Oral Hypoglycemics and Diabetic Nephropathy

Nortin M. Hadler

Department of Medicine and Microbiology/Immunology, University of North Carolina at Chapel Hill, and Department of Rheumatology, University of North Carolina Hospitals, Chapel Hill, North Carolina

It is all so logical. Americans are increasingly likely to be insulin resistant and at an earlier age (1); hence, more people are glycosylating themselves for longer periods of time (2). One would predict that this increasing frequency of type 2 diabetes bodes an ever-increasing incidence of untoward consequences, including diabetic nephropathy. A call to euglycemia is echoing across the land (3). Minions in pharmaceutical firms and advisory bodies are taking up the cause, much to the applause of the media, Wall Street, policy makers, and the polity. Glycosylated hemoglobin (HbA_{1c}) has become a shibboleth.

There is no argument that type 2 adult-onset diabetes represents a risk for premature macrovascular disease, resulting in myocardial infarctions, strokes, and peripheral vascular disease. There is no argument that type 2 adult-onset diabetes, no matter how defined, increases the likelihood of nephropathy. There is no argument that we have pharmaceuticals, new and old, that can lower blood glucose and HbA_{1c}. The argument I am raising relates to whether lowering HbA_{1c} or any other measure of blood glucose makes a clinically important difference for patients with type 2 adult-onset diabetes.

Blood glucose concentration and HbA_{1c} are surrogate measures. The extreme of hyperglycemia aside, elevations in blood sugar or in HbA_{1c} do not cause symptoms. Because they correlate with the frequency of untoward clinical outcomes, it is assumed that if they are reduced, then the incidence of microvascular and macrovascular disease will follow. "Clinical experience" and observational data seem consonant with this assumption. Surrogate measures are seductive because they tend to be more sensitive to change both temporally and quantitatively. "Hard outcomes," such as death, stroke, or renal failure, unfold at a pace that demands much more patience and many more patients, both of which can tax the resources of any investigative team committed to testing systematically any relevant therapeutic hypothesis. Hence, surrogate end points will always be seductively expedient despite long recognized limitations (4,5). Neither clinical experience nor observational data provide sufficient assurance that influencing the surrogate measures actually advantages the patient in a clinically meaningful way. That requires systematic clinical experiments with hard outcomes. Such already exist that seriously question the clinical effectiveness of our assault on the HbA_{1c} of patients with type 2 diabetes.

Part of the reason that these experiments are not persuasive is that we are blinded by the results of the Diabetes Control and Complications Trial (DCCT). These data bear close scrutiny. More than 1000 patients with type 1 diabetes were randomly assigned to either usual insulin therapy or intensive treatment with euglycemia as the goal. The results after 10 yr were published in 1993 (6). Meticulous control of blood sugar measurably delays the development of retinopathy, microalbuminuria, and peripheral neuropathy. These are not trivial benefits. It took 17 yr before there was any discernible advantage in terms of macrovascular complications (7). Fortunately, the frequent hypoglycemic episodes that result from attempting to maintain euglycemia took no toll on cognition (8). I am not belittling the DCCT/Epidemiology of Diabetes Interventions and Complications Study Group's tenacity or accomplishment, but meticulous control of blood sugar is far from a dramatic advance in the setting of type 1 diabetes. Why would one expect any more benefit to treating middle-aged or older insulin-resistant folks?

The classic study contrasting diet, insulin therapy, and a first-generation oral hypoglycemic in the management of type 2 diabetes was published by the University Group Diabetes Program in 1976 (9). In that study, the oral hypoglycemic was associated with more deaths than the alternatives. These were the early days of multicenter, randomized, controlled trials. This famous trial has been used ever since to teach about challenges in design and data analysis. It had flaws that may have led to an incorrect conclusion—or not. Very few trials of oral hypoglycemic agents since have been designed to consider such dramatic, definitive outcomes as death. Most focus on surrogate outcomes to generate the data on which the Food and Drug Administration bases the decision to license the product for sale as a prescription pharmaceutical. There have long been nagging doubts even in the diabetes research community.

In 1998, the United Kingdom Prospective Diabetes Study (UKPDS) Group published their landmark paper in *The Lancet* (10). The stated intent of the study was to determine whether improved blood glucose control did more than manage surrogate measures. Did it advantage or disadvantage the patient with type 2 diabetes in terms of macrovascular disease and its ravages, including heart attacks, renal failure,

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Correspondence: Dr. Nortin M. Hadler, Division of Rheumatology, Allergy and Clinical Immunology, Department of Medicine, University of North Carolina School of Medicine, 3300 Thurston Building CB #7280, Chapel Hill, NC 27599-7280. Phone: 919-966-0566; Fax: 919-929-6964; E-mail: nmh@med.unc.edu

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and death? Patients who have long-standing hyperglycemia and are at greatest risk for vascular catastrophe would not be a fair test of the hypothesis that treatment was beneficial; if there were no benefit, then it would be argued that they had closed the door when the cows were already out of the barn. To stand even a remote chance of an interpretable result required enrolling a large, younger population and following them for a very long time. Otherwise, there is too little likelihood of untoward outcomes in the control group to expect to be able to discern an effect in the experimental groups. This multicenter, practice-based study enrolled almost 4000 patients with newly diagnosed type 2 diabetes starting in the 1970s. To qualify for enrollment, patients had to be 48 to 60 yr of age with fasting blood glucose levels of 110 to 270 after 3 mo of dieting. The patients were nearly all white, one third were male, and they had an average body mass index of 28. Approximately one third smoked, and 20% were sedentary. On average, they had normal BP. They were randomly assigned such that one third received "conventional" therapy and the remainder "intensive" therapy. The conventional group attended clinics every 3 mo to receive advice and encouragement from a dietician. The intensive group was further randomly assigned to receive insulin therapy, a first-generation hypoglycemic agent or a second-generation hypoglycemic agent. Patients were followed an average of 10 yr. The study closed in September 1997.

These are not naïve investigators. To the contrary, they were prepared to apply all that biostatistics could offer to challenges such as crossover, dropout, missing data, noncompliance, and treatment failure. Some of the findings are strikingly disconcerting: It is clear that the intensive hypoglycemic therapies caused weight gain. It is clear that the intensive hypoglycemic therapies reduced blood glucose, sometimes too much, such that there was an impressive increase in episodes of symptomatic hypoglycemia. Some of the findings are disconcertingly only marginal: There is a suggestion that intensive therapies decreased the likelihood of some microvascular complications, notably retinopathy and microalbuminuria; however, this effect did not translate into fewer patients' experiencing overt kidney or eye damage. Intensive therapy did not alter the likelihood of peripheral neuropathy. It is also abundantly clear that there was no advantage from intensive therapies in terms of such macrovascular complications as heart attacks, strokes, or important peripheral vascular disease, including amputations, and there was no decrease in all-cause or in diabetes-specific mortality!

Ten years of intensive therapy offered no real advantage for 1000 middle-aged hyperglycemic people, so why in the name of science would anyone declare the UKPDS supportive of intensive therapy, including intensive therapy with oral hypoglycemics? Is it because the surrogate measures moved in the right direction? Wasn't the rationale of undertaking the UKPDS in the first place to demonstrate benefit beyond surrogate measures? How about the weight gain, a surrogate measure that does not bode well? From my perspective, the UKPDS is an argument for conventional therapy and not pharmaceutical interventions until some agent is proved actually to benefit the patient. Furthermore, if there is no benefit, then no adverse event is tolerable.

The UKPDS Group published a secondary analysis of this data set in 2000 (11). Some of the patients responded more readily and completely than others to whatever their treatment and therefore were less hyperglycemic over time. Those who responded most were less likely to experience microvascular and macrovascular events, including all-cause and diabetes-related death. The relationship is far from robust; the absolute risk reduction is not linear but log-linear, meaning that if you have an extraordinarily high blood sugar and you respond fully, then you may benefit in terms of clinically overt outcomes. Even the authors considered this relationship only hypothesis generating, yet this tenuous log-linear relationship has proved ever so influential. It is the notion that supports importunate claims of benefit for oral hypoglycemics and drives common clinical practice. HbA_{1c} plays into this dialectic. It is the simple blood test to "monitor" therapy. Patients are comfortable thinking that they are better off because the HbA_{1c} is lower. The surrogate blood test becomes the "disease" (12) begging treatment (13).

The American Diabetes Association (14) recommends screening of all adults after age 45 for type 2 diabetes. In April 2006, the Ambulatory Care Quality Alliance proposed HbA_{1c} monitoring as an indicator of the quality of care (http://www.ambulatoryqualityalliance.org), and the Centers for Medicare and Medicaid Services endorsed it 1 mo later. The American College of Physicians came out with a continuing education document (15) detailing a screening program and an intervention program that echoes this party line. All of this and more have caused another 1.5 million Americans to be labeled "diabetic" each year and to be treated aggressively toward euglycemia. Undoubtedly, those who participated in the committees that produced these recommendations believe strongly that the surrogate measures are not to be ignored given the threat to the health of the public. In an editorial in 2006, a leading investigator went so far as to say that the ravages of type 2 diabetes "are likely to become the major cause of preventable disease and premature death in this millennium" and went on to argue for early "glycemic control" with oral hypoglycemics (16). He was commenting on A Diabetes Outcome Progression Trial (ADOPT) and argued for the initial use of agents other than thiazolidinediones because rosiglitazone had been shown to increase risks for fluid retention and weight gain (17). I will have more to say about rosiglitazone shortly.

I take issue with the notion of "preventable death," because we all will die, and I am committed to deconstructing the notion of "premature death" (18). Despite common practice and a vast observational literature, I am not convinced that we accomplish anything that is clinically meaningful with the available oral hypoglycemics. I am unwilling to overlook the message of the UKPDS trial that clinically important benefits from oral hypoglycemics proved elusive. At least I can find like-minded individuals on the US Preventive Services Task Force (19), which found "insufficient evidence

to recommend for or against routine screening" for type 2 diabetes, a conclusion echoed in a recent *British Medical Journal* editorial (20).

Some are advocating that patients in clinics and in studies be "risk adjusted" so that if the HbA_{1c} drops further in a patient with a higher HbA_{1c}, then we should consider the drug more likely to be beneficial in the long run (21). There is a mantra, something like, "The attainment and maintenance of near-normal glycemia reduces the risk of long-term complications of diabetes," referencing the DCCT and UKPDS trials. This is the introduction to ADOPT (17), which compared the effectiveness of three classes of oral hypoglycemics, each with its own mechanism, over 4 yr in 4600 patients with diabetes: The biguanide metformin, the sulfonylurea glyburide, and the thiazolidinedione rosiglitazone. Each class lowered HbA_{1c} in the majority of patients. Rosiglitazone was slightly more effective in this regard at the price of more weight gain and edema but with fewer gastrointestinal events and fewer hypoglycemic episodes. A secondary analysis suggested that maybe there were more cardiovascular events with metformin than with the other two, but the incidence of any cardiovascular event was small—fatal heart attacks occurred in 0.1%, for example—and absolute difference between the agents for any cardiovascular event was trivial, approximately 1%. More disturbing is that long after ADOPT was published in the *New England Journal of Medicine* and therefore long after the initial data analysis, the safety data were reviewed only to discover that women who were on rosiglitazone experienced more fractures, mainly of the arm and foot, and maybe even more cardiac events (22). Arguments such as these are finding their way into the considerations of Food and Drug Administration advisors in the context of rosiglitazone labeling (23), yet the standard of care remains to treat the HbA_{1c}. For example, treatment failure of oral hypoglycemics was the focus of the discussion in "Clinician's Corner" in the *Journal of the American Medical Association* (24). The patient was a thin, otherwise well 74-yr-old woman who was found to be "hyperglycemic" incidentally and whose HbA_{1c} was 7.4% despite 6 yr of maximum dosages of all three oral hypoglycemics studied in ADOPT. The discusser was determined to reach the "ideal" HbA_{1c} at all cost and at all risk. Talk about treating a test and not a patient. Talk about missing the forest for the trees (18).

Disclosures

None.

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See related commentary, "Does Lowering of Blood Glucose Improve Cardiovascular Morbidity and Mortality," on pages 163–167.