Can J Diabetes 43 (2019) 1–2

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Editorial

What is the Real Usefulness of Glycated Hemoglobin Levels for Diabetes Screening in Patients With Cystic Fibrosis?

Cystic fibrosis (CF) is the most common lethal autosomal-recessive disease in Caucasians (1 in 3,800 births). CF is characterized by viscous mucus accumulation in various organs. The most important are the lungs, but it also occurs in multiple other organs, including the pancreas, which leads to both exocrine and endocrine deficiencies (1). Because of improved care, the life expectancy of patients with CF has increased significantly; they have a median life expectancy of more than 50 years in Canada (2). Accordingly, CF-related diabetes (CFRD), for which the main risk factor is age, has become the most common secondary complication of CF. By 10 years of age, 10% of patients already have CFRD; in adulthood, CFRD affects 40% to 50% of patients with CF, and another 35% have abnormal glucose tolerance (1). CFRD is a specific form of diabetes, but it shares some of the characteristics of type 1 (e.g. it occurs at a young age in mostly slim patients and includes a very significant, but not total, insulin-secretion deficit) and of type 2 diabetes (e.g. a long phase of postprandial glucose intolerance preceding diabetes onset). CFRD is associated with significant complications, including the classic microvascular complications of diabetes. CFRD is also associated with a higher risk for accelerated weight loss and reduced lung function, both translating into an increased risk for early mortality. In addition, symptoms associated with diabetes onset (e.g. fatigue, weight loss) can easily be confounded with symptoms of CF. In order to prevent the major complications associated with CFRD, annual screening is recommended (1). Classic methods for diagnosis, such as fasting blood glucose and glycated hemoglobin (A1C) levels, may be less sensitive in patients with CF than in the general population. For this reason, the recommended screening test for CFRD remains an annual oral glucose tolerance test (OGTT) starting at 10 years of age. However, OGTTs add to the burdens for both patients and CF health-care teams (OGGT duration, required materials, etc.) in an already extremely complex disease-management program. These barriers are reflected by low adherence to OGTT screening; an attendance rate of approximately 50% for planned OGTTs, even in large and experienced centers (2,3). Several factors may explain such low participation rates for this test, including postponment due to the presence of pulmonary exacerbation or to medications' interfering with glucose tolerance (e.g. steroids); the lack of interest in or aversion to the test; and the fear of a diagnosis of diabetes.

The OGTT has been identified as an important barrier, so active research is ongoing to replace or simplify the OGTT. Because A1C is convenient (nonfasting, single blood draw that is easy to combine with other laboratory tests required for CF monitoring), most teams have tried to compensate for the lower sensitivity by proposing a lower CF-specific A1C threshold for the diagnosis of CFRD. Indeed, rather than the 6.5% threshold used to diagnose for type 2 diabetes, an A1C threshold reduced to 5.8% for patients with CF has shown a sensitivity between 68.2% and 90.0% for CFRD diagnosis which, in our opinion, is an unreliable strategy for replacing the OGTT (2,4). However, rather than the low correlation observed between capillary blood glucose and A1C levels for patients with CF, a recently published study using continuous glucose monitoring reported a strong correlation between A1C and mean blood glucose levels as well as the percentage of time above 11.1 mmol/L compared with previous reports, suggesting that A1C levels could possibly capture dysglycemia, even for patients with CF (5). Still, for patients with CF, a clear CFRD diagnosis during an OGTT can contrast with a very low value for A1C levels, leaving clinical teams with an important diagnostic dilemma. A possible explanation is that OGTT and A1C levels are 2 very different makers of glucose intolerance: 1 shows glucose tolerance over a single glucose challenge, and the other shows the average blood glucose over the past 3 months. Thus, A1C levels are an appealing and practical measure, but they still lack sufficient sensitivity to replace OGTT for patients with CF.

In this issue of the *Canadian Journal of Diabetes*, Gilmour et al (3) have approached the use of A1C levels to diagnose CFRD from a different and elegant angle. They propose a stepwise approach, using A1C levels to reduce the number of required OGTTs. In 295 adult patients with CF for whom 717 concomitant OGTTs and A1C tests were available, using an A1C threshold of 5.5%, the research team observed that 91.8% of patients with CFRD were, indeed, found to have a specificity of 34.1%. They concluded that by not referring patients for OGTTs if they have A1C levels lower than 5.5%, it is possible to reduce the number of OGTTs by 36.7%. Therefore, using biannual A1C measurements and referring patients for OGTTs if their A1C levels are above 5.5% and/or if clinical evolution is suggestive of CRFD (e.g. unexplained weight and/or lung function) could be a practical approach to screening for CFRD and should minimize the risk for missed diagnoses.

Reducing the number of OGTTs performed annually has important implications for both patients and health-care teams by reducing, for example, burdens on the patients, required time, human resources and possible risk for bacterial contamination between patients. This approach will also allow refocusing available resources so as to increase actual screening rates and allow patients to have a better understanding of the importance and implications of CFRD.

Gilmour et al are proposing an easy way to simplify CFRD screening for patients and health-care teams. They have refocused the debate using A1C levels as a way to reduce the number of required OGTTs, rather than the ongoing debate opposing these 2 different measures of glucose tolerance. Although their findings are interesting and may provide a practical approach to CFRD screening,

https://doi.org/10.1016/j.jcjd.2018.11.001

external validation of this approach is essential before this stepwise strategy can be recommended.

Valérie Boudreau RD, MSc
Institut de Recherches Cliniques de Montréal, Montréal, Québec, Canada
Université de Montréal, Département de nutrition, Faculté de Médecine, Montréal, Québec, Canada

Quitterie Reynaud MD
Centre de référence Adulte de la Mucoviscidose, Service de médecine interne, Hospices civils de Lyon, Pierre Bénite, France
Université de Lyon, Équipe d'Accueil Health Services and Performance Research, Lyon, France

Rémi Rabasa-Lhoret MD, PhD
Cystic Fibrosis Clinic, Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada
Institut de Recherches Cliniques de Montréal, Montréal, Québec, Canada
Université de Montréal, Départements de nutrition, Faculté de Médecine, Montréal, Québec, Canada
E-mail address: remi.rabasa-lhoret@ircm.qc.ca

Author Disclosures

Conflicts of interest: None.

References

1. Moheet A, Moran A. CF-related diabetes: Containing the metabolic miscreant of cystic fibrosis. Pediatr Pulmonol 2017;52:S37–43.
2. Boudreau V, Reynaud Q, Dubois CL, et al. Screening for cystic fibrosis-related diabetes: Matching pathophysiology and addressing current challenges. Can J Diabetes 2016;40:466–70.
3. Gilmour JA, Sykes J, Etchells E, Tullis E. Cystic fibrosis-related diabetes screening in adults: A gap analysis and evaluation of accuracy of glycated hemoglobin levels. Can J Diabetes 2019;43:13–8.
4. Boudreau V, Coriati A, Desjardins K, Rabasa-Lhoret R. Glycated hemoglobin cannot yet be proposed as a screening tool for cystic fibrosis-related diabetes. J Cyst Fibros 2016;15:258–60.
5. Chan CL, Hope E, Thurston J, et al. Hemoglobin A1c accurately predicts continuous glucose monitoring-derived average glucose in youth and young adults with cystic fibrosis. Diabetes Care 2018;E-pub ahead of print.