 2023). These therapies have the advantage of being highly specific in their immune regulatory capacity in the absence of widespread immunosuppression, as advocated in personalised medicine. Dose-dependent sensitivities, routes of delivery and combination therapies with other immune-modulating drugs are being explored to enhance the therapeutic response and induction of immune tolerance (Grönholm & Lenardo, 2015).

3.5 Immune Tolerance Induction Using Dendritic Cells and Nanoparticle Platforms

New approaches to induce antigen-specific immune tolerance involve tolerogenic dendritic cells and nanoparticles. Altered dendritic cells induce tolerogenic presentation of beta-cell antigens, induce regulatory T-cells and suppress pathogenic T-cells (Sugandh et al., 2023). Nanoparticles deliver antigens to lymph nodes to induce tolerance without excessive suppression. These interventions can prevent or delay T1D in animal models, offering additional treatment options for high-risk patients and complementing other immunotherapies (Grönholm & Lenardo, 2015).

3.6 Modulating the Gut Microbiota to Prevent Autoimmunity

There is increasing evidence that the microbiome plays an important role in immune tolerance and risk of T1D (Kostic et al., 2015). Early-life microbiome dysbiosis is linked to induction of islet autoimmunity, suggesting that microbiome can be used to prevent

disease. Experimental manipulations involving probiotics, prebiotics and dietary interventions have shown decreased levels of inflammatory markers, induction of regulatory immune responses and prevention of islet autoimmunity (Sugandh et al., 2023). Adding microbiome analysis to the risk assessment may allow for individualised approaches and provide a personalised prevention strategy by targeting metabolism, immune responses and microbiome.

Chapter 4

Personalised Immunomodulatory Therapies in Established T1D

4.1 Broad vs. Targeted Immunotherapy: Mechanistic Overview

Immunotherapies for established T1D can be classified as broad immunosuppressive therapies and specific immunomodulation. Systemic immunosuppression (such as systemic steroids) is broad and suppresses the immune system, but has adverse side effects and does not necessarily preserve beta cell function (Lin et al., 2024). Specific immunotherapy targets specific aspects of the autoimmune response, such as autoreactive T-cells, B-cells and cytokines, and allows for better disease control (Cudini & Fierabracci, 2023). Research indicates that specific therapies improve beta-cell survival without global immunosuppression, and play a critical role in personalised management of T1D (Biswas et al., 2025).

4.2 B-Cell Depletion Therapies (e.g., Rituximab)

B-cells contribute to T1D by generating autoantibodies and presenting antigens to T-cells. Rituximab (an anti-CD20 monoclonal antibody) targets B-cells and retains C-peptide levels in patients with new-onset disease (Krishnamurthy et al., 2023). Randomised studies demonstrate that although the impact on beta-cell activity is temporary, rituximab can reduce inflammatory cytokines and effect immune function, delaying progression to insulin use (Karaoglu et al., 2025). Biological markers of B-cells, such as circulating autoantibodies and B-cell subsets, are valuable in monitoring responses and determining schedules.

4.3 Cytokine Pathway Blockade (IL-1, IL-6, and TNF-α Inhibitors)

Cytokine inhibition is a selective strategy to interfere with inflammatory pathways leading to beta-cell destruction. Anti-IL-1, -IL-6 and -TNF-α have been investigated to reduce systemic and local inflammation (Azad et al., 2024). These interventions decrease immune-mediated beta-cell damage without impairing immune responses, with preliminary studies showing preservation of residual beta-cell function in newly diagnosed T1D (Wang et al., 2025). Substantial benefit and minimal risk in patients selected by cytokine profiling ensures maximum benefit, which is the tenet of personalised immunotherapy.

4.4 Costimulatory Blockade and CTLA-4 Agonists

T cells require costimulatory signals for activation, so blockade of interactions (e.g. CD28 and B7) and CTLA-4 agonism are promising (Jacobsen & Schatz, 2025). These approaches block and suppress the autoreactive T cells, while allowing tolerance by regulatory T cells. This approach reduces insulitis, disease progression and beta cell mass in preclinical studies and phase I/II trials (Lin et al., 2024). Timing and patient selection, based on immunophenotyping and genetic risk stratification, will be important.

4.5 Regulatory T Cell (Treg) Therapy and Engineering Approaches

Regulatory T cells (Tregs) are key to immune tolerance and autoimmunity. Ex vivo expanded and genetically engineered Tregs can be administered to T1D patients to prevent autoimmunity and preserve beta-cell mass (Cudini & Fierabracci, 2023). Antigen-specific Tregs target beta-cell antigens without immunosuppression. Phase I/II trials show safety, feasibility and preliminary effectiveness in maintaining C-peptide (Biswas et al.,

2025). Tailoring therapy to individual patients, using markers such as autoantibody titers and beta-cell function, is improved.

4.6 Adoptive Cell Therapies and Immune Reset Strategies

Adoptive cell treatment delivers immune cells to patients to reset the immune response (Karaoglu et al., 2025). Bone marrow transplants have been demonstrated to induce temporary remission, but are too risky for widespread use. Immune reset through T-cell reprogramming and co-infusions with tolerogenic dendritic cells aim to induce sustained immune tolerance with few side effects (Azad et al., 2024). Immunophenotyping helps determine the type of cellular products and their timing for enhanced efficacy in advanced T1D.

4.7 Combination Immunotherapy Regimens

Monotherapies may not preserve beta-cell function due to multifaceted autoimmune processes. Combination therapies, including B-cell depletion, cytokine blockade and induction of Tregs, have a greater impact (Wang et al., 2025). Tailored approaches use immune profiling, disease stage and beta-cell function to determine combinations of therapy. Combination studies show improved preservation of C-peptide, reduced consumption of insulin and improved safety (Jacobsen & Schatz, 2025).

4.8 Biomarkers of Immunotherapy Response and Resistance

Biomarkers are a key component of individualised immunotherapy for treatment selection, dosing and efficacy. Cytokines, antibodies, T cell sub-phenotypes and C-peptide are indicators of treatment success (Subramanian et al., 2024). Emerging markers including

immune gene signatures and beta-cell stress markers can predict response and allow selection of patients who are likely to respond to a particular therapy (Karampelias et al., 2025). Multidimensional biomarker use in practice allows personalised immunomodulation in T1D.

Chapter 5

Advances in Beta-Cell Replacement and Regeneration

5.1 Islet Transplantation: Progress and Limitations

Islet transplantation has been successful for treating brittle type 1 diabetes, particularly severe hypoglycemia (Shapiro et al., 2017). Refinements in the isolation, immunosuppression and engraftment of islets have resulted in improved islet survival and immediate glycemic control. However, long-term outcome is limited by immunologically-mediated loss, alloimmune rejection and the need for immunosuppression (Shapiro et al., 2017). The bottlenecks are the supply and quality of the islets. However, islet transplantation demonstrates the principle of beta-cell replacement, by replacing insulin production.

5.2 Stem Cell-Derived Beta Cells (ESCs and iPSCs)

Functional beta cells can be derived from an unlimited source of stem cells from either embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) (Pagliuca et al., 2014). Stem-cell-derived beta cells now uniformly express insulin and have glucose-stimulated insulin secretion (Nair et al., 2019). In vitro maturation and endocrine cell clustering in three dimensions help to stabilise and transplant stem cell beta cells (Nair et al., 2019). These beta cells have displayed long-term reversal in animal models in preclinical studies, but more research into immunoprotection and full beta cell maturation is needed for human use (Vegas et al., 2016).

5.3 Gene-Edited Beta Cells for Immune Evasion

Recent developments in gene editing technology, like CRISPR/Cas9, have enabled beta cell modifications to evade the immune system and develop immune-evasive therapies (Karaoglu et al., 2025). Beta cells can be modified to down-regulate HLA expression or to express immune checkpoints, to render them less susceptible to T-cells and natural killer cells (Karaoglu et al., 2025). In animal models, there is increased survival and sustained insulin secretion in an allogeneic environment (Karaoglu et al., 2025). This approach provides a patient-specific solution to this platform, where the patient's immune system defines the modifications required to protect the beta cells, possibly alleviating systemic immunosuppression and maintaining beta cell function (Azad et al., 2024).

5.4 Encapsulation Technologies and Bioartificial Pancreas Systems

Encapsulation provides immunoisolation of transplanted beta cells from immune attack, while allowing diffusion of nutrients and insulin (Korsgren, 2017). Macro- and micro-encapsulation technologies have been developed, employing polymers with ideal oxygen transport and immune isolation properties (Desai & Shea, 2017). Bioartificial pancreas devices incorporate encapsulated beta cells with scaffolds and blood supply to enable natural insulin release (Vegas et al., 2016). These are promising in preclinical studies, but need further development to overcome problems of survival, fibrosis and release for clinical applications.

5.5 Regenerative Medicine Approaches for Beta-Cell Neogenesis

Regenerative therapies aim to induce beta-cells to regenerate or undergo neogenesis. The influence of growth factors, small molecule drugs and extracellular environment has been investigated to stimulate beta-cell replication (Rezania et al., 2014). Lineage tracing studies show alpha cells can differentiate into beta cells and ductal progenitors can be activated to join the beta cell population in response to specific stimuli (Pagliuca et al., 2014). These approaches are still largely experimental, but can be combined with cell replacement strategies and can potentially lead to minimally invasive regeneration strategies, particularly when combined with immune modulation therapies to protect the newly generated cells (Nair et al., 2019).

5.6 Combination Approaches: Immunotherapy with Cell Replacement

Combining immunotherapy with beta-cell replacement or regeneration increases survival and function of beta cells. Combination therapies, such as Tregs, costimulatory blockade or anti-inflammatory cytokines, with transplantation, enhance beta-cell survival (Shapiro et al., 2017). Personalised combination therapies, administered based on immunoprofiling, maintain beta cells and minimise systemic immunosuppression (Vegas et al., 2016). Early clinical and preclinical results demonstrate enhanced C-peptide preservation and sustained blood glucose levels, and suggest immunotherapies and cell therapies may synergistically modify the disease (Azad et al., 2024).

Chapter 6

Personalised Glycemic Management Technologies

6.1 Evolution of Insulin Therapy and Delivery Systems

Insulin has progressed from fixed dose multiple daily injections to more personalised treatment with basal-bolus therapy and insulin pump (Berget et al., 2019). The availability of fast- and slow-acting insulin analogs result in more physiological insulin delivery, reducing hypoglycemia and improving glucose control. Modern insulin pumps have bolus calculators and varying dose adjustments made according to carbohydrate, activity and glucose trend, allowing for more flexible lifestyle and metabolic adaptation (Martin et al., 2019). This, together with continuous glucose monitoring (CGM) systems, enables real-world data-driven therapy optimisation in children and adults, as well as a patient-centred, personalised approach to managing diabetes.

6.2 Continuous Glucose Monitoring (CGM) and Predictive Analytics

Continuous glucose monitoring (CGM) represents a shift from intermittent to continuous measurement of interstitial glucose (Dicembrini et al., 2021). CGM devices provide alerts for impending hypoglycemia or hyperglycemia to allow actions to be taken. New algorithms predict glucose excursions based on CGM and enable insulin adjustments (Laffel et al., 2020). CGM allows for individualised glucose targets, optimisation of treatment based on time in range and variability as well as lifestyle and compliance. These systems transform

diabetes management from reactive to proactive, and allow precision medicine by incorporating long-term glucose trends into treatment.

6.3 Closed-Loop and Artificial Pancreas Systems

Closed-loop systems integrate CGM and insulin pumps to provide a bio-engineered artificial pancreas that modulates insulin levels according to glucose levels (Templer, 2022). Clinical studies demonstrate closed-loop systems increase time in range, reduce hypoglycemia events and decrease patient burden compared to conventional insulin pump or injection therapy (Bally et al., 2018). The use of predictive models enables dynamic adaptation to food, exercise and stress. Personalised insulin profiles and algorithms improve effectiveness and safety, and represent a major breakthrough in automated, personalised glucose management for type 1 diabetes (Bally et al., 2018).

6.4 Integration of Wearables and Digital Health Tools

Continuous glucose monitoring (CGM), wearable activity monitoring and digital monitoring systems offer continuous glucose levels, activity, heart rate and other data (Siddiqui et al., 2018). These technologies allow for real-time insulin optimisation, personalised diet recommendations and trend analysis for glucose prediction. The digital connection enables remote monitoring by healthcare providers, offering telehealth support and counselling (Cappon et al., 2017). Wearable technologies combined with CGM and prediction algorithms provide a data-driven, integrated health platform enabling patient empowerment, adherence and personalised diabetes management, as well as strategies to mitigate longer term risks and optimise metabolism.

6.5 Pharmacogenomics in Insulin Sensitivity and Response

Pharmacogenomics can help predict insulin response and sensitivity and hypoglycemia (Florez, 2017). Genetic tests can pick up variants in insulin metabolism, insulin receptor activity and pharmacokinetics to guide insulin dosing and selection of other therapies. Most research has been in type 2 diabetes, but recent studies demonstrate it is relevant for type 1 diabetes, particularly for predicting response to insulin therapies, and the choice of adjunct therapies such as SGLT inhibitors or GLP-1 receptor agonists (Venkatachalapathy et al., 2021). Integration of pharmacogenomic data and monitoring can lead to personalised treatment strategies for best glucose control.

6.6 Adjunctive Therapies (SGLT Inhibitors, Metformin, GLP-1 RAs)

Adjunctive therapies have metabolic benefits. Sodium-glucose cotransporter (SGLT) inhibitors promote renal excretion of glucose, and metformin sensitises the body to insulin, particularly if insulin secretion remains (Goyal et al., 2020). GLP-1 mimics increase insulin secretion in response to glucose and may reduce insulin doses to achieve better postprandial glucose control. Choosing adjunctive therapy depends on the patient's phenotype, insulin production, other medical conditions and complications, such as hypoglycemia and diabetic ketoacidosis (Sugandh et al., 2023).

Chapter 7

Biomarkers for Monitoring Disease Progression and Treatment Response

7.1 Immunologic Biomarkers of Therapeutic Response

Immunological biomarkers such as autoantibodies, T cell subsets and cytokines are critical for assessing the efficacy of T1D immunomodulatory therapies (Sugandh et al., 2023). The dynamic of these markers can be associated with a reduction in the number of autoreactive immune cells, expansion of regulatory T cells or induction of tolerance (Krishnamurthy et al., 2023). Immune biomarkers can be assessed to identify early responders and non-responders, to facilitate treatment adjustment. These can be integrated with genetic risk and personalised immune profiling to enhance immunotherapy, allowing treatment optimisation and maximum beta-cell function.

7.2 Molecular and Transcriptomic Signatures of Beta-Cell Stress

Molecular and transcriptomic profiling of peripheral blood or islets reveal signs of beta-cell stress, apoptosis and immune cell activation (Grönholm & Lenardo, 2015). Key markers, such as endoplasmic reticulum stress and pro-apoptotic genes, predict loss of C-peptide and residual beta-cell function. These findings can be used to detect subclinical disease early and can inform treatment before onset of hyperglycemia. Combining transcriptomic signatures with immunologic and metabolic markers enhances prediction and offers

information about the mechanisms of disease progression in an individual patient consistent with the Personalised medicine approach to T1D.

7.3 Metabolic Indicators of Residual Insulin Production

The most widely used metabolic marker of residual insulin secretion and beta-cell reserve remains C-peptide (Maddaloni et al., 2022; Washburn et al., 2021). Quantitative levels of C-peptide (stimulated and fasting) help in classification, treatment and prognosis of the disease. New metabolic markers, such as the proinsulin-to-C-peptide ratio, glucose dynamics, and metabolomics also provide additional information about beta-cell function. These metabolic markers combined with immunologic and molecular markers, enable real-time monitoring and optimal adjustment of insulin, immunomodulators or cellular therapies.

7.4 Standardization and Validation Challenges

Biomarkers, however, are difficult to standardise and implement. Variability in the assay, inter-laboratory variability and lack of threshold values affect reproducibility (Ehlers, 2016). Longitudinal studies are required to validate predictive and prognostic utility in different patient groups. Standards, quality control and multi-centre trials are needed for clinical utility. Addressing these challenges is essential to unleash the potential of biomarker-driven Personalised medicine to benefit T1D patients in a safe, efficient and fair way.

Chapter 8

Ethical, Regulatory, and Implementation Considerations

8.1 Ethical Issues in Genetic and Biomarker Screening

T1D genetic and biomarker screening has privacy, security and psychological considerations (Shlyakhto, 2022). Genetic and/or biomarker screening and identification of at-risk children can make families anxious, distort decision-making and induce stigma. Ethics guidelines should enhance judicious use of predictive data, prevent discrimination and protect the rights of children. Health-care professionals and researchers must balance the science with respect for autonomy, confidentiality and informed consent, particularly when predicting early disease where few therapeutic options may be available.

8.2 Informed Consent and Psychosocial Impact in Pediatric Populations

Informed consent for children requires discussion with parents and child's assent (as appropriate for age) (Shlyakhto, 2022). Psychosocial issues of genetic risk disclosure, immunotherapy or experimental trials should be discussed. Genetic counselling and psychosocial support is required to minimise distress and aid comprehension. For ethical research in children, the benefits, risks and uncertainties should be clear to establish trust and enable voluntary informed consent.

8.3 Regulatory Pathways for Precision Therapeutics and Diagnostics

Regulatory considerations of precision therapeutic and diagnostic approaches for T1D are complex and relate to safety, efficacy and manufacturing (Lin et al., 2024). Regulators require extensive preclinical and clinical studies, biomarker validation, pharmacodynamic analyses and post-marketing safety monitoring. Multicountry harmonisation is required for international applicability, particularly for cell or gene-edited therapies. Fast but rigorous regulatory pathways are required to enable clinical development.

8.4 Health Economics and Access to Personalised Care

Personalised solutions in T1D, such as immunotherapy, new CGM and islet therapies, may be expensive, which may limit access (Shapiro et al., 2017). Health economic analysis is important to evaluate cost effectiveness relative to conventional approaches, such as quality-adjusted life years, prevention of chronic complications, and health care services. Policy frameworks should recognise affordability, reimbursement and resource allocation to support equitable access to the benefits of precision medicine and avoid increasing health care inequities.

8.5 Addressing Equity and Global Disparities in T1D Management

Global inequalities in health, diagnosis and treatment limit the delivery of precision medicine for T1D (Giwa et al., 2020). The development of technology transfer, training, low-cost therapies and telemedicine programs are critical to ameliorate these. Tailoring programs to low-resource environments and personalised care are needed to achieve equity. International strategies and investment in public health can improve health disparities and increase access to Personalised medicine in the world.

Chapter 9

Translational Challenges and Future Research Directions

9.1 From Bench to Bedside: Barriers to Clinical Translation

Biological, technical and practical challenges make the translation of new approaches to type 1 diabetes (T1D) from preclinical to clinical settings complex. Differences in age, residual beta cell mass and function, genetic and immune attributes limit the broad applicability of the treatment and can influence treatment outcomes (Vegas et al., 2016). Cell therapies, such as stem-cell-derived beta cells or immune-resistant cells through genetic engineering, require robust and reliable production processes to preserve cell viability and function for transplantation. Immune mismatching is also an issue, with both auto- and alloimmune responses needing to be suppressed to prevent rejection. Making use of multi-omic data (genomics, immunophenotyping, metabolomics and microbiome) for therapeutic purposes involves advanced data analysis and decision-making. There are also ethical, economic and practical (cost-effectiveness, safety and access) barriers that may prevent implementation. To overcome these challenges, approaches such as multi-disciplinary teamwork between immunologists, endocrinologists, bioengineers and data scientists, standardised procedures to produce products, robust clinical trials and validated processes to optimise and test products can be used.

9.2 Heterogeneity in Trial Design and Endpoint Selection

The diversity of patients enrolled in T1D clinical trials hampers the response to therapy and statistical analyses. Age, disease duration, beta cell function, immune status and genetic factors influence the response to treatment (immunotherapy, beta cell replacement and adjunct therapies) (Biswas et al., 2025). Trial endpoint choice is critical; commonly used endpoints include maintaining C-peptide, autoantibodies, immunophenotype, metabolic indicators (HbA1c and time in range) and multiple clinical responses. Inconsistent definitions and frequency of endpoint testing limit meta-analysis and pooling of data. Personalised trial designs that stratify by biomarker, genetic or immune profiling, may enhance efficiency, power and interpretation of efficacy. Standardised protocol and multi-site and reporting guidelines also increase reproducibility and generalisability. Finally, adaptive trial designs and Bayesian methods enable flexibility to account for individual differences, with the possibility of dose or inclusion criterion change during the trial. Recognising and accounting for trial heterogeneity is essential for successful translation of interventions trialled in unrepresentative experimental settings to become safe, effective, generalisable and equitable treatments for the general population with T1D.

Chapter 10

Conclusion

10.1 Summary of Key Insights

The last few decades of type 1 diabetes (T1D) research have demonstrated the value of personalised medicine. The ability to integrate genetic, immunologic, molecular and metabolic factors to identify at-risk individuals and define treatment needs specific to each disease will achieve personalised medicine. Improved therapies that include immunomodulation, beta-cell regeneration and improved glucose control preserve beta-cell function and glucose control. Multimodal therapies that include immunotherapy, stem-cell-derived beta cells and continuous glucose-monitoring systems offer the possibility of long-term, individualised therapies. These approaches address the autoimmune basis of T1D, as well as the metabolic dysfunctions that are common in the current standard of care for T1D, to offer a more selective approach to improving patient outcomes and quality of life, rather than generally targeting metabolic complications.

10.2 Clinical Implications for Personalised Management of T1D

There are important clinical implications of personalised approaches to T1D. Personalised approaches to treatment optimise dosing, avoid hypoglycemia and reduce the risk of long-term microvascular and macrovascular complications. Biomarker-based approaches enable clinicians to provide pharmacologic, immunologic and regenerative treatments based on beta-cell function and other factors. Information technology, including continuous glucose

monitoring and closed-loop insulin pumps, enhances adherence, promotes biochemical stability and empowers patients. This personalised strategy facilitates a shift from reactive to predictive medicine. By incorporating personalised biological and behavioural data, doctors can predict disease progression, personalise treatment and enhance patient outcomes.

10.3 Future Outlook: Toward Curative and Preventive Therapies

Regenerative therapies such as stem cell derived beta cells, genetically engineered cellular therapies and antigen-specific immunomodulation promise to change the face of T1D treatment. These therapies target the autoimmune disease and the beta-cell dysfunction, and extend symptomatic therapies such as insulin therapy to disease-modifying and possibly preventative therapies. Personalised risk assessment, diagnosis and therapy is enabled using multi-omic profiling, computer modelling and predictive algorithms. These predictive tools may prolong the preclinical phase to prevent the clinical manifestation of the disease, and help monitor the disease process. Combined strategies, such as immunotherapy and regenerative or bioengineering beta-cell replacement, are likely to provide a synergy of effects and improve long-term outcomes.

10.4 The Promise and Responsibility of Personalised Medicine

Personalised medicine for T1D is promising but presents ethical, societal and economic concerns. Justice, privacy and consent are important, particularly for genetic, biomarker and stem cell therapies. Health care and research practitioners need to balance the benefits of innovation against safety, cost and social considerations, while ensuring that new treatments do not increase health care inequalities. Personalised interventions need to

consider health care capacity, finance and tracking for success and equity. Effective translation requires the translation of scientific and ethical research and practice. Fair and ethical approaches to Personalised medicine promise to transform T1D treatment, enabling targeted, preventive and potentially curative interventions to improve outcomes and quality of life for a wide range of patients around the world.

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