Defining Disease Progression and Drug Durability in Type 2 Diabetes Mellitus

Sanjay Kalra,[1] Nor Azmi Kamaruddin,[2] Jayanti Visvanathan,[3] Ravi Santani[4]

1. Department of Endocrinology, Bharti Hopsital, Karnal, India; 2. Endocrine Unit, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia; 3. Medical Affairs, Novartis (Singapore) Pte Ltd, Singapore; 4. Medical Affairs, Novartis Corporation (M) Sdn Bhd, Petaling Jaya, Malaysia

This communication shares insights into the definition of disease progression and drug durability in type 2 diabetes. Disease progression may be defined as gradual worsening of beta-cell function, clinically observed as an increase in drug dosage, drug frequency or number of glucose lowering drugs needed to maintain HbA1c control; and/or a ≥0.5% rise in HbA1c, unexplained by acute, modifiable factors, while using the same drug regimen; and/or as the occurrence or worsening of cardiovascular or microvascular complications, in spite of standard care, over a pre-specified time period. Durability of a drug or a drug combination may be defined as its ability to postpone or delay progression of disease, in a safe and well tolerated manner. Thus, all drugs that are able to prevent disease progression (i.e., postpone loss of glycaemic control, need for intensification of therapy or onset or worsening of complications) may be termed 'durable'.

The term 'disease progression' is ubiquitous in clinical medicine. It has been used in various medical specialties such as oncology, nephrology, dermatology and cardiology.[1–3] Type 2 diabetes (T2D), however, is a complex disease, which eludes simple definition of disease progression. The exhaustive list of pathophysiologic mechanisms that contribute to T2D is matched by an equally notable array of evidence-based drugs and drug combinations.[4–6] These are backed by robust clinical trials with designs and objectives as diverse as T2D.[7] Therefore one may not necessarily find uniform definitions of concepts that are presumed to be commonly understood by other disciplines.

Two such constructs, which defy easy definition in T2D care, are the phrases 'disease progression' and 'drug durability'. In this editorial, we explore various definitions of diabetes progression and drug durability, before suggesting a comprehensively crafted description of both that should be acceptable to all.

Defining disease progression – why is it important?

Experts have long explored the various facets of disease progression and drug durability in T2D. The definition and characteristics of progression of T2D have been reviewed in detail.[8] A stepwise approach to disease progression, including conversion from prediabetes to diabetes, the need for medication, loss of glycaemic control and occurrence of complications, has been proposed.[8]

A recent review of data identified the following risk factors for progression from prediabetes to diabetes: relatively higher fasting or postprandial glycaemia; a steeper rate of increasing fasting glucose; higher body mass index, blood pressure and triglycerides; and lower HDL cholesterol levels.[9] Among people with T2D who had glycated haemoglobin (HbA1c) <7% or no glucose lowering medications at baseline, predictors of diabetes progression (HbA1c ≥7% or initiation of hypoglycaemic agent) include high baseline HbA1c, younger age, and weight gain. Each decade of increasing age reduces the progression risk by 15% and each 1 lb (0.453 Kg) of increased weight is associated with 2% increased odds of progression.[10] The chances of requirement of glucose lowering medication among disease progressors, decreases by 40% with every decade of age, and decreases by 2.3% with each 1 mg/dl decrease from baseline LDL level.[10] Loss of glycaemic control is a precursor of progression of T2D, and seems to be an integral part of the syndrome's natural history. However, not all patients lose glycaemic control at the same rate. According to the United Kingdom Prospective Diabetes Study (UKPDS), higher sulfonylurea failure rates are noted in individuals who are younger, have lower body weight, higher glucose concentrations, lower β-cell reserve and those randomised to glibenclamide rather than chlorpropamide.[11]

Drug durability has conventionally been studied from a limited, monotherapeutic perspective. A Diabetes Outcome Progression Trial (ADOPT), which compared failure rates of various drugs,

reported a monotherapy failure of 15% with rosiglitazone, 21% with metformin and 34% with glyburide, at 5 years of therapy.[12] In recent years, however, our approach to the management of T2D has changed. Earlier use of combination therapy is indicated, using drugs with a complementary mode of action.[13] This evolution in therapy calls for a reassessment of the definition and scope of disease progression, as well as drug durability. This need is made more important by the fact that T2D now occurs in younger adults, who have a longer life expectancy to live with diabetes.[14]

The characteristics of diabetes and methods for measuring its progression

The natural history of T2D is marked by a gradual decline in beta-cell secretory function; insulin sensitivity, on the other hand, remains constant, and shows no such decline. Disease progression, therefore, can be defined in terms of degree and rate of beta-cell secretory defect, or beta-cell failure.[15] Both anatomical (beta-cell apoptosis) and functional (insulin secretory defect) markers have been used by experts to measure the rate of beta-cell failure. However, a combined anatomical–functional view of beta-cell health, appears the best approach. The three-stage model which lists beta-cell sufficiency, partial/reversible insufficiency, and complete/irreversible insufficiency, also appears a rational way of describing disease progression in T2D.[16] Objective markers are needed, however, and fasting and stimulated serum C-peptide are useful markers for functioning of beta cells. This has minimal relevance in clinical practice, and is used primarily in research settings. Such a definition of disease progression has been used in trials in type 1 diabetes prevention.[17] For T2D, the coefficient of failure, a simple tool developed by Wallace and Mathews, can be used to quantify disease progression in terms of beta-cell function, with various drug therapies.[18]

T2D is also characterised by the inevitable decrease in effectiveness of prescribed drugs, and a gradual increase in the intensity of glucose-lowering therapy requirements.[11,12] The necessity to intensify therapy by increasing doses of drugs, increasing frequency of dosage, or adding new drugs, can be taken as a marker of disease progression. While the number of oral drugs prescribed may be a discontinuous variable, insulin dose requirement is a continuous variable which lends itself to this indication. Disease progression in clinical trials in insulin can be assessed by the number of injections required, as well as by the total daily dose requirement.[19]

A simple way of assessing disease progression over time is to measure change in HbA1c.[10] A clinically significant change in HbA1c (recommended as an increase by ≥0.5%) using a particular therapy, suggests that beta-cell function has declined over time; this implies progression of disease, in spite of the prescribed therapy.[20]

Current discourse highlights the need for multifaceted, comprehensive management of diabetes, as opposed to a purely glucocentric one. This approach may extend to the definition of disease progression as well. Vascular complications tend to increase with advancing duration of T2D. Improvement in HbA1c, however, can reduce the risk of both macrovascular and microvascular complications. The progression of diabetes may be tracked by the surrogate marker of cardiovascular events.[21] Occurrence of one or more cardiovascular events will imply worsening of T2D. Non-fatal myocardial infarction, non-fatal stroke, and hospitalisation for heart failure are the commonly accepted objective endpoints of cardiovascular progression.

In addition to cardiovascular outcomes, renal health is an integral part of T2D health. Renal outcomes have been the subject of exploratory analyses in earlier cardiovascular outcomes trials, but are now being prespecified as secondary outcomes.[22] Significant fall in estimated glomerular filtration rate (eGFR), rise in serum creatinine, rise in albuminuria, and need for renal replacement therapy are well accepted objective endpoints of renal progression of disease. The same endpoints can be used to track disease progression of T2D as well. These signposts are especially important, as reliance on glycaemic markers such as HbA1c may be misleading in a situation where worsening renal function causes hypoglycaemia.

Diabetes retinopathy is a complication which can be diagnosed and staged objectively, with minimal inter-observer bias. This has been extensively used in large trials such as The Diabetes Control and Complications Trial (DCCT) and The Epidemiology of Diabetes Interventions and Complications (EDIC) to grade progression of disease.[23] New onset, or worsening of retinopathy, therefore, is an attractive candidate for defining disease progression in T2D.

Comprehensive definition

A comprehensive definition of disease progression would be one which can be used in a wide variety of patients, attending heterogeneous clinical care settings. We suggest the following: disease progression may be defined as gradual worsening of beta-cell function, clinically observed as an increase in drug dosage, drug frequency or number of glucose lowering drugs needed to maintain HbA1c control; and/or a ≥0.5% rise in HbA1c, unexplained by acute, modifiable factors, while using the same drug regimen; and/or as the occurrence or worsening of cardiovascular or microvascular complications, in spite of standard care, over a pre-specified time period.

This definition includes pathophysiological, pharmacological and clinically relevant constructs and endpoints. It is easily understandable for both individuals living with T2D and their health care providers, and it can also be used across various healthcare settings, even if resource constraints prevent comprehensive monitoring of the disease progression. The objective aspect of this definition lends itself to measurement and comparison. Modern studies which offer insight into all aspects of this multifaceted definition of disease progression are needed.[24,25]

Progression, outcomes and durability

The last decade, we have witnessed more focus on clinical outcomes in T2D. This is evident from the heightened interest in cardiovascular outcome trials.[21] While such trials are necessary, there is debate regarding their cost-effectiveness and relevance. The concept of disease progression differs from that of outcomes. While progression is dynamic, and is seen as a journey to an end, outcomes suggest a fatalistic approach to a fatal ending. Trials on disease progression study participants, while outcome trials, which are event-driven, tend to study events. Ideally, disease progression should be prevented before it reaches an irreversible stage. Outcome trials, on the other hand, enrol participants who are at high risk, in whom it is assumed that cardiovascular events are inevitable. The concept of prevention of disease progression, therefore, is a health-oriented one, which appeals more than the pathogenetic outcome-oriented approach.[26]

Disease progression is an overarching term which includes the concept of glucose lowering drug(s) durability. Pharmacological research treats

durability of a drug as its capacity to maintain HbA1c control over an extended period of time.[27] A more comprehensive definition, however, is in order. We suggest that the durability of a drug, or a drug combination, be defined as its ability to postpone or delay progression of disease, in a safe and well-tolerated manner. Thus, all drugs which are able to postpone loss of glycaemic control, the need for intensification of therapy, and/or onset or worsening of complications, may be termed durable. For such an effect to take place and for a drug to be labelled as durable, we suggest 12 months' use as a minimum time frame. This choice can be explained by the fact that efficacy data relating to most anti-diabetic molecules is 12 months, and changes in therapeutic choice are suggested at 3-month intervals.[28]

Summary

The definition proposed for disease progression has been drafted with T2D in mind, and does not extend to prediabetes. Most cases of prediabetes remain undiagnosed, and are evident only when they cross the threshold of T2D. Nevertheless, it is important to assess disease progression in this cohort as well, and this issue should be explored further. One of the main limitations of the proposed definition is that complications of T2D are multifactorial, and to attribute the same to failure of the anti-diabetic medication may be unwarranted. While we have included this in our definition to highlight the importance of thinking beyond HbA1c, we understand that this may not be relevant in all clinical situations.

Disease progression is not just a definition, but a framework for optimal strategy and clinically relevant goals. Delaying disease progression is not only a desired target, but a necessary strategy as well. To achieve this target, one must preferentially use glucose-lowering drugs which are proven to retard disease progression as well as the onset of complications in T2D. ❑

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