Progress in Diabetes Research—What’s Next

David M. Nathan, MD

The pandemic of diabetes threatens to overwhelm clinicians’ collective ability to treat the associated metabolic abnormalities and long-term complications. Yet even in the setting of the pandemic, clinical research has yielded remarkable progress that has improved the long-term prognosis of diabetes.

The Diabetes Control and Complications Trial (DCCT) and its long-term follow-up definitively established hyperglycemia as the—or at least a—major cause of complications of diabetes by demonstrating that intensive therapy achieving a glycated hemoglobin (HbA1c) level of approximately 7% reduced the development and progression of retinopathy, nephropathy, and neuropathy by 30% to 76%, compared with conventional treatment that achieved an HbA1c level of approximately 9%. The long-term follow-up results have demonstrated that the relative benefits of intensive therapy persist for at least 10 years after the end of the intensive intervention, even after the HbA1c levels in the treatment groups converged, a phenomenon termed “metabolic memory.” Long-term follow-up also showed that intensive therapy was associated with a 57% reduction in cardiovascular disease.

Although the benefits of using insulin in a more physiologic manner to achieve near-normal glycemia translated into a 5-year projected expansion of life-span in type 1 diabetes, the burden of this intensive therapy was placed squarely on the patients. These burdens included a 3-fold increased risk of hypoglycemia compared with conventional treatment and the need to self-monitor glucose levels at least 4 times per day, inject insulin frequently or use an insulin pump, and adjust therapy assiduously based on glucose levels, meal size and composition, and activity level.

The challenge clinical research has faced is to decrease that burden. Several articles in this theme issue of JAMA devoted to diabetes focus on the ongoing efforts to address this challenge. Couri et al describe long-term follow-up and insulin secretion status of patients from their original study, in which they performed nonmyeloablative autologous stem cell transplantation to treat very recent–onset type 1 diabetes. While the results of this uncontrolled study are unique in providing the longest remissions of type 1 diabetes with clear evidence of improved beta-cell function, the adverse effects of the treatment, including acute drug toxicity, risk of infections, and sterility, may outweigh the benefits. Nevertheless, the study demonstrates that sufficient beta-cells remain in the pancreas of early onset type 1 diabetes to sustain normoglycemia for a mean of 2.5 years in approximately 50% of such patients. If the risks of this therapy are considered acceptable, controlled trials with longer follow-up will be required.

While type 1 diabetes has benefited from a wealth of clinical research, what about progress in the treatment of type 2 diabetes? In 1983, an estimated 35 million people worldwide had type 2 diabetes; that number now approaches 225 million. The 7-fold increase in diabetes has occurred in the setting of lifestyle changes, including a more sedentary existence and overnutrition, which have resulted in an epidemic of obesity in much of the world. In concert with an aging population and a polygenic background that impairs insulin secretion, type 2 diabetes has flourished. Although first viewed as a benign form of diabetes without the long-term complications that beset type 1 diabetes, type 2 diabetes poses a similar risk for microvascular complications and increases the risk of cardiovascular disease (CVD) by 2- to 5-fold. The UK Prospective Diabetes Study (UKPDS) demonstrated a benefit of intensive therapy that achieved a mean HbA1c level of approximately 7% on eye, kidney, and nerve complications, compared with a standard dietary “policy” with rescue medication therapy as needed that had a mean HbA1c of 7.9%. Long-term follow-up has shown a similar, persistent effect of intensive therapy in type 2 diabetes, which the UKPDS investigators referred to as the “legacy” effect. The long-term follow-up has also demonstrated a beneficial effect of intensive therapy on CVD.

The major clinical questions that remain for type 2 diabetes include the following: how to address the epidemic, which currently causes 1.6 million new cases per year in the United States; how to treat type 2 diabetes most effectively, given the 10 classes of antidiabetic drugs that are currently available and the need to achieve and maintain near-normal glycemia over time; and how to reduce the risk for CVD, the major cause of mortality? Clinical trials have dem-

Author Affiliation: Diabetes Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Corresponding Author: David M. Nathan, MD, MGH Diabetes Center, 50 Staniford St, Ste 340, Boston, MA 02114 (dnathan@partners.org).
onstrated the effectiveness of lifestyle interventions in reducing the risk of diabetes by 58%. The challenge now is to translate these results into practice. Similarly, the expanded armamentarium of diabetes medications should contribute to improved glycemia and a salutary effect on complications; however, many persons with type 2 diabetes “escape” the benefits of tight control, owing in part to a dilatory approach to diabetes treatment.

A recent consensus algorithm has emphasized initiation of metformin at the time of diagnosis, rapid addition of other medications if glycemic goals are not achieved, and the use of the most effective and cost-effective medications with long-term experience to achieve a goal HbA1c of less than 7%. In addition, numerous studies have demonstrated that the same lipid and blood pressure-modifying medications that reduce CVD in nondiabetic populations improve outcomes in type 2 diabetes. However, even with these interventions, persons with type 2 diabetes remain at substantially higher risk for CVD than the nondiabetic population. Three recent studies have tried to determine whether even more aggressive diabetes management than currently recommended, with the goal of achieving HbA1c levels near 6.0%, would ameliorate this risk. All 3 trials failed to demonstrate a benefit of such intensive therapy on CVD, and 1 had significantly more mortality in the intensively treated group. Therefore, clinicians are left with trying to achieve an HbA1c goal of less than 7%, which reduces microvascular and cardiovascular disease over time, but no rationale to try to achieve an HbA1c of less than 6% if more than lifestyle changes are required.

The study by Whitmer et al in this issue of JAMA suggests that further caution regarding intensive therapy of type 2 diabetes may be warranted. Based on an analysis of registry data from a large ongoing epidemiologic cohort, the authors report that among elderly patients with type 2 diabetes who had no documented prior diagnoses of dementia, cognitive impairment, or memory complaints, episodes of hypoglycemia severe enough to result in emergency department or hospital treatment were associated with increased risk of being diagnosed with dementia. The results of this observational study differ from DCCT clinical trial results, which showed no adverse effects of intensive therapy in general or of recurrent severe hypoglycemia in particular on objectively measured cognitive status over 18 years of follow-up. Whittem et al point out that there may be differences in the effects of hypoglycemia on older compared with younger brains. However, a major concern with this study is establishing the direction of causality—mild or undetected cognitive impairment may predispose patients to hypoglycemia. Although the authors recognize this study limitation and perform analyses to address it, the concern is difficult to dispel completely. Forthcoming clinical trial data should help clarify whether hypoglycemia, which is much less frequent in type 2 than type 1 diabetes, does lead to dementia.

Also in this issue, Young et al, on behalf of the Detection of Ischemia in Asymptomatic Diabetes (DIAD) Study investigators, report the results of the first large-scale clinical trial to test whether adenosine-stress radionuclide testing in asymptomatic patients with type 2 diabetes can reduce cardiac morbidity or mortality, presumably by identifying high-risk individuals who might benefit from an intervention. Asymptomatic patients with type 2 diabetes have been of particular concern because they are at higher risk for CVD than nondiabetic persons, but may not have typical warning symptoms in the form of angina owing to their neuropathy. Although the study results showed no significant differences in cardiac death or nonfatal myocardial infarction (MI) among patients in the screening vs no screening groups, the rate of cardiac events was much lower than anticipated, probably owing to aggressive application of prophylactic measures during usual care, and this may have resulted in an underpowered study. Nonetheless, the study results suggest that more aggressive screening for coronary artery disease does not appear to improve the outcome of asymptomatic individuals with type 2 diabetes.

Another report in this issue of JAMA relevant to cardiovascular disease and diabetes by Kosiborod et al examines the role of hypoglycemia in the outcomes of patients with an acute MI and hyperglycemia (glucose >140 mg/dL) on admission. A previous clinical trial showed that diabetic patients with acute MI had 28% lower mortality 3.4 years after the MI if their glucose levels during their MI hospitalization were managed more stringently. Since then, intensive therapy has been actively promoted in many intensive care units for patients with known diabetes and patients with “stress” hyperglycemia. The enthusiasm for this therapy has been tempered recently after several observational studies suggested that intensive therapy in this setting was associated with hypoglycemia and worse outcomes. In the observational study by Kosiborod et al, the occurrence of hypoglycemia was associated with higher mortality among patients who did not receive insulin (compared with patients who did not experience hypoglycemia), but not in patients who were treated with insulin. This study seeks to provide some reassurance that the major risk associated with hypoglycemia is in a subgroup of patients with acute MI and nonmedication hypoglycemia, presumably secondary to severe coincident disease states such as sepsis, liver failure, and end-stage congestive heart failure. However, the current study does not directly refute the previous concerns, which have now been heightened by the NICE-SUGAR (The Normoglycaemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation) trial results demonstrating increased mortality in critically ill patients treated with intensive glucose control.

Advances in the therapy of diabetes mellitus resulting from clinical research should lead to improved health. The challenge is to ensure widespread availability of prevention strategies and safe, affordable treatments so that all individuals...
can benefit. The reports in this issue of JAMA show that despite the strides that have been and continue to be made, optimal care of patients with diabetes remains an elusive, albeit critical, goal.

Financial Disclosures: None reported.

REFERENCES