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EDITED AND REVIEWED BY
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SPECIALTY SECTION

This article was submitted to
Clinical Diabetes,
a section of the journal
Frontiers in Endocrinology

RECEIVED 10 December 2022

ACCEPTED 12 December 2022

PUBLISHED 06 January 2023

CITATION

Li X, Zhang M, Yan J and Liu Z (2023)
Editorial: Heterogeneity of clinical
phenotypes in type 1 diabetes
and of beta cell deterioration
in type 1 diabetes.
Front. Endocrinol. 13:1120555.
doi: 10.3389/fendo.2022.1120555

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Editorial: Heterogeneity of clinical phenotypes in type 1 diabetes and of beta cell deterioration in type 1 diabetes

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KEYWORDS

type 1 diabetes, heterogeneity, precision medicine, disease management, omic analyses

Editorial on the Research Topic

Heterogeneity of clinical phenotypes in type 1 diabetes and of beta cell deterioration in type 1 diabetes

Precision medicine is of particular importance in diabetes as it is a highly heterogeneous syndrome (1) that contains genetic, environmental, behavioral and other etiological and pathophysiological components. Information garnered through many large multicenter cohort studies, multi-integration of bio-information obtained using genomics, epigenomics, proteomics and metabolomics approaches, and the utilization of data-driven classification strategies have drastically altered our understanding of diabetes, especially type 2 diabetes (T2DM), heterogeneity. Indeed, patients with T2DM can be stratified using the clustering method into five subgroups with distinctive characteristics, which has been replicated in cohorts with diverse backgrounds, and this stratification has been proved to be effective for complication prevention and treatment tailoring (2–4). The application of machine learning methods in diabetes classification in more integrative data sources and a soft-clustering strategy to sub-classify patients using genome-wide association studies (GWAS) (5) have all been proved useful. A continuous classification for diabetes has been attempted using the “palette model” concept (6). Newly diagnosed patients with T2DM could be classified into four distinctive subgroups and one subgroup with mixture characteristics (7). On the other hand, while studies in precision medicine have been thriving in T2DM, our understanding of heterogeneity in type 1 diabetes (T1DM) remains limited.

With an autoimmune pathogenesis and the insulin dependency nature, T1DM has traditionally been perceived as a more homogeneous entity compared to T2DM. However, recent evidence suggests that T1DM is also a heterogeneous disease and significance advances have been made in precision prediction, prevention, diagnosis, and treatment in T1DM (8). Mounting evidence has confirmed the importance of precision medicine in T1DM. An insightful understanding of the etiology of T1DM revealed the role of novel omics biomarkers in addition to genetics and immunity (9). Clinical parameters such as islet autoantibodies, age of disease onset, body mass index (BMI), C-peptide, as well as genetic factors such as human leukocyte antigen (HLA) and genetic risk score (GRS) were utilized in T1DM sub-phenotyping using hypothesis-driven and data-driven approaches (10–12). Continuous glucose monitoring (CGM) and artificial intelligence have been used to direct personalized insulin use and glucose management (13). Different patterns of beta cell function decline have also been observed in patients with T1DM (14). These new developments have critically advanced our understanding of the underlying pathophysiology and molecular mechanisms of T1DM and are instrumental in personalized management of T1DM.

The current issue of *Frontier in Endocrinology* summarizes recent advances in heterogeneity in T1DM with a special emphasis in beta cell function deterioration. Amongst the articles included, three clinical study articles provided new insights into diagnosis, phenotyping, and treatment of T1DM. The comparative effectiveness of continuous subcutaneous insulin infusion (CSII) therapy versus multiple daily insulin injection (MDI) in persons with T1DM was evaluated using real-world data, and the authors found that CSII therapy was safer and more effective for the management of Chinese T1DM patients, resulting a lower HbA1c and better CGM-derived glycemic metrics without an improvement in hypoglycemia risks when compared with MDI therapy. In the study examining the association between metabolic syndrome (MetS) and glycemic variability in patients with T1DM using CGM systems, it was found that MetS was associated with worse glycemic control with high glucose variability (GV) and HbA1c levels. Thereby, efforts should be made to manage MetS components in patients with T1DM in order to achieve a better glycemic control. Finally, in an effort to refine the diagnosis of T1DM partial remission (PR), a new formula based on insulin dose and glycosylated albumin (GA) proved to be more precise and the cut-off value of C-peptide levels for representing transient “recovery” of beta cell function varies based on age.

Two studies performed omics detection to explore novel biomarkers for T1DM. One study was conducted in 1,005 islet autoantibody positive T1DM patients and 1,257 healthy controls to investigate the role of Single Nucleotide Polymorphisms (SNPs) in N6-methyladenosine (m6A) regulators in T1DM.

Intronic variants in *PRRC2A* and *YTHDC2* were found to be associated with T1DM tendency in a Chinese Han population, which indicates a role of m6A regulators and their intronic SNPs in the pathogenesis of T1DM. The other study on proteome profiling was performed in plasma samples and plasma-derived extracellular vesicles from pre-diabetic non-obese diabetic (NOD) mice and revealed new and potentially endotype specific biomarkers for T1DM occurrence.

The rest two articles are reviews on β -cell protection and therapy for latent autoimmune diabetes in adult (LADA) and the T cell immunometabolism and therapeutic implications in T1DM, respectively. In the first review, the authors described the natural history of LADA and summarized the factors related to β -cell function in LADA patients. They also evaluated the impact of current anti-hyperglycemic therapies on islet β -cell protection in LADA patients and discussed the opportunities and challenges for disease treatment in the future. In a mini review, the authors provided an overview of metabolic reprogramming of T cells, summarized the key metabolic pathways involved in the disease progression, and proposed the potential options for β -cell protection in T1DM.

Precision medicine in T1DM is currently a hot research topic given the limited understanding of disease pathophysiology and high disease heterogeneity. This special issue of *Frontier in Endocrinology* aims to provide an in-depth and integrative understanding of precision medicine for T1DM, reveal novel biomarkers related to diabetes sub-classification and disease progression, and explore new ways to diagnose, predict, prevent and manage T1DM. Precision prediction, diagnosis, treatment, and prevention will enable us to care patients with T1D in a person-centered manner, thus more effective and safer, in the near future.

Author contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved for its publication.

Acknowledgments

The editors thank the contributions from all the authors, for their novel findings and elaborate work.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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