OBSERVATIONS

Prognostic Relevance of Hypoglycemia Following an Oral Glucose Challenge for Cystic Fibrosis–Related Diabetes

An annual oral glucose tolerance test (OGTT) has become part of standard care in cystic fibrosis (CF) to screen for CF-related diabetes (CFRD) in patients older than 10 years of age (1). Up to 15% of patients with CF develop hypoglycemia during an OGTT (2), and there is some discussion whether such a response indicates an increased risk for the development of CFRD. In fact, a reactive hypoglycemia has been considered as an early stage of CFRD (3). However, the prognostic value of such a reactive hypoglycemia with respect to future glucose control has never been studied. Based on a delayed insulin secretion in CF, which might be relevant to both a hypoglycemic as well as a hyperglycemic response to a glucose challenge (4), we hypothesized that the hypoglycemic response to a glucose challenge could indicate a stage preceding CFRD. The objective of this study therefore was to determine the prognostic value of a hypoglycemic response during an OGTT for future impaired glucose tolerance (IGT) and CFRD.

We retrospectively analyzed data collected between 2001 and 2009 from 1,779 patients who participated in a longitudinal prospective study on "Early Diagnosis of Diabetes Mellitus in Patients with Cystic Fibrosis." All patients were 10 years of age or older and performed standardized OGTTs (5), at least on an annual basis. OGTT results were categorized following the World Health Organization guidelines (5). All patients included into the current analysis (n = 841) had at least two valid OGTTs each and a normal glucose tolerance to the first challenge. The patients with normal glucose tolerance were divided into two subgroups: one group with an entirely normal, nonhypoglycemic plasma glucose level 2 h after the challenge (3.3–7.7 mmol/L; 60–139 mg/dL) and one group with a hypoglycemic 2-h plasma glucose level (<3.3 mmol/L; <60 mg/dL). The groups were compared regarding the incidence of IGT and CFRD at the last available OGTT using χ^2 statistics. A hypoglycemic response to the first oral glucose challenge was observed in 53 of the 841 participants (6.3%). There was no difference between patients with an entirely normal, nonhypoglycemic response (n = 788) and those with a hypoglycemic response to the first OGTT in the incidence of CFRD (10.3 vs. 13.2%) or IGT (12.9 vs. 11.3%) at the last OGTT 3.5 ± 1.8 years later. Likewise, groups did not differ in age, sex distribution, BMI, and time interval between first and last OGTT.

The 7% incidence of hypoglycemia observed in our study was lower than the 15% previously reported for CF patients (2). A hypoglycemic response to an OGTT does not indicate a risk for future CFRD or IGT, at least not in the following 3.5 years. This finding is in contrast to our hypothesis. We had expected that a dysregulation of insulin secretion in CF would be responsible for reactive hypoglycemia and also—at least in part—for glucose intolerance and overt diabetes in this disease. Our data indicate that the mechanisms underlying reactive hypoglycemia are different from those involved in glucose intolerance or CFRD in CF.

KERSTIN RADIKE, MD[1]
KATHARINA MOLZ,[2]
REINHARD W. HOLL, MD[2]
BRITTA POETER,[3]
HELGE HEBESTREIT, MD[1]
MANFRED BALLMANN, MD[3]

From the [1]Children's Hospital, University of Würzburg, Würzburg, Germany; the [2]Institute of Epidemiology, University of Ulm, Ulm, Germany; and the [3]St Josef Hospital Pediatric Clinic, Ruhr University Bochum, Bochum, Germany.

Corresponding author: Kerstin Radike, radike_k@klinik.uni-wuerzburg.de.

DOI: 10.2337/dc10-2286. Clinical trial reg. no. NCT00662714, clinicaltrials.gov.

Acknowledgments—This study was supported by a grant from the Mukoviszidose e.V. (German CF foundation) and Novo Nordisk. Assistance was provided at all study centers. No other potential conflicts of interest relevant to this article were reported.

K.R. researched data, contributed to discussion, and wrote and reviewed the manuscript. B.P. contributed to discussion and reviewed the manuscript. K.M. researched data and reviewed the manuscript. R.W.H. researched data, contributed to discussion, and reviewed and edited the manuscript. H.H. researched data, contributed to discussion, and reviewed and edited the manuscript. M.B. researched data, contributed to discussion, and reviewed and edited the manuscript.

Parts of this study were presented in abstract form at the 33rd European Cystic Fibrosis Conference, Valencia, Spain, 16–19 June 2010.

References

1. Moran A, Brunzell C, Cohen RC, et al.; the CFRD Guidelines Committee. Clinical care guidelines for cystic fibrosis-related diabetes (Position Statement). Diabetes Care 2010;33:2697–2708
2. Battezzati A, Battezzati PM, Costantini D, et al. Spontaneous hypoglycemia in patients with cystic fibrosis. Eur J Endocrinol 2007;156:369–376
3. UK Cystic Fibrosis Trust Diabetes Working Group. Management of cystic fibrosis-related diabetes mellitus [article online], 2004. Available from http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/. Accessed 19 January 2011
4. Holl RW, Heinze E, Wolf A, Rank M, Teller WM. Reduced pancreatic insulin release and reduced peripheral insulin sensitivity contribute to hyperglycaemia in cystic fibrosis. Eur J Pediatr 1995;154:356–361
5. World Health Organization. *Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1. Diagnosis and classification of diabetes mellitus*. Geneva, World Health Organization, 1999 (WHO/NCD/NCS/99.2)