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Measuring what matters in Diabetes: Re-evaluating the use of surrogate markers

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Optimal diabetes care is predicated on balancing the immediate and long-term sequelae of the disease and its therapies, improving patient health and well-being, and mindfully stewarding healthcare resources for both the patient and society. Professional societies, public health organizations, regulatory agencies, patients, and clinicians have focused on hemoglobin A1c (HbA1c) levels to gauge the quality of diabetes care[1]. Over time, HbA1c has supplanted other indicators of the quality of diabetes care, such as blood glucose levels and symptoms of hyperglycemia, despite being a surrogate rather than direct marker of glycemic control, reflecting average glycemia during the preceding 3 months. Although potentially more challenging to measure or difficult to change, other measures of diabetes care may better represent the outcomes that are truly meaningful to people living with diabetes, including immediate symptoms of hypoglycemia or hyperglycemia, burden of treatment,[2] quality of life, and long-term sequelae of inadequately controlled diabetes.

Concerns about reliance on HbA1c levels have been raised previously, particularly, particularly because clinical outcomes of glycemic control are not agnostic to the medications used to achieve it.[3] For instance, Lipska and Krumholz[3] point out that patients achieved better cardiovascular and kidney-related outcomes with use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists vs placebo controls independent of any reduction in HbA1c level. The preferential use of HbA1c levels in research, policy, and practice stems from the demonstrated association between lower HbA1c levels and improved microvascular disease endpoints in pivotal trials

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that evaluated the benefits of intensive glycemic control.[4,5] However, these studies did not demonstrate improvements in outcomes that are most meaningful to patients, such as blindness, end-stage kidney disease (ESKD), painful neuropathy, amputations, stroke, and mortality. Instead, these trials relied on surrogate endpoints (e.g. albuminuria, photocoagulation, nerve conduction abnormalities) or composite outcomes with a clear gradient of importance (e.g. mortality and cataract extraction as 1 outcome).[4] A positive result on a composite endpoint that results from benefits in surrogate endpoints is misleading if misperceived to suggest that all components of the composite shared in the benefit of lower HbA1c levels. Thus, HbA1c is a surrogate marker for a proxy of uncontrolled disease.

A time and place for surrogate markers

Surrogate endpoints remain the gold standard in many clinical trials, including those used by the U.S. Food and Drug Administration (FDA) for the evaluation and approval of diabetes therapies and there is good reason for this. It takes time for diabetes complications to develop, symptomatic complications are less frequent than their preclinical precursors, and ideal diabetes management would preempt symptomatic complications altogether. From the regulatory and research perspectives, clinical trials examining outcomes that are important to patients require extended follow-up and large numbers of participants, making these studies more expensive and logistically complicated. Surrogate markers like HbA1c levels, nerve conduction abnormalities, and albuminuria are more immediate, prevalent, and therefore attractive to researchers and industry, allowing for quicker evaluation of drug efficacy. Similarly, for clinicians, HbA1c is an effective monitoring tool that is responsive to real-time changes in care. It is also a number that patients can understand and monitor. HbA1c levels are actionable and modifiable in ways that newly developed complications and death are not. Nevertheless, even though HbA1c level is a valuable forewarning of future events in patients with diabetes and plays an important role in reflecting the patient's average level of glycemia, it should not be the outcome that matters more than, or is prioritized at the expense of, meaningful outcomes that are important to patients.

Fallacy of the Surrogate

The rationale for using HbA1c level as a surrogate for diabetes outcomes is predicated on the assumption of its direct correlation with outcomes that patients ultimately value, including clinical microvascular disease (e.g. ESKD/dialysis, blindness, neuropathic pain, amputation), macrovascular disease (e.g. myocardial infarction, stroke, painful neuropathy), quality of life, and death. Yet, the strength of this relationship has been called into question. Meta-analyses revealed a null association between intensive glycemic control and these patient-important outcomes, with the sole exception of a 10% to 15% relative-risk reduction of non-fatal myocardial infarction.[4]

In major clinical trials including patients with type 2 diabetes, favorable surrogate and composite-driven outcomes as well as improvements in several hard clinical outcomes (such as death or myocardial infarction that were detected among participants in the UK Prospective Diabetes Study[6] after an extended observation period) corroborated the positive results for patients with type 1 diabetes in the Diabetes Control and Complications Trial/

Epidemiology of Diabetes Interventions and Complications trials[7] to establish the centrality of the HbA1c level in diabetes management. However, the importance of glycemic control for patients with type 2 diabetes cannot be extrapolated from data developed among patients with type 1 diabetes. These conditions diverge on key pathophysiologic, metabolic, and treatment-related factors, with the glucose-centric model of type 1 diabetes not immediately transferrable to the management of type 2 diabetes.

Moreover, HbA1c level may be misleading and its singular prioritization could lead to patient harm. Pursuit of low glycemic targets may necessitate polypharmacy and use of insulin, contributing to hypoglycemia, treatment burden,[2] and higher costs of care. Moreover, because HbA1c level is a measure of average level of glycemia during approximately 3 months, it does not capture daily glycemic variation. For example, a normal HbA1c level may create a false sense of security for patients and clinicians who may be unaware about underlying glycemic lability and hypoglycemia.

In addition, HbA1c level is not without methodologic limitations and has inherent variability within and among testing laboratories. Levels of HbA1c are affected by a variety of health conditions (including chronic kidney and liver disease), anemias, and hemoglobinopathies. Black have higher HbA1c levels than white patients for the same average glucose level, potentially contributing to observed disparities in diabetes management, outcomes, and hypoglycemia.

Inadequacy of the HbA1c Level

Cardiovascular outcomes trials were mandated by the FDA since 2008 to examine the cardiovascular safety of glucose-lowering drugs. With minimal differences in HbA1c levels achieved in the intervention vs. active comparator treatment groups, variation in study endpoints could be attributed to the study drugs rather than the presumed benefit of reduction in HbA1c level. As a result, 2 GLP-1 receptor agonists (liraglutide and semaglutide) and 3 SGLT-2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) were demonstrated to reduce major microvascular and macrovascular events and death independent of glycemic control.[8] Clinical practice guidelines now acknowledge the non-glycemic benefits of these medication classes and suggest their use independent of the need to lower HbA1c.[9] However, if HbA1c level does not fully capture the macrovascular and microvascular benefits of glucose-lowering therapy, why continue to rely on this measure as the primary marker of diabetes care quality?

Outcomes to Measure Instead

Consideration should be given to reverse the routine use of surrogate markers and refocus on what is important to people living with diabetes and their caregivers: symptomatic hypoglycemia and hyperglycemia, vision deterioration, symptomatic peripheral and autonomic neuropathy, lower-extremity ulceration or amputation, kidney function impairment, cardiovascular disease, and others. Measures of immediate glycemic control obtained through self-monitoring of blood glucose level or continuous glucose monitoring can reveal glycemic lability, symptomatic hyperglycemia, and hypoglycemia. Patient-

reported outcomes, including those assessing self-reported hypoglycemia, treatment adverse effects, diabetes distress, disordered eating behaviors, burden of treatment,[2] and financial hardship may reveal vital aspects of the life of a patient with diabetes that warrant treatment modification or other targeted interventions.

Integration of these meaningful, patient-centered, tangible outcomes might improve patient care, drug development, and regulatory functions. Trials that focus on patient-reported outcomes may need to be larger and more expensive, and will inevitably require a collaborative effort between academic and clinical sites, regulatory bodies, professional societies, pharmaceutical companies, and funding agencies. However, the success of cardiovascular outcomes trials has demonstrated that such collaboration is not only possible, but potentially transformative. Funding agencies and the FDA can put greater emphasis on outcomes that are important to patients. Performance measurement can similarly shift toward hard outcomes, patient-reported outcomes, and goal-concordant care. Encouraging clinicians to embrace patient-centered care unencumbered by constraints of the HbA1c level could allow them to instead focus on outcomes identified by patients and their caregivers.

More than 30 million people in the United States live with diabetes, as do more than 450 million around the globe. The U.S. 21st Century Cure Act sought to place patients at the forefront of the healthcare system, engaging patients as participants in patient-focused drug development guided by their input and experience. To improve the quality and value of diabetes care, it will be necessary for patients and all those involved in their care to focus on what truly matters to the people living with diabetes – improving their lives, not their laboratory numbers.

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