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The pathogenesis, natural history, and treatment of type 1 diabetes – time (thankfully) does not stand still

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> For time and the world do not stand still. Change is the law of life. And those who look only to the past or the present are certain to miss the future. – John F. Kennedy

In 2001, a Review article[1] saw publication in *The Lancet* that over time has served as 'citation classic'; this, for its (then) timely messages regarding the pathogenesis, natural history, and treatment of type 1 diabetes. That work described multiple features of the disorder including its pathogenic complexity, genetic diversity, the potential role for environment in disease initiation, and emerging care and treatment paradigms; all with the purpose of '*offering a new perspective on our understanding of type 1 diabetes pathogenesis and principles for therapeutic management of the disorder*'[1]. Twenty years later, we asked ourselves the question, "What has changed?" With this brief Comment, we take on the substantial challenge to discuss some of the many knowledge voids that have been filled in the past two decades and the most promising areas of therapeutic progress.

We will begin with a need to re-address the natural history model of type 1 diabetes; one whose graphical portrayal was originally published in *The New England Journal of Medicine* in 1986, and that has been subject to countless reproductions or adaptations[2]. This model has served for decades as a remarkably effective roadmap in guiding the field's questions on the etiopathogenesis, prediction, prevention, and efforts to reverse type 1 diabetes. While its conceptual nature remains intact, many of its key features (e.g., quantity of functional beta cells at onset, duration of C-peptide production post-onset) have, with time, come under question by ourselves and others[3,4]. However, in terms of natural history prior to disease onset, key paradigm shifts include notions that beta-cell function (Y-axis) at 100% is not the same for all individuals, the rate of beta cell loss varies (i.e., more

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rapid in young children and importantly, subject to periods of waxing and waning beta cell directed immunity (insulitis)), and the slope or threshold for disease progression varies with insulin resistance; likely explaining peak appearance in puberty, pregnancy and earlier presentation with obesity. With this, we believe an important step moving forward is to address the dimensionality of the existing model to better represent disease complexity. Indeed, it has become clear that the natural history of type 1 diabetes is determined by three predominant aspects: age, genetic susceptibility, and the intensity of autoimmunity (i.e., immune dysregulations) likely interact to determine the natural history of type 1 diabetes. Beyond these, contributions of the environment, exocrine pancreas, and beta cells themselves (e.g., number, functional defects, susceptibility to self-destruction) also likely to influence disease progression. The true impact of these later factors on disease development is complex and remains the subject of active investigation; hence, we chose not to build them into our model at this time.

In similar form, ideas on the role of both genetics and environment have seen radical change. While the notion of a polygenic disorder has long been appreciated, genetic susceptibility or resistance to disease is far more complex than previously considered, with more than 150 loci involved[5]. Additionally, the impact of genetics on type 1 diabetes appears dependent on the stage of its development. While genes classically associated with the disease (i.e., the HLA locus) are likely most important in the initiation of islet autoimmunity, these seem to have less of an impact on progression to clinical diabetes. Using this knowledge, genetic risk scores based on genome wide association studies are now in place to determine early risk for developing type 1 diabetes and even therapeutic agent selection. Determining which (if any) environmental triggers initiate islet autoimmunity remains challenging and continues to be a work in progress, with enteroviruses and the gut microbiome being the two most commonly implicated factors.

Perhaps the concept most subject to change over this time is that beta cells are no longer an ‘innocent bystander’ in the pathogenesis of type 1 diabetes as they clearly exhibit stress-induced changes, prohormone processing defects, over expression of HLA class I molecules, and generate modified antigens (e.g., hybrid insulin peptides and other posttranslational modifications) that contribute to beta cell killing by the immune system. Beyond this, the measurement of islet autoantibodies from small quantities of blood has also made the disease for more pragmatic and hence, predictable. We also have a far better grasp on understanding the order of autoantibody formation and mechanisms that control it. While exceptions exist, children carrying HLA-DR4/DQ8 predominantly develop insulin autoantibodies as their first autoantibody while those with HLA-DR3/DQ2 acquire GAD autoantibodies first[6]. Such findings are but one example of yet another emerging concept, one of disease “endotypes;” a notion that not all type 1 diabetes cases are the same. The field has also embraced a “staging” model for the disease, with two or more positive autoantibodies with euglycaemia defined as stage 1, two or more autoantibodies with dysglycaemia representing stage 2, and dysglycaemia in the diabetes range defined as stage 3[7]. This current staging paradigm allows for clinical trials seeking to delay or halt disease progression to be optimally conducted along the spectrum of type 1 diabetes development. A limited number of immune intervention studies have been noted to delay loss of C-peptide in stage 3 disease, with several other agents showing promise in terms of their ability

to delay, and possibly halt, further loss of residual beta cell function. Such findings are important as extending the 'honeymoon' period can improve long-term prognosis. However, no immunotherapy has yet received regulatory approval and therefore largely remains a research-based effort.

Another area seeing radical change is related to therapies. The newest standard treatment modalities for new-onset and established disease include analogue insulins, continuous glucose monitoring devices, subcutaneous insulin pumps, and most recently, hybrid or (almost) closed-loop systems (e.g., an "artificial pancreas")[8]. These technologies have revolutionized the day-to-day management of this disease and we believe they and other advances will continue to do so, including the use of stem cell based surrogate islet cells, a concept not even on the radar in 2001.

As noted in President Kennedy's quotation, it would be errant to ignore what the future holds and what knowledge voids must be addressed next. The features in the **Panel** span the spectrum and stages of type 1 diabetes development. Most importantly, screening paradigms for type 1 diabetes risk need to move from academic research settings into standard clinical practice. Better definition of disease endotypes and refining the criteria for type 1 diabetes stages will allow for improved understanding of disease mechanisms, dissecting heterogeneity, and applying personalized medicine therapies (i.e., immune interventions, beta cell specific, stem cell derived). Improved biomarkers of disease activity (e.g., ascertainment of insulitis) are needed to better time therapeutic interventions and monitor efficacy. Additionally, questions remain including who to treat, when to treat, and with what agent or combination of agents. Despite the remarkable innovative and technological advances for clinical management of type 1 diabetes, the numbers of children and adults achieving optimal diabetes control (as measured by haemoglobin A1c values (HbA1C) or continuous glucose monitor-derived metrics) remain astoundingly low[9]. Finally, despite 2021 being the 100th anniversary year for the discovery of insulin, greater access to insulin and diabetes technology across the globe and socioeconomic classes is still a pressing need[10].

Acknowledgments

Thankfully time does not stand still and as these new knowledge voids are addressed, we believe substantial improvements will be made to delay and prevent clinical type 1 diabetes onset in at-risk individuals and lessen the daily burden of those living with the disease.

Declaration of interests:

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