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Precision medicine in type 1 diabetes mellitus

For years, the diagnosis and clinical management of type 1 diabetes mellitus (T1DM) have been considered relatively straightforward, and this condition has been treated as a single clinical entity based on the pathophysiology of the gradual loss of insulin-producing beta cells. However, we now understand that it is a polygenic disease involving multiple interacting environmental factors, which contributes to significant heterogeneity in its development and presentation.

Currently, we know that **individuals with T1DM exhibit differences in immunological, inflammatory, metabolic, insulin resistance, and beta cell decline rates**. Therefore:

- The onset of the disease spans across the entire age range.
- Genetic susceptibility is complex, and immunopathological studies show considerable variability among individuals.
- Progression rates, patterns of beta cell function decline, and insulin secretory capacity differ markedly.
- Complication rates, glycemic control, and therapeutic efficacy are variable.

In this context, **precision medicine in T1DM represents an approach to optimize the management of various aspects, such as disease prediction, prevention, diagnosis**, prognosis, and monitoring, integrating multidimensional data and considering individual variability in factors such as genetics and the environment. Precision medicine will allow us to tailor diagnosis and therapy to population subgroups of similar characteristics. Additionally, precision medicine approaches continue to evolve with the addition of new technologies, Big Data, artificial intelligence, decision support systems, and patient involvement. This emerging approach will enable more precise prevention and treatment strategies, contrasting with the one-size-fits-all approach that has been used until now.

The implementation of precision medicine in T1DM is necessarily linked to the natural course of the disease.

PRECISION IN PREDICTING THE ONSET OF T1DM

T1DM is considered an autoimmune disease, in which there is destruction of insulin-producing pancreatic beta cells by the host immune system. However, on this immunological basis, multiple interrelated factors come into play: genetic, environmental, age of onset, or metabolic aspects, such as the rate at which C-peptide declines. The implementation of a "precision" vs "classical" medicine approach involves using data analysis to improve early prediction of islet autoimmunity, identify high-risk individuals, and compare new interventions to delay or prevent the disease. Additionally, for those individuals in whom disease progresses, precise control would significantly reduce the onset of diabetic ketoacidosis (DKA).

The **main biomarkers** for predicting future development of T1DM include genetics, age, No., types, and titers of autoantibodies and age at which they appear, dysglycemia and C-peptide levels. Although these markers can be used individually, they provide greater predictive power when used in combination. In the future, the increasing availability of **genetic information**, along with **autoantibody detection** to identify T1DM at an **early** stage will lead us to an era of prediction when we can foresee T1DM and potentially prevent or delay its onset.

PRECISION IN PREVENTION

Scientific evidence shows that children and adults present differences in the progression of the disease, with children having a higher risk of developing diabetes and a more accelerated rate of progression, with the associated clinical implications. Additionally, progression since the development of the first autoantibody may vary based on the age of onset. Most prevention efforts involve developing **interventions in the immune system** to preserve beta cells, with drugs such as teplizumab, rituximab, or anti-TNF-alpha. Oral insulin or peptides have also been investigated, as well as a promising future intervention involves the use of stem cells to increase the reserve of residual beta cells.

DIAGNOSTIC PRECISION

Correct classification of the T1DM subtype is crucial for appropriate precision treatment. The age at diagnosis will determine which autoantibody appears first in these individuals, and factors such as rapid progression of insulin deficiency determine treatment and can aid in categorization. Additionally, knowledge of genetics provides information on disease heterogeneity and the potential to subcategorize it into more homogeneous patient groups **(endotypes)**, »

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which can be used to improve treatment and progression prediction. Up until now, the clinical characteristics used to classify the type of diabetes were age at diagnosis and body mass index (BMI). However, currently we know that these characteristics often overlap in adults with diabetes, and the high prevalence of T2DM increases the difficulty of confirming a diagnosis of T1DM in adults. Pancreatic islet autoantibodies can aid in classification, and recent clinical practice guidelines from the ADA and EASD recommend determining these autoantibodies at the time of diagnosis in all adults with a clinical suspicion of T1DM. Additionally, C-peptide levels measured within the first few years after diagnosis can be useful to confirm T1DM if results indicate severe insulin deficiency. Their levels at diagnosis may overlap with those seen in other types of diabetes; however, the progressive trajectory of C-peptide loss in the years immediately following diagnosis more clearly separates T1DM, and the utility of C-peptide levels to discriminate T1DM is higher 3 and 5 years after diagnosis.

- For **sub-phenotyping of T1DM**, the following **parameters** are being used:
- Islet autoantibodies
- Age of disease onset
- Body mass index (BMI)
- C-peptide
- Genetic factors such as human leukocyte antigen (HLA)
- Genetic risk score

PRECISION IN TREATMENT

It is based on the fact that the same treatment for diabetes can result in very different responses. Therefore, efforts should

» focus on finding the most effective treatments for each T1DM patient profile based on their individual characteristics, including disease status. Although gradual improvements in insulin formulation and administration, along with technology advancements in continuous glucose monitoring and hybrid closed-loop systems have allowed significant progress in individualizing therapy, minimizing adverse treatment responses, much still remains to be investigated, including pharmacogenomics and search for targeted therapies.

PRECISION IN PROGNOSIS AND MONITORING

Precision in prognosis relates to the risk of complications, combining biological factors, lifestyle, social and cultural characteristics. Although beta cell loss and insulin secretion defects are the basis of all T1DM, the rate of loss of these cells can vary widely, and the mass of pancreatic beta cells and their insulin production capacity predict the risk of DKA or the need for insulin treatment. Currently, we know that progression to T1DM is much faster at a younger age, especially in children younger than 14 years. Key factors for predicting outcomes in individuals with T1DM that should be considered when determining monitoring include:

- **Clinical characteristics of the state of the disease**
- **Glycemic control**
- **Genetic propensity (based on DNA/family history)**
- **Social/cultural and physical environment**
- **Individual behavior characteristics**
- **Access to care**
- **Disease status monitoring intervals**
- **Improvements in monitoring, such as continuous glucose monitoring, have a significant impact on predicting the risk of complications.** D

CONCLUSIONS

The heterogeneity of T1DM has implications for prediction, prevention, diagnosis, treatment, prognosis, and monitoring of the disease. Therefore, a better understanding of its pathophysiology and progression will allow us to develop targeted and personalized therapies.

The future of precision medicine applied to T1DM will enable early identification of at-risk individuals, subgroup categorization for intervention, definition of T1DM endotypes, and optimization of treatment for those who develop the disease to reduce the risk of complications.

Mechanisms of age-influenced variability in progression to T1DM, tissue-level pathogenesis, immunological phenotype, and beta cell loss progression after diagnosis need to be deeply investigated. We need to address individual needs and their risk characteristics or susceptibilities and direct medical intervention before, not after disease onset. This effort will necessarily require team integration to develop a plan for implementing precision medicine in T1DM.

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