Overview on Heterogeneity of Diabetes

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Perspective

It has been 100 years since the discovery of insulin-without question one of the most impactful medical achievements of the 20th century. Before Frederick G. Banting and his colleagues made this momentous discovery, diabetes was fatal, claiming the lives of people who developed it within a few months to a few years. However, the isolation and extraction of insulin, and its subsequent commercialization, transformed diabetes into the manageable chronic condition it is today, made even more so as therapeutic, technological, and clinical research advances in diabetes continued to improve diabetes management.

Indeed, although the discovery of insulin changed the diabetes landscape forever, one could reasonably argue that the modern era of diabetes management only really began in the final quarter of the last century. For example, who could have imagined in 1976-more than 50 years after the advent of insulin-that the glycated hemoglobin (HbA1c) test, first performed at that time on five hospitalized patients with diabetes [1], would become a gold standard test for assessing diabetes, determining therapeutic indications, and even diagnosing diabetes?. The initial report describing the HbA1c test stated that "hemoglobin AIc concentration appears to reflect the mean blood sugar concentration best over previous weeks to months" and that "the periodic monitoring of hemoglobin AIc levels provides a useful way of documenting the degree of control of glucose metabolism in diabetic patients" [1]. Since the publication of that landmark article, the translational advances in terms of both clinical application of HbA1c measurement and resulting improvements in diabetes medical management have been impressive and have transpired at a much quicker pace.

So much has occurred that it is hard to believe that it was only 1993-less than 30 years ago-when the results of the Diabetes Control and Complications Trial were published and the world fully understood both the crucial importance of achieving near-normal glycemic control and the substantial value of the HbA1c test in monitoring that effort. Less than 20 years ago, in 2002, we learned from the Diabetes Prevention Program research study that the onset of type 2 diabetes can be delayed or avoided through lifestyle modification or pharmacotherapy. And, less than 3 years ago, yet another landmark study were published, this one reporting that a course of the anti-CD3 antibody teplizumab could delay progression to clinical type 1 diabetes in high-risk individuals [2]. These were all major research achievements that further altered the course of diabetes management.

Other important breakthroughs also occurred in rapid succession. New drug classes—specifically sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists-have come to market, offering cardiovascular and renoprotective benefits beyond their glycemic effects as assessed by HbA1c. There have also been tremendous advances in bariatric surgery, and the American Diabetes Association's (ADA's) Standards of Medical Care in Diabetes now includes guidance on its role in the treatment of appropriate patients with type 2 diabetes [1]. Technology has also contributed significantly to the improved management of diabetes, with impressive advances made in continuous glucose monitoring and the advent of commercially available hybrid closed-loop insulin delivery systems. There have also been expansions in the knowledge base supporting diabetes care, education, and support, emphasizing that there is no "one-size-fits-all" diet for individuals with diabetes [3], recognizing that patients should be at the center of the clinical decision-making cycle for diabetes management, and underscoring the need to mitigate inequities in the distribution of social determinants of health and the provision of medical care.

All of these developments have informed the currently recommended strategies for managing diabetes, as reflected in guidelines from numerous professional organizations, including the ADA's Standards of Medical Care in Diabetes. Collectively, these advancements have led us to today's more individualized approach to treatment. Using type 2 diabetes as an example, we are now encouraged to base the selection of pharmacological therapies on the presence or absence of comorbidities such as atherosclerotic cardiovascular disease and chronic kidney disease independent of a patient's HbA1c-a change based on clinical research evidence to date. In addition, providers are also encouraged to factor in the relative importance of each patient's weight status, hypoglycemia risk, and financial constraints [4].

However, these more individualized recommendations, although invaluable, are generally not considered to be "precision medicine," which can be defined as "an emerging approach for disease prevention and treatment that takes into account people's individual variations in genes, environment, and lifestyle". Essentially, precision medicine is the process of applying biological science to match the most appropriate therapy to the most appropriate person at the most appropriate time. As we enter the second century of diabetes care since the discovery of insulin, precision medicine truly represents the next frontier for diabetes, and in the coming years, diabetes research will be increasingly focused on furthering this approach.

In 2016, Florez JC, et al. [4] reported that the future of research on how best to stratify diabetes medicine will require a full understanding of the interaction of all nongenetic elements to which people may be exposed (nutrition, physical activity, sleep, stress, etc.) with the quantifiable elements of our physiome (e.g., genome, proteome, and metabolome). Only in this way will precision therapies become a routine part of medical management for all people with diabetes, as they are now only for those with rare monogenic forms of the disease for which physiomic factors have been more fully elucidated.

To celebrate the completion of the first century of diabetes innovation and usher in a new era in which precision medicine is certain to flourish, the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism and Diabetes (CIHR-INMD) and the U.S. National Institutes of Health's National Institute of Diabetes and Digestive and Kidney Diseases (NIH-NIDDK) recently held a joint symposium [5]. Titled "Heterogeneity of Diabetes: β-Cells, Phenotypes, and Precision Medicine," this first-ever collaboration between the premier diabetes research institutes of Canada and the U.S. gathered researchers from both countries and beyond virtually to discuss the challenges and opportunities in their quest to better understand the heterogeneity of diabetes and thus gain insights that could chart new directions in treatment and prevention.

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