EDITORIAL (SEE PP. 2660, 2677, 2697)

Clinical Care Guidelines: Too Much of a Good Thing?

Cystic fibrosis (CF) is one of the most common life-threatening inherited disorders in Caucasian populations, affecting ~30,000 children and adults in the U.S. and 70,000 worldwide. Due to advances in pulmonary care and nutrition, the life expectancy for CF has increased from less than 5 years in the 1950s to greater than 37 years at present, with many patients living into their fifth and sixth decades (1).

Hyperglycemia is an increasingly recognized extra-pulmonary complication of CF. The prevalence of CF–related diabetes (CFRD) increases with age, affecting 20% of adolescents and 50% of adults by 30 years of age (2). Unfortunately, prospective, controlled data regarding CFRD are limited. Therefore, the approach to detection, classification, and management of this important consequence of CF varies widely between centers and individual care providers.

To address this deficiency, and in an attempt to provide more uniform standards of care for patients with CFRD, a committee of CF and diabetes experts met in 2009 to develop clinical care guidelines for CFRD. The results of their collaboration are published in this issue of *Diabetes Care*, accompanied by a technical review that summarizes the epidemiology, pathophysiology, and prognostic implications of CFRD (3,4).

The updated guidelines are based on an extensive review of the available evidence and are important for a number of reasons. They highlight the spectrum of glucose intolerance in CF patients and the ways in which CFRD is a distinct clinical entity from other types of diabetes. For example, the recommendation against using A1C as a screening tool for CFRD and the recommendation to maintain high caloric intake are critical differences from the care of non-CF diabetic patients. We are reminded that prandial glucose excursions (and thus prandial insulin needs) far outweigh fasting blood glucose elevations until later in the course of CFRD, and that insulin needs exponentially increase during acute illness (and, conversely, rapidly drop during recovery). Recognition of these unique aspects of CFRD is necessary to optimize the care of patients with CFRD and to prevent inadvertent harm.

The guidelines process always necessitates extrapolating from a variety of evidence sources of variable quality and generally of modest scope. As a result, usually the guidance can be characterized as well-intentioned, informed guessing. In the best of circumstances, the guideline will result in codifying practices with clear benefit, eliminating practices with clear harm, and avoiding recommendations where data are insufficient.

In the case of the CFRD guidelines, 24 of the 30 recommendations are graded as Level E under the American Diabetes Association (ADA) classification system, i.e., based on consensus or expert opinion. Notably, the four recommendations graded as Level B (Level B or D under U.S. Preventive Services Task Force [USPSTF] classification, depending on whether the data are for or against the recommendation) relate to screening (avoiding A1C, commencing at 10 years of age), classification (not distinguishing between CF with and without fasting hyperglycemia), and A1C goals (7% in most patients with CFRD). The recommendations to use insulin for treating CFRD and to avoid using oral agents except in research settings are the sole guidelines graded as Level A (Levels B and D, respectively, by USPSTF schema).

The remaining guidance is based on increasing knowledge about the prevalence of CFRD and its negative impact on nutritional status, pulmonary function, and mortality. It is clear that an inverse association exists between hyperglycemia and BMI, lung function, and survival (5–9). However, the causal nature of this relationship is not clear. There are several hypotheses to explain this relationship, one being that insulin deficiency in patients with CF leads to the loss of calories and muscle mass, ultimately causing decline in pulmonary status and earlier death. Multiple studies have demonstrated that insulin therapy in CFRD can improve the above-mentioned outcomes, but only one of these studies was a randomized controlled trial (10). Thus, it must also be considered that the association between insulin deficiency/hyperglycemia and negative CF outcomes might not be causative, but rather due to other potential mechanisms such as the presence of more advanced pancreatic endocrine dysfunction in the sickest patients.

This concern about causality is not unique to CFRD. It has featured prominently in discussions about inpatient glycemic control as well as aggressive outpatient control aimed at lowering A1C below 7.0%. With respect to inpatient glycemic control, epidemiologic data consistently linked inpatient hyperglycemia to poor outcomes. Several large controlled trials showed marked improvements in morbidity and mortality with aggressive control of blood glucose in intensive care unit patients (11,12), but subsequent studies did not confirm the benefit in broader inpatient populations (13). Similarly, because a strong epidemiologic association exists between even modest levels of hyperglycemia and macrovascular disease in the outpatient population, multiple large-scale trials were undertaken to prove the cardiovascular and mortality benefits of treating diabetics to near-normal A1C (14–16); the result was no benefit in most cases and perhaps harm (14). The evidence base that epidemiology and "physiologic thinking" do not always translate to clinical benefits grows month by month.

What are the potential harms of these guidelines, which rely heavily on expert opinion as a result of a generally weak evidence base? One danger is that patients, care providers, and institutions, all eager for action to address the growing problem of hyperglycemia in patients with CF, will implement the universal screening and early insulin treatment without adequate safety measures. The guidelines suggest that hypoglycemia is not as severe or as frequent in CFRD compared with other forms of diabetes. While neuroglycopenic symptoms and life-threatening hypoglycemia might be less common in CFRD, symptomatic hypoglycemia with a robust adrenergic response occurs quite frequently. This is a frightening experience for patients, and

the incidence would be expected to increase with treatment of milder degrees of hyperglycemia. In the inpatient setting, more aggressive treatment must be accompanied by appropriate education and follow-up to facilitate rapid decreases in insulin doses with recovery and particularly with continued clinical improvement at home.

Patients who have negative experiences with insulin therapy may be less willing to adhere to multiple daily insulin injections and frequent blood glucose monitoring, both of which become essential later in life as their diabetes progresses. Patients with CF and their families already struggle with the burden of a chronic, life-threatening illness; more intensive effort and attention to diabetes will increase that burden, perhaps to the detriment of other health care behaviors for which the evidence base for benefit is greater. Hospitals and CF programs will invest more time, money, and personnel to implement these more intensive diabetes treatment protocols, which may or may not achieve the intended goals but certainly will inhibit other initiatives. A final concern, with the furthest reaching implications, is that these guidelines could create issues regarding what "standard of care" ethically can be used in the comparison group in future studies of intensive management of CFRD. Specifically, these guidelines are not based on long-term, large-scale trials with end points important to patients such as quality of life, disability, or death. But future institutional ethical review boards could hold investigators accountable for providing care in line with these guidelines, inhibiting much-needed research to actually demonstrate that these guidelines are effective in improving quality of life, functional status, and survival.

This is not to say we should avoid embracing these CFRD guidelines for fear of treatment side-effects or concern about the complexity of implementation. On the contrary, we know that CFRD develops in most patients with CF over time and, therefore, it should be regarded as an integral aspect of CF care rather than as a separate disease entity. We know that microvascular complications occur in a significant number of patients with CFRD, so screening for and treating eye, kidney, and neurologic diseases are imperative. We know that CFRD is different in many ways from type 1 and type 2 diabetes, and thus all members of the CF team should be educated about the unique aspects involved in caring for these patients. CF programs should establish review processes with measurements prior to and after interventions and a comprehensive CFRD care team consisting of representatives from pulmonary, endocrine, nutrition, and diabetes education. At the University of North Carolina School of Medicine, we have developed a CFRD quality improvement initiative with the establishment of a CFRD database, goal setting, and monthly reviews of outcomes and next steps.

Our hope is that the clinical care guidelines for CFRD will be utilized as they were intended: to guide us in an area of certain import but uncertain evidence. The questions they have generated should serve as the basis for future research, which is critical to identifying adverse outcomes caused by insulin deficiency/hyperglycemia and the interventions that will attenuate these risks.

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