Optimizing Care in Diabetes: a Quixotic Challenge

Reported elsewhere in this issue is an analysis by the Division of Diabetes Translation (a component of the National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services) of follow-up data linked to National Health Interview Surveys noting that, in both sexes, American adults with diabetes surveyed between 1997 and 2006 had a substantial decline in absolute mortality rate compared with nondiabetic adults (1). The authors caution that this favorable news may be modulated by a future rise in diabetes prevalence should diabetes incidence not be "curtailed." Inferred from this study is affirmation of two main current strategic clinical goals to cope with pandemic diabetes: *1*) reduction of the rate of new-onset diabetes and 2) interdiction of potentially fatal complications in individuals with diagnosed diabetes.

Intervention to modify lifestyle has been termed "the most important single action to prevent type 2 diabetes mellitus" (2). As advocated by the International Diabetes Federation, as much as 80% of new-onset diabetes may be preventable by combining increased physical activity, weight loss, and reduced consumption of sugar and saturated fat (3). Modifying lifestyle to include eating five or more fruits and vegetables daily, regular exercise, no more than moderate alcohol consumption, and not smoking tobacco, sharply reduced the risk of all-cause mortality in 11,761 adult men and women participating in the National Health and Nutrition Examination Survey III (4). A major problem in attempting to sustain lifestyle changes, however, is that without continuous medical team support and encouragement, adherence to a healthy lifestyle pattern was noted to decrease over an 18-year period of surveillance, with documented reduction in practice of three of five healthy lifestyle habits (5). Fradkin (6) recently assessed contemporary diabetes management, finding it to be "suboptimal, particularly in disproportionately affected poor and minority populations." Efforts to improve the quality of care in patients with diabetes have been continuous but sometimes yield conflicting results, as noted below.

A promising approach to diabetes prevention has been provided by a project now in progress in New York's largely Spanish speaking East Harlem community, in which the concept of co-ownership of research by an academic institution and a community "using a participatory approach" in a randomized controlled 2-year trial achieved statistically significant and sustained weight loss in 99 subjects whose glucose levels were in the prediabetes range (7). Although there have been other encouraging advances in blocking conversion from prediabetes to overt diabetes, a perhaps equally important story is the overall impact of current treatment regimens on delaying clinical expression of major complications of diabetes including blindness, limb amputations, strokes, kidney failure, and heart disease (8). Over the past decade, though, conflicting interpretations of outcome in prospective, controlled trials have generated mixed messages as to exactly how rigidly two major risk factors for complications of diabetes, hyperglycemia and hypertension, should be handled. As a result, this is additional stress for health care providers.

Illustrating the extent of change in targeted treatment outcomes is the evolving Standard of Care for targeted A1C by the American Diabetes Association (ADA) that in 2002 was to "develop or adjust the management plan to achieve normal or near-normal glycemia with an A1C goal of <7%" (9). A lower A1C is associated with a lower risk of myocardial infarction and cardiovascular death. A year ago, the ADA stated that "a reasonable A1C goal for many nonpregnant adults is <7%" (10). By 2012, however, although the ADA "glycemic goal" in adults with diabetes remained as "lowering A1C to below or around 7%," the recommendation was accompanied with the caution that "less-stringent A1C goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, [and] extensive comorbid conditions" (11). The evidence prompting this redirection came from multiple sources. Typical of many reports is the 2009 notation in the *Annals of Internal Medicine*, the official journal of the American College of Physicians, that "randomized trial evidence does not strongly support tight glycemic control as more beneficial than harmful in reducing the risk for diabetic complications" (12), noting that as A1C fell below 7.5%, mortality increased. As such, a target A1C of 7.5% rather than 7.0% in type 2 diabetes was proposed based on charting of mortality in a cohort of 27,995 patients treated with combinations of oral hypoglycemic agents and a cohort of 20,005 patients managed with insulin-based regimens in the U.K. General Practice Database and reported in the *Lancet* by Currie et al. (13). Reaching a similar conclusion, using data on 71,092 subjects in The Diabetes and Aging Study of the Kaiser Permanente California Registry, Huang et al. (14) stated that "a target A1C <8.0% for older patients is advised." Adding to the need for caution in preparing definitive "marching orders" for management of metabolic control according to A1C levels is the reanalysis by Riddle et al. (15) of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial results leading to the quixotic inference that factors associated with persisting higher A1C levels, rather than lower A1C per se are as likely to increase mortality in patients with diabetes. Thus, in 2012, the primary care physician greeting a newly diagnosed 65-year-old diabetic patient has blurry marching orders as to what extent of glucose regulation may not only be best in terms of slowing diabetes complications but safest in extending life.

A similar dilemma exists when planning components of management, termed "renoprotection," to prevent in diabetic patients onset and treat progression in renal disease that has been largely attributed to hypertension induced by a perturbed renin-angiotensin-aldosterone system. Striving for "tight blood pressure control" using drugs capable of blocking angiotensin became a standard thought vital to preserve the kidney in diabetes. As an example, the Diabetes Exposed to Telmisartan and Enalapril (DETAIL) study was a head-to-head comparison of telmisartan (an angiotensin receptor blocker [ARB]) and enalapril (an ACE inhibitor [ACEi])

in 250 patients with hypertension, type 2 diabetes, and early-stage nephropathy. DETAIL was notable for using glomerular filtration rate (GFR), assayed by iohexol, as the measure of overall renal function. A total of 216 patients (103 on telmisartan and 113 on enalapril) completed the 5-year study, with equivalent change in GFR. Over 5 years, no patient went into end-stage renal disease or required dialysis. There were also no increases in albumin excretion rate nor increased serum creatinine beyond 200 mmol/L. Cardiovascular morbidity and mortality were extremely low in both treatment groups, a remarkable outcome for a group in which almost 50% of patients had evidence of cardiovascular disease at randomization (16).

Subsequently, as was true for reevaluation of intensive metabolic control of hyperglycemia in diabetes, a growing number of negative reports have questioned the benefit and even imputed an increased risk of death associated with strict hypertensive control. Illustrating this negative viewpoint is the report by Appel et al. (17) of a prospective trial of 1,094 randomly assigned black patients with hypertensive chronic kidney disease receiving either intensive or standard blood-pressure control that "in overall analysis, intensive blood-pressure control had no effect on kidney disease progression." The inefficacy of intensive blood pressure reduction was extended to those with hypertension and diabetes in the ACCORD trial, which concluded that "intensive blood pressure control in patients with hypertension and type 2 diabetes mellitus does not reduce the overall rate of cardiovascular events" (18), a finding important enough to be included in the Nephrology Update of the American College of Physicians as cited in the *Annals of Internal Medicine* for 2011 (19). Disappointment has also been reported due to the inefficacy of treatment with an ACEi in slowing progressive diabetic nephropathy when initiated in its early stage of microalbuminuria (20). Recent alerts as to an increased hazard to life when an ACEi and an ARB are combined, superimposed on the disillusionment over the combination's inefficacy, have transformed the intent to continuously formulate an up-to-date plan for care of patients with diabetes into a test of having read the most recent literature.

On the positive side of the global diabetes pandemic is the sharp and continuing decline in the rate of end-stage renal disease per 100,000 persons with known diabetes that has been continuing (21) since its first report by the Centers for Disease Control and Prevention in 2007 (22). This wonderfully encouraging ongoing decrease in a disabling and fatal disease has also resulted in sharply falling rates of blindness and limb amputations in individuals with diabetes. As a confirmed optimist, I believe that within a decade, whether via autologous or homologous stem cells, epigenetic controls, or still unimagined means, the now dreaded onslaught of diabetes will be halted and even reversed—at the least in the industrialized world.

Eli A. Friedman, MD

From the Division of Renal Disease, Department of Medicine, State University of New York Downstate Medical Center, Brooklyn, New York.

Corresponding author: Eli A. Friedman, elifriedmn@aol.com.

DOI: 10.2337/dc12-0345

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

References

1. Gregg EW, Cheng YJ, Saydah S, et al. Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006: findings from the National Health Interview Survey. Diabetes Care 2012;35:1252–1257
2. Nilsen V, Bakke PS, Gallefoss F. Effects of lifestyle intervention in persons at risk for type 2 diabetes mellitus - results from a randomised, controlled trial. BMC Public Health 2011;11:893 [Open Access]
3. Tuomilehto J, Lindström J, Eriksson JG, et al.; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–1350
4. Matheson EM, King DE, Everett CJ. Healthy lifestyle habits and mortality in overweight and obese individuals. J Am Board Fam Med 2012;25:9–15
5. King DE, Mainous AG 3rd, Carnemolla M, Everett CJ. Adherence to healthy lifestyle habits in US adults, 1988-2006. Am J Med 2009;122:528–534
6. Fradkin JE. Confronting the urgent challenge of diabetes: an overview. Health Aff (Millwood) 2012;31:12–19
7. Horowitz CR, Eckhardt S, Talavera S, Goytia C, Lorig K. Effectively translating diabetes prevention: a successful model in a historically underserved community. Transl Behav Med 2011;1:443–452
8. Khavandi K, Brownrigg J, Hankir M, et al. Interrupting the natural history of diabetes mellitus: lifestyle, pharmacological and surgical strategies targeting disease progression. Curr Vasc Pharmacol 2012 [Epub ahead of print]
9. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2002;25(Suppl. 1):S33–S49
10. American Diabetes Association. Standards of medical care in diabetes—2011. Diabetes Care 2011;34(Suppl. 1):S11–S61
11. American Diabetes Association. Standards of medical care in diabetes—2012. Diabetes Care 2012;35(Suppl. 1):S11–S63
12. Montori VM, Fernández-Balsells M. Glycemic control in type 2 diabetes: time for an evidence-based about-face? Ann Intern Med 2009;150:803–808
13. Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481–489
14. Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. Diabetes Care 2011;34:1329–1336
15. Riddle MC, Ambrosius WT, Brillon DJ, et al.; Action to Control Cardiovascular Risk in Diabetes Investigators. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care 2010;33:983–990
16. Barnett A. Prevention of loss of renal function over time in patients with diabetic nephropathy. Am J Med 2006;119(Suppl .1):S40–S47
17. Appel LJ, Wright JT Jr, Greene T, et al.; AASK Collaborative Research Group. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med 2010;363:918–929
18. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585
19. Arora N, Chertow GM. Update in nephrology: evidence published in 2010. Ann Intern Med 2011;154:824–829, W-299
20. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009;361:40–51
21. Burrows NR, Li Y, Geiss LS. Incidence of treatment for end-stage renal disease among individuals with diabetes in the U.S. continues to decline. Diabetes Care 2010;33:73–77
22. Centers for Disease Control and Prevention. Racial differences in trends of end-stage renal disease, by primary diagnosis—United States, 1994–2004. Morbidity & Mortality Weekly Report 2007;56:253–256